Shionogi Study Title:	A Multicenter, Randomized, Open-label Clinical Study of S-649266 or Best Available Therapy for the Treatment of Severe Infections Caused by Carbapenem-resistant Gram-negative Pathogens
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History of Statistical Analysis Plan Amendments

Version 1 (Original)	13 Jul 2017
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Statistical Analysis Plan: 1424R2131

Study Title:	A Multicenter, Randomized, Open-label Clinical Study of S-649266 or Best Available Therapy for the Treatment of Severe Infections Caused by Carbapenem-resistant Gram-negative Pathogens
Study Number:	1424R2131
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RECORDS ON REVISIONS

Version	Date for creation or modification	Person in charge	Remarks
Ver 1.0	13 Jul 2017	[redacted]	Originally prepared
Ver 2.0	24 Jul 2018	[redacted]	・Update per Clinical Study Protocol Version 4 ・Update objective of this study ・Specify time point for vital sign (Section 10.3) ・Delete section ECG analysis (Section 10.4) ・Add description for subjects with *Stenotrophomonas maltophilia* will be included in CR MITT population (Section 5.3) ・Update criteria for eradication for cUTI subject (section 9.1) ・Add description for DSMB ・Specify using corrected APACHE II score 9.3.2.2 ・Add the rule of analysis visit and baseline definition (Sections 6.3 and 6.5) ・Add logic for missing time (Section 6.4.1) ・Add data handling if reported bacteria name is different between local and central (Section 6.7.1) ・Add definition of additional antibiotics (Section 6.8) ・Add definition of study drug regimen and add subgroup analysis using it (Sections 6.9, 9.4.1.1, and 9.4.1.2) ・Add analysis for new infection (Section 9.4.1.2) ・Add analysis regarding susceptibility (Section 7.2) ・Add sensitivity clinical and microbiological outcome (Section 9.2) ・Add indeterminate at TOC carried forward

[redacted]

			to FU (Sections 9.1.2 and 9.1.4) ・Add subgroup analysis for type of CR baseline pathogen, region and APACHE II (Section 9.3.3) ・Add analysis for HABP/VABP/HCABP + BSI/sepsis (Section 9.4.1) ・Add analysis for cUTI for mortality (Section 9.4.1) ・Clarify using standard unit for laboratory data analysis (Section 10.2) ・Specify decimal space for PK analysis (Section 14) ・Change decimal space for standard deviation and error. (section 14)
2.1	15 Aug 2018	[redacted]	・Clarify analysis for baseline pathogen (section 7.2) ・Add decimal space for calculated value. (section 14) ・Add calculation formula for appendix 2.
2.2	03 Dec 2018	[redacted]	・Change the wording from sensitivity to supplementary per ICH E9 R1 ・Clarify the interim analysis for DSMB ・Exclude neomysin oral administration from additional antibiotics (section 6.8). ・Clarify Composite of Survival and No Change in Antibiotic Treatment will be determined by Shinogi internally rather than EDC data (section 9.4.1.9). ・Exclude PTT from LAB analysis (section 10.2) ・Minor update of wording
2.3	12 Feb 2019	[redacted]	・Specify meical monitor will adjudicate additional antibiotics based on available data, and delete sentences about neomisyin oral administration.
2.4	11 Apr 2019	[redacted]	・Delete signature page to use Veeva Vault eSigniture due to chage TMF management plan. ・Terminology change from microbiological

[redacted]

			eradication/failure to eradication/persistence. (Section 9.1.6, 9.1.7, 9.2.6) ・Change terminology from protocol deviation list to protocol deviation specification. Also clarify criteria for ME population is specified in the document. (section 5.4 and 8.1) ・Change the definition of new/super infection to new pathogen on or after Day 3 by the input from medical group. (section 9.1.5)
3.0	27 Jun 2019	[redacted]	・Add time imputation for lab data and microbiological data if time is missing (section 6.4.1 and 6.4.2) ・Add CR MITT 2 Population (section 5.3.1) and analysis using CR MITT2 (section 7.1, 9.4.1.1 and 9.4.1.2) ・Add data handling for subject who receive cefiderocol after BAT completion (section 5.5 and 10.1.1) ・Add analysis window for premature EOT ・Differentiate persistence and recurrence which was originally counted together (section 9.1.6) and update table 9-3 ・Add overall mortality until EOS. In addition, add overall mortality including death after EOS. (section 9.4.1.6) ・Add analysis for fatal AE (section 10.1) ・Clarify if investigator consider BSI subject as clinically cured and no need to collect blood sample, considered as presumed eradication (section 9.1.3.3 and 9.1.4.3).

[redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
APACHE II	Acute Physiology and Chronic Health Evaluation II
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BAL	bronchoalveolar lavage
BAT	best available therapy
BMI	body mass index
BSI	bloodstream infections
CFUs	colony-forming units
CI	confidence interval
CLSI	Clinical and Laboratory Standards Institute
CR-ME	Carbapenem-resistant Microbiologically Evaluable Population
CR Micro-ITT	Carbapenem-resistant Microbiological Intent-to-treat Population
CrCl	creatinine clearance
cUTI	complicated urinary tract infection
DSMB	data safety monitoring board
EA	Early Assessment
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FiO_2	fraction of inspired oxygen
FU	Follow-up
HABP	hospital-acquired bacterial pneumonia
HCABP	healthcare-associated bacterial pneumonia
IMP	investigational medicinal product
ITT	intent-to-treat
IWRS/IVRS	interactive web or voice response system
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities

MIC	minimum inhibitory concentration
Micro-ITT	Microbiological Intent-to-treat Population
mITT	modified intent-to-treat
$\%T_{f>MIC}$	percentage of the dosing interval for free-drug plasma concentration to be above the minimum inhibitory concentration
PaO_2	partial pressure of arterial oxygen
PK	pharmacokinetics
PSB	protected specimen brush
PT-INR	prothrombin time-international normalized ratio
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SIRS	systemic inflammatory response syndrome
SOC	System Organ Class
SOFA	Sequential Organ Failure Assessment
TIBC	total iron-binding capacity
TOC	Test of Cure
ULN	upper limit of normal
VABP	ventilator-associated bacterial pneumonia
WBC	white blood cell (count)
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) presents details, including methods of analyses, of the efficacy and safety analyses described in Section 9: "PLANNED STATISTICAL METHODS" of the protocol (Protocol No. 1424R2131: Version 4 dated 16 Nov 2017). Details of outputs (or mock-ups of tables, figures, and listings) from analyses in this SAP, will be included in a separate document ("Tables, Figures, and Listings Shells") prepared separately. Any deviations from this analysis plan will be substantiated by sound statistical rationale and will be documented in the final clinical study report.

2. STUDY OVERVIEW

This is a Phase 3, multicenter (multinational), open-label, parallel-group, randomized, active-controlled study in approximately 150 subjects with documented carbapenem-resistant Gram-negative bacterial infections. Subjects meeting eligibility criteria and assessed by the investigator to require 7 to 14 days of intravenous treatment in hospital will be randomized (2:1) to either cefiderocol 2 g received intravenously over 3 hours, every 8 hours, or best available therapy (BAT).

The treatment duration for cefiderocol or BAT is anticipated to be 7 to 14 days, which are consistent with published treatment guidelines for serious infections. Based on the investigator's clinical assessment of the subject, treatment may be extended up to 21 days.

3. STUDY OBJECTIVES

3.1 Primary Objective

- To assess, at Test of Cure (TOC)[1], the clinical outcome to therapy with cefiderocol or BAT in adult subjects with either hospital-acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP)/healthcare-associated bacterial pneumonia (HCABP) or bloodstream infections/sepsis (BSI/sepsis)[2] caused by carbapenem-resistant Gram-negative pathogens
- To assess, at TOC, the microbiological outcome to therapy with cefiderocol or BAT in adult subjects with complicated urinary tract infection (cUTI) caused by carbapenem-resistant Gram-negative pathogens

3.2 Secondary Objectives

- To assess the safety of cefiderocol
- To assess the clinical outcome of treatment with cefiderocol or BAT in subjects with either HAP/VABP/HCABP or BSI/sepsis at End of Treatment (EOT)[3] and Follow-up (FU)[4]
- To assess the clinical outcome of treatment with cefiderocol or BAT in subjects with cUTI at EOT, TOC, and FU

- To assess the microbiological outcome of treatment with cefiderocol or BAT in subjects with either HABP/VABP/HCABP or BSI/sepsis at EOT, TOC, and FU
- To assess the microbiological outcome of treatment with cefiderocol or BAT in subjects with cUTI at EOT and FU
- To assess the microbiological outcome of treatment with cefiderocol or BAT in subjects with bacteremia (regardless of the primary infection diagnosis) at EOT, TOC, and FU
- To assess the composite clinical and microbiological outcome of treatment with cefiderocol or BAT in subjects with cUTI at EOT, TOC, and FU
- To assess the all-cause mortality at Day 14 and Day 28 in subjects with HABP/VABP/HCABP and BSI/sepsis
- To compare cefiderocol with BAT in subjects with HABP/VABP/HCABP, cUTI, or BSI/sepsis based on the composite endpoint of survival and no change in antibiotic treatment due to either lack of therapeutic benefit or drug-related toxicity at TOC

[1] TOC is defined as End of Treatment (EOT) + 7 days (± 2 days).

[2] BSI/sepsis is a group of patients with documented carbapenem-resistant Gram-negative infections in the bloodstream (BSI) or in a body site other than the urinary tract (cUTI) or lung (HABP/VABP/HCABP) and in case of sepsis, evidence of systemic inflammatory response syndrome (SIRS) is required.

[3] EOT = End of Treatment is defined as the last day of study therapy.

[4] FU = Follow-up is defined as EOT + 14 days (± 3 days).

4. STUDY DESIGN

4.1 Study Blinding

This is an open-label study.

4.2 Randomization to Treatment Groups

The treatments will be randomized to subject identification numbers by the IXRS® provider in a 2:1 fashion, i.e., 2 × cefiderocol and 1 × BAT. An interactive web or voice response system (IWRS/IVRS) will be used to assign subjects to identification numbers for which treatment has already been randomly assigned. Randomization will be performed by the stochastic minimization method using their infection site (HABP/VABP/HCABP, cUTI, and BSI/sepsis), APACHE II score (≤ 15 and ≥ 16), and region (North America, South America, Europe, and Asia-Pacific) as allocation factors. To avoid deterministic allocation based on the ongoing allocation results, probabilistic allocation will be incorporated.

The population with HABP/VABP/HCABP will be approximately 50% of randomized subjects; cUTI is limited to no more than 30% of randomized subjects, and the remainder of subjects will be enrolled under the BSI/sepsis diagnosis. The randomization ratio of subjects between treatment groups based on clinical diagnosis will be maintained through the allocation factor of clinical diagnosis at the time of randomization. The process for

subject number assignment and treatment assignment is described in the study procedure manual.

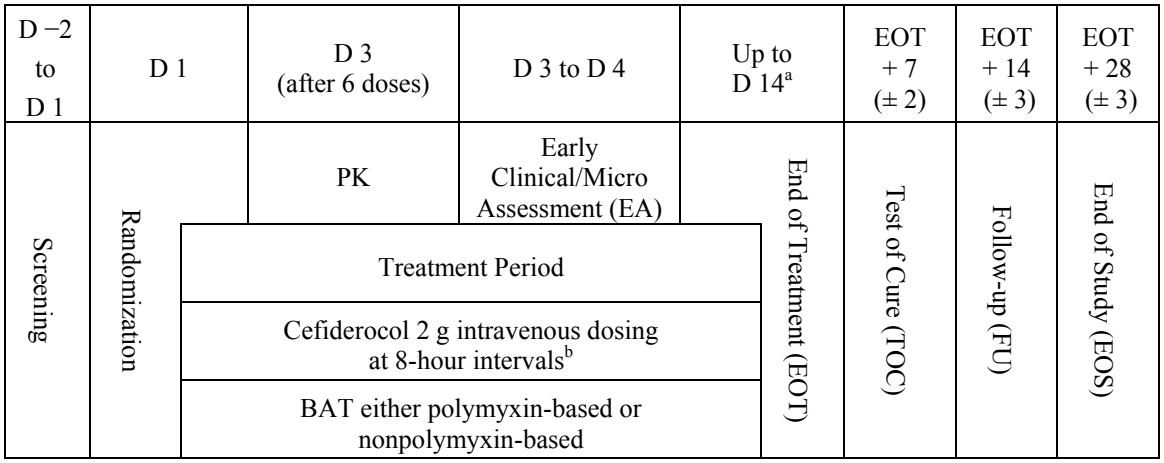
4.3 Sample Size

Approximately 150 subjects will be randomized 2:1 (2 × cefiderocol and 1 × BAT) to each group. This sample size will ensure that approximately 100 subjects are treated with cefiderocol.

4.4 Study Schematic

The study design is shown in Figure 4-1. The study time and events table is shown in Appendix 1.

Figure 4-1 Study Schematic



BAT = best available therapy; D = days; EA = Early Assessment; eCRF = electronic case report form; EOT = End of Treatment (last day of study treatment); PK = pharmacokinetics

Each day is a calendar date (i.e., D2 is the next day/date after D1 in calendar).

a The treatment duration can be extended up to 21 days based on the investigator's clinical assessment of the subject. A clear reason should be documented in the eCRF.

b Dosing adjustments for augmented renal clearance and renal impairment (see Table 5-2 in protocol).

5. ANALYSIS POPULATIONS

The following analysis populations will be defined in this study.

5.1 Intent-to-treat Population

The Intent-to-treat population is defined as all randomized subjects who received at least 1 dose of the study treatment.

5.2 Microbiological Intent-to-treat Population

The Microbiological Intent-to-treat (Micro-ITT) population includes all ITT subjects who have a baseline Gram-negative pathogen from an appropriate clinical specimen, regardless if the pathogen is carbapenem resistant or not. Subjects should not be excluded from this population based upon events that occurred postrandomization (e.g., lost to follow-up).

5.3 Carbapenem-resistant Microbiological Intent-to treat Population

The Carbapenem-resistant Microbiological Intent-to-treat (CR Micro-ITT) population includes all Micro-ITT subjects whose at least 1 of the baseline Gram-negative pathogens is carbapenem resistant and the carbapenem-resistant pathogen is confirmed by central laboratory. Subjects with *Stenotrophomonas maltophilia* as baseline pathogen will also be included in this population. If subsequent central laboratory results confirm that the pathogen is not carbapenem resistant, the subject with the pathogen will not be included in this population.

5.3.1 Carbapenem-resistant Microbiological Intent-to-treat 2 Population

The Carbapenem-resistant Microbiological Intent-to-treat 2 (CR Micro-ITT 2) population includes all subjects in the CR Micro-ITT population. In addition, this CR Micro-ITT 2 population will include subjects whose at least 1 of the baseline Gram-negative pathogens is carbapenem resistant confirmed by local laboratory if there is no central laboratory data available.

5.4 Carbapenem-resistant Microbiologically Evaluable Population

The Carbapenem-resistant Microbiologically Evaluable (CR-ME) population includes all CR Micro-ITT subjects who follow important components of the study as specified in the protocol with no major protocol violations.

Criteria for inclusion are:

- ≥ 5 days of intravenous study treatment unless treatment was a failure
- Underwent TOC assessment
- Subjects without any major protocol inclusion or exclusion violations
- Subjects with no violations of restrictions for concomitant therapy, including concomitant antibiotics effective against Gram-negative bacteria

Details will be specified in protocol deviation specification.

5.5 Safety Population

The Safety population includes all randomized subjects who receive at least 1 actual dose of the study treatment (ITT population). The population will be analyzed according to the treatment that the subjects actually received study drug regimen, rather than the treatment to which the subjects were randomized.

Note that, as this is an open-label study, it has been observed that one subject received cefiderocol after completing the randomization assigned study treatment of BAT,. This subject will be included in the Safety Population as having received BAT. However, a limited number of key safety analyses will be repeated with this subject assigned to the cefiderocol arm. (see section 10.1.1 for details).

5.6 Pharmacokinetic Concentration Population

The Pharmacokinetic (PK) Concentration population includes all subjects who undergo plasma sampling and have at least 1 evaluable PK assay result for cefiderocol. This population will be used for the concentration listing, plotting of the concentration-time data, and the concentration summary.

6. STATISTICAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

6.1 Statistical Reporting

In this SAP, unless otherwise stated, summary statistics include the number of subjects, arithmetic mean, standard deviation (SD), minimum, median, and maximum. SAS® (Version 9.2 or later version) will be used for all statistical analyses. If the APACHE II score is corrected after randomization, the corrected score will be used in the analysis.

6.2 Statistical Testing

No inferential testing will be performed except for the exploratory analysis described in Section 9.4.1.7. If statistical tests are performed, they will be performed at the 0.05 significance level using 2-sided tests, except where otherwise noted. No multiplicity adjustment of statistical tests will be applied in this study.

6.3 Analysis Windows

Measurements for efficacy or safety endpoints will be performed according to the schedule as shown in Section 4.4. The following analysis window (Table 6-1) will be used for analysis at a particular visit or time point to be included in by-visit summary statistics for the specified variables. Day 1 is defined as initial day of administration of drug.

If there are multiple available values in an analysis time window, the closest value to the target day captured from scheduled visit or unscheduled visit will be used for analysis, and if there are multiple values within the same day, the latest value will be used.

Table 6-1 Analysis Window

Time Point	Target Day	Analysis Time Window
Early Assessment	Day 3 or 4	Not applicable
End of Treatment	End of last infusion	Not applicable
Test of Cure	Date of end of last infusion + 7	-2 to + 2 days
Follow-up	Date of end of last infusion + 14	-3 to + 3 days
PK sampling		
Just prior to the next infusion	Next infusion start date and time	-1 to 0 hours
1 hour after the infusion	Infusion start date and time + 1hr	± 15 minutes
At the end of infusion	Infusion end date and time	-15 minutes to end of infusion
1 hour after end of infusion	Infusion end date and time + 1hr	± 0.5 hours
Premature EOT	Start date and time of last infusion	Within 24 hours after last dose

EOT = End of Treatment; PK = pharmacokinetic

Pharmacokinetic samples that are collected before the sixth dose administration will not be used for the summary of plasma cefiderocol concentrations (Pharmacokinetic samples just prior to the sixth dose will be included.). The target of the second PK sampling will be within 24 to 72 hours after the dosing adjustment. The target of PK sampling for premature EOT will be within 24 hours of the last dose.

For all values including values obtained at an unscheduled visit, the analysis time window above will be applied. Values other than considered as TOC or FU, obtained at visit reported as EA and EOT will be used for analysis at EA and EOT, respectively. If a subject is received study drug more than 21 days, Day 21 will be considered as the date of end of last infusion. Unscheduled visits within an analysis time window for scheduled visit will be used to provide values for that scheduled visit.

6.4 Missing Data

6.4.1 Missing or Partial Dates and Times

For classification of prior and concomitant medications, if the medication cannot be classified into concomitant medications or prior medications due to a partially missing date, the rules below will be applied for the classification. This rule will be applied for collection time of laboratory data as well if time is missing.

For start date:

- If the year and month are observed but the day is missing, the first day of the month will be used.
- If the year is observed but the month is missing, the first day of the year, 01 Jan, will be used.

If the year is observed but the time is missing, the first time of the day, 12:00 AM, will be used. And, for end date:

- If the year and month are observed but the day is missing, the last day of the month will be used.
- If the year is observed but the month is missing, the last day of the year, 31 Dec, will be used.

- If the year is observed but the time is missing, the end time of the day, 23:59 AM, will be used.

If micro sample collection time is missing, the end time of the day, 23:59 AM, will be used.

The imputed dates will not be displayed in the listings.

6.4.2 Missing Microbiological or Clinical Outcome

For clinical and microbiological outcomes, subjects who are lost to follow-up or have missing or "indeterminate" outcomes will be included in the denominator as indeterminate for cure/eradication rate, i.e., considered as not responders. If judged by the investigator that a subject died due to pneumonia, BSI/sepsis or cUTI, the clinical outcome will be considered as clinical failure after the event of death. If a subject died due to other reasons, the clinical outcome will be considered as "indeterminate" after death.

For clinical outcome, if a subject recived additional antibiotics for target disease (i.e, baseline infection) before the target date, the outcome will be considered as "clinical failure". If a subject did not receive additional antibiotics for target disease before the target date, the outcome will be considered as "indeterminate".

Missing values for other individual data points will remain as missing unless otherwise specified. All analysis will be based on observed case unless otherwise stated.

6.5 Baseline Definition

- For microbiological endpoints, baseline pathogens are determined from appropriate clinical specimens collected within the 3 days prior to randomization in this study for subjects who have been treated previously with an empiric antibiotic regimen and failed treatment, both clinically and microbiologically (as defined in general inclusion number 4). For the other subjects, baseline pathogens are determined from appropriate specimens collected within the 48 hours prior to the start of the first infusion of study treatment. Clinical specimens obtained by the site within the 2 days prior to signing informed consent form could be acceptable as screening/baseline cultures for this study. If appropriate specimens are collected on multiple dates before the first infusion, the specimens collected on the latest date for each pathogen will be used to determine baseline pathogens.

If multiple specimens are collected within the above time range for baseline, the following rules will be applied:

- In case same Gram-negative pathogens with different quantification are obtained from multiple samples from the same specimen type (i.e., blood, urine, respiratory specimen, or infection site that caused septic shock) that qualified a patient eligible for this study, the pathogen with the highest quantification/classification is considered as the baseline pathogen. The priority of quantitation is listed below:
    1. Highest value in quantification
    2. Largest value in semiquantification
    3. Largest value in no-quantification
- In case same Gram-negative pathogens with same quantification are obtained from different specimens, the pathogen with the highest minimum inhibitory concentration (MIC) for 1. cefiderocol 2. Meropenem, 3. Imipenem, 4. colistin is considered as the baseline pathogen.

The appropriate clinical specimen type is sputum, tracheal aspirate, bronchoalveolar lavage (BAL) fluid, protected specimen brush, pleural fluid, lung biopsy for HABP/VABP/HCABP, blood for BSI/sepsis, or urine for cUTI. Tissue from primary infection site is also applicable for all baseline infection. Specimen that was collected from other site may be considered as appropriate specimen. This will be determined by the medical monitor.

Only for subjects with cUTI, the pathogen whose quantification is 10^5 colony-forming units (CFUs)/mL or more will be considered as baseline pathogen.

For the other efficacy and safety endpoints, baseline is defined as the last measurement obtained prior to receipt of the first infusion of study drug.

6.6 Study Day Definition

Day 1 is the calendar day on which each subject takes initial investigational medicinal product (IMP). However, Day 1 is the calendar day of randomization for subjects who did not take any IMP. Previous day to Day 1 is expressed as Day -1, and days before Day -1 in Screening Period are expressed as Day -2, Day -3, …, etc.

6.7 Handling for Microbiologic Data

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

If a pathogen name is different between local and central laboratory, the name of the central laboratory will be used for the analysis. In that case, quantification will be considered as missing.

6.8 Additional Antibiotics

Additional antibiotics are defined as systemic antibiotics with Gram-negative activity. The medical group will determine which medications have Gram-negative activity. If the route of administration is ophthalmic, transdermal, nasal, topical, or vaginal, the medication will not be considered as a systemic antibiotic.Concomitant medications ending before initial study treatment start date/time plus 3 hours will not be considered as additional antibiotics. Antibiotics for Gram-negative pathogens that are allowed to be received (see Clinical Study Protocol Section 5.2.1.1) from Day 1 or Day 2, they will not be considered as additional therapy, but if they are received on Day 3 or after, they will be considered as additional therapy.

Medical monitor will adjudicate additional antibiotics based on the available data if needed.

6.9 Study Drug Regimen at Day 1 and 2

For efficacy analysis, response rate in the cefiderocol group will be calculated by cefiderocol monotherapy or not, and in the BAT group by colistin-based regimen or not.

Colistin-based regimen includes subjects who received "COLISTIN", "POLYMYXIN" or "POLYMYXIN B" based on WHO Drug Dictionary Preferred Term (PT).

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

7.1 Subject Disposition and Discontinuation

Subject disposition will be summarized for the all screened subjects. The following subjects' disposition categories will be included:

- Subjects who were screened
- Subjects who were screen failed

For the subjects who were screen failed, they will be also summarized by respective reasons.

Subject disposition will be summarized by treatment group for the all randomized subjects. The following subjects' disposition categories will be included:

- Subjects who were randomized
- Subjects who were randomized and treated
- Subjects who completed treatment
- Subjects who did not complete treatment
- Subjects who completed the study
- Subjects who discontinued early from the study

Subjects who received study drug for 7 days or more (for cUTI subjects, 5 days or more) will be considered as subjects who completed treatment. Subjects who did not complete treatment and subjects who discontinued early from the study will be also summarized by respective reasons.

The number of subjects in the ITT population, Micro-ITT population, CR Micro-ITT population, CR-ME population, and Safety population will be obtained by treatment group. The reasons for excluding subjects from each of the populations listed above will be summarized by treatment group.

7.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized with descriptive statistics for the CR Micro-ITT population, , CR Micro-ITT 2 population, CR-ME population, Micro-ITT population, and Safety population. The distribution of demographic and other baseline characteristics shown in Table 7-1 will be summarized by treatment group. Summary statistics will be calculated for quantitative scale items, and frequency and proportion of subjects in each category will be obtained for qualitative (i.e., binary and nominal) scale items. Quantitative scale items except for height, body mass index, SOFA and CPIS will be categorized and tabulated by treatment group.

The baseline pathogen will be summarized for Micro-ITT and CR Micro-ITT. The baseline carbapenem-resistant pathogen will also be summarized. The pathogen which is collected from blood specimen at baseline will also be summarized.

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

The reported medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized for the CR Micro-ITT population and Safety population for each treatment group by MedDRA System Organ Class (SOC) and PT.

Table 7-1 Demographic and Baseline Characteristics

Quantitative scale items	Age, height, weight, body mass index, creatinine clearance, total APACHE II score, baseline fever, SOFA score, CPIS
Binary or nominal scale items	Gender, race, ethnicity, region, infection site, clinical diagnosis, baseline fever group, medical history, prior therapy with Gram-negative coverage, number of Gram-negative pathogens from appropriate specimen, causal infection for BSI/sepsis, severity of the disease

APACHE II = Acute Physiology and Chronic Health Evaluation II; CPIS = clinical pulmonary infection score; SOFA = Sequential Organ Failure Assessment

Note: See Section 14 for categories.

8. STUDY CONDUCT

8.1 Protocol Deviations

For all randomized subjects, major protocol deviations will be listed. Major protocol deviations will be specified in the “Protocol deviation specification” separately. A final list of major protocol deviations will be determined based on data review prior to database lock.

8.2 Treatment Exposure and Compliance

Extent of treatment exposure is defined as the actual dosing period during which subjects took medication as follows:

(The day of the final IMP dose) – (The day of the first IMP dose) + 1 [day]

For the CR Micro-ITT population and Safety population, summary statistics of duration of treatment exposure will be calculated by treatment group based on EDC data. Also categorized duration of treatment will be summarized by treatment group (see Section 14 about category).

8.3 Study Drug Regimen

Best available therapy and adjunctive antibiotics taken from randomization to the end of study will be coded using World Health Organization (WHO) Drug Dictionary (Sep 2015 or later). The number and percentage of subjects taking BAT or adjunctive medications will be summarized by Anatomical Therapeutic Class (ATC) and PT for each treatment group for the CR Micro-ITT population and Safety population. Although a subject may have taken 2 or more medications, the subject is counted only once within an ATC classification. The same subject may contribute to 2 or more PTs in the same classification. All study drug administration data will be listed by subjects.

In addition, study drug regimen for Gram-negative pathogen that is received at Day 1 and Day 2 after first study drug administration will be summarized by treatment group for CR MITT and safety population. Study drug regimen includes only cefiderocol or BAT/adjunctive therapy and does not include concomitant medications. Generic names will be used for this summary.

8.4 Prior Therapy and Concomitant Therapy Other Than Best Available Therapy/Adjunctive Antibiotics

Prior and concomitant medications will be coded using the WHO Drug Dictionary. If a subject received cefiderocol as concomitant medication, this will be reported as cefiderocol. Prior medications are defined as medications that were taken prior to the first dose date/time of the study drug. Concomitant medications are defined as medications that were taken on or after the first dose date/time of the study drug.

The number and percentage of subjects taking concomitant medications or procedures will be summarized by ATC and PT for each treatment group for the CR Micro-ITT population and Safety population. Although a subject may have taken 2 or more medications, the subject is counted only once within an ATC classification. The same subject may contribute to 2 or more PTs in the same classification. Prior medications or procedures will be summarized in the same manner for the CR Micro-ITT population and Safety population.

9. EFFICACY

The primary population for efficacy analyses will be the CR Micro-ITT population. CR-ME population will be used as a supplementary analysis for primary efficacy endpoint. Micro-ITT population will be used to check the consistency of results for primary efficacy endpoints. Also, unless stated otherwise, a confidence interval (CI) of proportion will be calculated using the Clopper-Pearson method.

9.1 Efficacy Assessment

9.1.1 Clinical Outcomes for EOT and TOC

The clinical outcomes will be assessed by the investigator according to the following criteria established for each infection site at EOT and TOC. In case treatment duration is extended beyond 14 days, an additional clinical outcome will be assessed on Day 14. The clinical outcomes will be entered in the electronic case report form (eCRF).

9.1.1.1 HABP/VABP/HCABP

- **Clinical Cure:** Resolution or substantial improvement of baseline signs and symptoms of pneumonia including a reduction in SOFA score and clinical pulmonary infection score（CPIS), and improvement or lack of progression of chest radiographic abnormalities such that no antibacterial therapy is required for the treatment of the current infection.
- **Clinical Failure:** No apparent response to therapy; persistence or worsening of baseline signs and/or symptoms of pneumonia; reappearance of signs and/or symptoms of pneumonia; development of new signs and/or symptoms of pneumonia requiring antibiotic therapy other than, or in addition to, study treatment therapy; progression of chest radiographic abnormalities; or death due to pneumonia.
- **Indeterminate:** Lost to follow-up such that a determination of clinical cure/failure cannot be made.

9.1.1.2 cUTI

- **Clinical Cure:** Resolution or substantial improvement of baseline signs and symptoms of cUTI, or return to preinfection baseline if known, such that no antibacterial therapy is required for the treatment of the current infection.
- **Clinical Failure:** No apparent response to therapy; persistence or worsening of baseline signs and/or symptoms of cUTI; or reappearance of signs and/or symptoms of cUTI; development of new signs and/or symptoms of cUTI requiring antibiotic therapy other than, or in addition to, study treatment therapy; or death due to cUTI.
- **Indeterminate:** Lost to follow-up such that a determination of clinical cure/failure cannot be made.

9.1.1.3 BSI/Sepsis

- **Clinical Cure:** Resolution or substantial improvement of baseline signs and symptoms including a reduction in SOFA score, such that no antibacterial therapy is required for the treatment of BSI/sepsis. Subjects with bacteremia must have eradication of bacteremia caused by the Gram-negative pathogen.
- **Clinical Failure:** No apparent response to therapy; persistence or worsening of baseline signs and/or symptoms, reappearance of signs and/or symptoms;

development of new signs and/or symptoms requiring antibiotic therapy other than, or in addition to, study treatment therapy; or death due to BSI/sepsis.

- **Indeterminate:** Lost to follow-up such that a determination of clinical cure/failure cannot be made.

9.1.2 Clinical Outcomes for Follow-up

The clinical outcomes will be assessed by the investigator according to the following criteria established for each infection site at FU. The clinical outcomes will be entered in the eCRF.

9.1.2.1 HABP/VABP/HCABP

- **Sustained Clinical Cure:** Continued resolution or substantial improvement of baseline signs and symptoms of pneumonia, such that no antibacterial therapy is required for the treatment of pneumonia in a subject assessed as cured at TOC.
- **Relapse:** Recurrence of signs and/or symptoms of pneumonia, appearance of new signs and/or symptoms of pneumonia, or new chest radiographic evidence of pneumonia in a subject assessed as cured at TOC.
- **Indeterminate:** Lost to follow-up such that a determination of clinical sustained cure/relapse cannot be made, or subject received additional antibacterial therapy for the treatment of the current infection. Indeterminate at TOC will be carried forward.
- **Clinical Failure:** Clinical failure at TOC will be carried forward regardless of lost to follow-up.

9.1.2.2 cUTI

- **Sustained Clinical Cure:** Continued resolution or improvement of baseline signs and symptoms of cUTI, or return to preinfection baseline if known, in a subject assessed as cured at TOC.
- **Relapse:** Recurrence of signs and/or symptoms of cUTI, or appearance of new signs and/or symptoms of cUTI in a subject assessed as cured at TOC.
- **Indeterminate:** Lost to follow-up such that a determination of clinical sustained cure/relapse cannot be made, or subject received additional antibacterial therapy for the treatment of the current infection. Indeterminate at TOC will be carried forward.
- **Clinical Failure:** Clinical failure at TOC will be carried forward regardless of lost to follow-up.

9.1.2.3 BSI/Sepsis

- **Sustained Clinical Cure:** Continued resolution or substantial improvement of baseline signs and symptoms associated with reduction in SOFA score, such that no antibacterial therapy is required for the treatment of the subjects original BSI/sepsis in a subject assessed as cured at TOC.

- **Relapse:** Recurrence of signs and/or symptoms of BSI/sepsis, or appearance of new signs and/or symptoms of the subjects original BSI/sepsis in a subject assessed as cured at TOC.
- **Indeterminate:** Lost to follow-up such that a determination of clinical sustained cure/relapse cannot be made, or subject received additional antibacterial therapy for the treatment of the current infection. Indeterminate at TOC will be carried forward.
- **Clinical Failure:** Clinical failure at TOC will be carried forward regardless of lost to follow-up.

9.1.3 Microbiological Outcomes per Baseline Pathogen for EOT and TOC

The microbiological outcomes per baseline pathogen will be determined by the sponsor according to the following criteria established for each infection site at EOT and TOC. In case treatment duration is extended beyond 14 days, an additional microbiological outcome will be assessed on Day 14.

9.1.3.1 HABP/VABP/HCABP

- **Eradication:** Absence of the baseline Gram-negative pathogen from an appropriate clinical specimen. If it is not possible to obtain an appropriate clinical culture and the subject has a successful clinical outcome, the response will be presumed to be eradication.
- **Persistence:** Continued presence of the baseline Gram-negative pathogen from an appropriate clinical specimen.
- **Indeterminate:** No culture obtained from an appropriate clinical specimen or additional antibacterial therapy for the treatment of the current infection.

9.1.3.2 cUTI

- **Eradication:** A urine culture shows the baseline Gram-negative uropathogen found at entry at $\geq 10^5$ CFUs/mL are reduced to $< 10^3$ CFUs/mL.
- **Persistence:** A urine culture shows that the baseline Gram-negative uropathogen found at entry at $\geq 10^5$ CFUs/mL grows $\geq 10^3$ CFUs/mL.
- **Indeterminate:** No urine culture obtained from an appropriate clinical specimen or additional antibacterial therapy for the treatment of the current infection.

9.1.3.3 BSI/Sepsis

- **Eradication:** Absence of the baseline Gram-negative pathogen from a blood culture and/or other primary source as applicable. In the case of sepsis, if the subject has a successful clinical outcome and it is not possible to obtain an appropriate clinical culture, the response will be presumed to be eradication. In the case of BSI, if the subject has a successful clinical outcome and the investigator considers no further need to obtain a clinical culture, the response will be presumed to be eradication.

- **Persistence:** Continued presence of the baseline Gram-negative pathogen from a blood culture or other primary source.
- **Indeterminate:** No culture obtained from an appropriate clinical specimen or additional antibacterial therapy for the treatment of the current infection. The exception to this is noted in 9.1.3.3 definition of Eradication.

9.1.4 Microbiological Outcomes per Baseline Pathogen for Follow-up

Microbiological outcomes by baseline pathogen will be determined by the sponsor according to the following criteria established for each infection site at FU.

9.1.4.1 HABP/VABP/HCABP

- **Sustained Eradication:** Absence of the baseline Gram-negative pathogen from an appropriate clinical specimen after TOC. If it is not possible to obtain an appropriate clinical culture and the subject has a successful clinical response after TOC, the response will be presumed sustained eradication.
- **Recurrence:** Recurrence of the baseline Gram-negative pathogen from an appropriate clinical specimen taken after TOC, and the TOC culture is negative.
- **Indeterminate:** No culture obtained from an appropriate clinical specimen or subject received additional antibacterial therapy for the treatment of the current infection. Indeterminate at TOC will be carried forward.
- **Persistence:** Persistence at TOC will be carried forward.

9.1.4.2 cUTI

- **Sustained Eradication:** A culture taken any time after documented eradication at TOC, and a urine culture obtained at FU shows that the baseline uropathogen found at entry at $\geq 10^5$ CFUs/mL remains $< 10^3$ CFUs/mL.
- **Recurrence:** A culture taken any time after documented eradication at TOC, up to and including FU that grows the baseline uropathogen $\geq 10^3$ CFUs/mL.
- **Indeterminate:** No urine culture or subject received additional antibacterial therapy for the treatment of the current infection. Indeterminate at TOC will be carried forward.
- **Persistence:** Persistence at TOC will be carried forward.

9.1.4.3 BSI/Sepsis

- **Sustained Eradication:** Absence of the baseline Gram-negative pathogen from a blood culture or other primary source after TOC as applicable. In the case of sepsis, if the subject has a successful clinical outcome after TOC and it is not possible to obtain an appropriate clinical culture, the response will be presumed to be sustained eradication. In the case of BSI, if the subject has a successful clinical outcome and the investigator considers no further need to obtain a clinical culture, the response will be presumed to be eradication.

- **Recurrence:** Recurrence of the baseline Gram-negative pathogen from a blood culture or other primary source after TOC and the TOC culture is negative.
- **Indeterminate:** No culture from an appropriate clinical specimen or subject received additional antibacterial therapy for the treatment of the current infection. Indeterminate at TOC will be carried forward. . The exception to this is noted in 9.1.4.3 definition of Eradication.

- **Persistence:** Persistence at TOC will be carried forward.

9.1.5 New Pathogens

New pathogens that emerge on or after Day 3 will be categorized as either superinfection or new infection as follows: Superinfection and new infection will be listed by Gram-negative pathogen and the others.

- **Superinfection:** The identification from an appropriate clinical specimen of a new pathogen from the original infection site.
- **New Infection:** The identification from an appropriate clinical specimen of a new pathogen from an infection site different from the original infection site.

9.1.6 Per Subject Microbiological Outcomes

As shown in Table 9-1, subjects who experience eradication of all baseline Gram-negative pathogens at EOT and TOC will be considered " Eradication" and subjects who experience persistence of any baseline Gram-negative pathogen will be considered "persistence." Subjects whose experiences are other than above will be considered "indeterminate." At FU, subjects who experience sustained eradication of all baseline Gram-negative pathogens after documented eradication at the TOC will be considered "sustained eradication" and subjects who experience eradication at TOC but recurrence of any baseline Gram-negative pathogen will be considered as "recurrence", and subjects who are considered as "persistence" at TOC will be "persistence." Subjects whose experiences are other than above will be considered "indeterminate."

Table 9-1 Per Subject Microbiological Outcome

Visit	Per Subject Microbiological Outcome	Definition
EOT, TOC	Eradication	Eradication of all baseline Gram-negative pathogens
	Persistence	Persistence of any baseline Gram-negative pathogens
	Indeterminate	Other than those above
FU	Sustained eradication	Sustained eradication of all baseline Gram-negative pathogens after documented eradication at the TOC
	Persistence	Persistence of any baseline Gram- at the TOC
	Recurrence	Recurrence of any baseline Gram-negative pathogens for subjects eradication at the TOC
	Indeterminate	Other than those above

EOT = End of Treatment; FU = Follow-up; TOC = Test of Cure

For the subjects who have Gram-positive pathogens at baseline, the Gram-positive pathogens will be shown in the listing of local microbiological test and not be taken into account in either per pathogen microbiological outcome or per subject microbiological outcome.

9.1.7 Definition for Composite of Clinical and Microbiological Outcome

The definition for composite of clinical and microbiological outcome based on possible combinations per subject microbiological outcome and clinical outcome is shown in Table 9-2 for EOT and TOC, and in Table 9-3 for FU.

Table 9-2 Clinical and Microbiological Outcome: EOT and TOC

Per Subject Microbiological Outcome	Clinical Outcome	Composite of Clinical and Microbiological Outcome
Eradication	Clinical cure	Response
Eradication	Clinical failure	Failure
Eradication	Indeterminate	Indeterminate
Persistence	Clinical cure	Failure
Persistence	Clinical failure	Failure
Persistence	Indeterminate	Failure
Indeterminate	Clinical cure	Indeterminate
Indeterminate	Clinical failure	Failure
Indeterminate	Indeterminate	Indeterminate

Table 9-3 Composite Outcome: Follow-up

Per Subject Microbiological Outcome	Clinical Outcome	Composite of Clinical and Microbiological Outcome
Sustained eradication	Sustained clinical cure	Response
Sustained eradication	Clinical failure	Failure
Sustained eradication	Clinical relapse	Failure
Sustained eradication	Indeterminate	Indeterminate
Persistence	Sustained clinical cure	Failure
Persistence	Clinical failure	Failure
Persistence	Clinical relapse	Failure
Persistence	Indeterminate	Failure
Recurrence	Sustained clinical cure	Failure
Recurrence	Clinical failure	Failure
Recurrence	Clinical relapse	Failure
Recurrence	Indeterminate	Failure
Indeterminate	Sustained clinical cure	Indeterminate
Indeterminate	Clinical failure	Failure
Indeterminate	Clinical relapse	Failure
Indeterminate	Indeterminate	Indeterminate

9.1.8 Clinical Pulmonary Infection Score

Clinical pulmonary infection score is a surrogate for diagnosis and treatment response. Points (0, 1, or 2) will be assigned for observed findings for 5 variables, including body temperature, white blood cell (WBC) count, tracheal secretions, partial pressure of arterial oxygen (PaO_2), fraction of inspired oxygen (FiO_2), and chest radiograph.

9.1.9 Sequential Organ Failure Assessment Score

The SOFA score is a scoring system to determine the extent of a subject's organ function or rate of failure. The score is based on 6 different scores, 1 each for the respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems.

9.2 Supplementary Efficacy Assessment

9.2.1 Analysis Time Window

Only for supplementary analysis described in Section 9.2, the time window below will be applied (Table 9-4). If there are multiple available values in an analysis time window, the data captured as corresponding visit will be used for analysis. If there is no such data, the closest value to the target day will be used for analysis, and if there are multiple values within the same day, the latest value will be used.

Table 9-4 Analysis Window

Time Point	Target Day/Time	Analysis Time Window
End of Treatment	Date of end of last infusion	-1 to + 3 days
Test of Cure	Date of end of last infusion + 7	-3 to + 3 days
Follow-up	Date of end of last infusion + 14	-3 to + 3 days

9.2.2 Supplementary Clinical Outcomes for EOT and TOC

9.2.2.1 HABP/VABP/HCABP

- **Clinical Cure:** Resolution or substantial improvement of baseline signs and symptoms of pneumonia including a reduction in SOFA and CPIS scores, and improvement or lack of progression of chest radiographic abnormalities such that no antibacterial therapy is required for the treatment of the current infection.
- **Clinical Failure:** No apparent response to therapy; persistence or worsening of baseline signs and/or symptoms of pneumonia; reappearance of signs and/or symptoms of pneumonia; development of new signs and/or symptoms of pneumonia requiring more than 48 hours of antibiotic therapy other than, or in addition to, study treatment therapy; progression of chest radiographic abnormalities; or death due to pneumonia or death after Day 4 (including) regardless of the reason. If EOT is clinical failure, TOC is also clinical failure.
- **Indeterminate:** Lost to follow-up due to death other than pneumonia at Days 1, 2 or 3, withdrawal, or no assessment.

9.2.2.2 cUTI

- **Clinical Cure:** Resolution or substantial improvement of baseline signs and symptoms of cUTI, or return to preinfection baseline if known, such that no antibacterial therapy is required for the treatment of the current infection.
- **Clinical Failure:** No apparent response to therapy; persistence or worsening of baseline signs and/or symptoms of cUTI; or reappearance of signs and/or symptoms of cUTI; development of new signs and/or symptoms of cUTI requiring more than 48 hrs antibiotic therapy other than, or in addition to, study treatment therapy; or death due to cUTI or death after Day 4 (including) regardless of the reason. If EOT is clinical failure, TOC is also clinical failure.
- **Indeterminate:** Lost to follow-up due to death other than cUTI at Days 1, 2 or 3, withdrawal, or no assessment.

9.2.2.3 BSI/Sepsis

- **Clinical Cure:** Resolution or substantial improvement of baseline signs and symptoms including a reduction in SOFA score, such that no antibacterial therapy is required for the treatment of BSI/sepsis. Subjects with bacteremia must have eradication of bacteremia caused by the Gram-negative pathogen.
- **Clinical Failure:** No apparent response to therapy; persistence or worsening of baseline signs and/or symptoms, reappearance of signs and/or symptoms; development of new signs and/or symptoms requiring more than 48 hrs antibiotic therapy other than, or in addition to, study treatment therapy; or death due to BSI/sepsis or death after Day 4 (including) regardless of the reason. If EOT is clinical failure, TOC is also clinical failure.
- **Indeterminate:** Lost to follow-up due to death other than BSI/Sepsis at Days 1, 2 or 3, withdrawal or no assessment.

9.2.3 Supplementary Clinical Outcomes for Follow-up

9.2.3.1 HABP/VABP/HCABP

- **Sustained Clinical Cure:** Continued resolution or substantial improvement of baseline signs and symptoms of pneumonia, such that no antibacterial therapy is required for the treatment of pneumonia in a subject assessed as cured at TOC.
- **Relapse:** Recurrence of signs and/or symptoms of pneumonia, appearance of new signs and/or symptoms of pneumonia, or new chest radiographic evidence of pneumonia or death regardless of the reason in a patient assessed as cured at TOC.
- **Indeterminate:** Lost to follow-up due to death other than pneumonia at Days 1, 2 or 3, withdrawal, no assessment, or received additional antibacterial therapy more than 48 hrs between TOC and FU for the treatment of the current infection.
- **Clinical Failure:** Clinical failure at TOC will be carried forward.

9.2.3.2 cUTI

- **Sustained Clinical Cure:** Continued resolution or improvement of baseline signs and symptoms of cUTI, or return to preinfection baseline if known, in a subject assessed as cured at TOC.
- **Relapse:** Recurrence of signs and/or symptoms of cUTI, or appearance of new signs and/or symptoms of cUTI in a subject assessed as cured at TOC.
- **Indeterminate:** Lost to follow-up due to death other than cUTI at Day 1, 2 or 3, withdrawal, no assessment, or received additional antibacterial therapy more than 48 hrs between TOC and FU for the treatment of the current infection.
- **Clinical Failure:** Clinical failure at TOC will be carried forward.

9.2.3.3 BSI/Sepsis

- **Sustained Clinical Cure:** Continued resolution or substantial improvement of baseline signs and symptoms associated with reduction in SOFA score, such that no antibacterial therapy is required for the treatment of the subjects original BSI/sepsis in a subject assessed as cured at TOC.
- **Relapse:** Recurrence of signs and/or symptoms of BSI/sepsis, or appearance of new signs and/or symptoms of the subjects original BSI/sepsis or death due to BSI/sepsis in a subject assessed as cured at TOC.
- **Indeterminate:** Lost to follow-up due to death other than BSI/sepsis at Days 1, 2 or 3, withdrawal, no assessment, or received additional antibacterial therapy more than 48 hrs between TOC and FU for the treatment of the current infection.
- **Clinical Failure:** Clinical failure at TOC will be carried forward.

9.2.4 Microbiological Outcomes per Baseline Pathogen for EOT and TOC

The microbiological outcomes per baseline pathogen will be determined by the sponsor according to the following criteria established for each infection site at EOT and TOC.

9.2.4.1 HABP/VABP/HCABP

- **Eradication:** Absence of the baseline Gram-negative pathogen from an appropriate clinical specimen. If it is not possible to obtain an appropriate clinical culture and the subject has a successful clinical outcome, the response will be presumed to be eradication. In the case of BSI, if the subject has a successful clinical outcome and the investigator considers no further need to obtain a clinical culture, the response will be presumed to be eradication.
- **Persistence:** Continued presence of the baseline Gram-negative pathogen from an appropriate clinical specimen or death due to pneumonia. If EOT is persistence, TOC is also persistence.
- **Indeterminate:** Lost to follow-up due to death not related to current infection, withdrawal, no assessment, or additional antibacterial therapy for the treatment of the current infection.

9.2.4.2 cUTI

- **Eradication:** A urine culture shows the baseline Gram-negative uropathogen found at entry at $\geq 10^5$ CFUs/mL are reduced to $< 10^3$ CFUs/mL.
- **Persistence:** A urine culture shows that the baseline Gram-negative uropathogen found at entry at $\geq 10^5$ CFUs/mL grows $\geq 10^3$ CFUs/mL or death due to cUTI. If EOT is persistence, TOC is also persistence.
- **Indeterminate:** Lost to follow-up due to death not related to current infection, withdrawal, no assessment, or additional antibacterial therapy for the treatment of the current infection.

9.2.4.3 BSI/Sepsis

- **Eradication:** Absence of the baseline Gram-negative pathogen from a blood culture and/or other primary source as applicable. If the subject has a successful clinical outcome and it is not possible to obtain an appropriate clinical culture, the response will be presumed to be eradication. In the case of BSI, if the subject has a successful clinical outcome and the investigator considers no further need to obtain a clinical culture, the response will be presumed to be eradication.
- **Persistence:** Continued presence of the baseline Gram-negative pathogen from a blood culture or other primary source or death due to BSI/sepsis. If EOT is persistence, TOC is also persistence.
- **Indeterminate:** Lost to follow-up due to death not related to current infection, withdrawal, no assessment, or additional antibacterial therapy for the treatment of the current infection.

9.2.5 Microbiological Outcomes per Baseline Pathogen for Follow-up

Microbiological outcomes by baseline pathogen will be determined by the sponsor according to the following criteria established for each infection site at FU.

9.2.5.1 HABP/VABP/HCABP

- **Sustained Eradication:** Absence of the baseline Gram-negative pathogen from an appropriate clinical specimen after TOC. If it is not possible to obtain an appropriate clinical culture and the subject has a successful clinical response after TOC, the response will be presumed eradication.
- **Recurrence:** Recurrence of the baseline Gram-negative pathogen from an appropriate clinical specimen taken after TOC and the TOC culture is negative or death due to pneumonia.
- **Indeterminate:** Lost to follow-up due to death not related to current infection, withdrawal, no assessment, or additional antibacterial therapy for the treatment of the current infection.
- **Persistence:** Persistence at TOC will be carried forward.

9.2.5.2 cUTI

- **Sustained Eradication:** A culture taken any time after documented eradication at TOC, and a urine culture obtained at FU shows that the baseline uropathogen found at entry at $\geq 10^5$ CFUs/mL remains $< 10^3$ CFUs/mL.
- **Recurrence:** A culture taken any time after documented eradication at TOC, up to and including FU that grows the baseline uropathogen $\geq 10^3$ CFUs/mL or death due to cUTI.
- **Indeterminate:** Lost to follow-up due to death not related to current infection, withdrawal, no assessment, or additional antibacterial therapy for the treatment of the current infection.
- **Persistence:** Persistence at TOC will be carried forward.

9.2.5.3 BSI/Sepsis

- **Sustained Eradication:** Absence of the baseline Gram-negative pathogen from a blood culture or other primary source after TOC as applicable. In the case of sepsis, if the subject has a successful clinical outcome after TOC and it is not possible to obtain an appropriate clinical culture, the response will be presumed to be sustained eradication. In the case of BSI, if the subject has a successful clinical outcome and the investigator considers no further need to obtain a clinical culture, the response will be presumed to be eradication.
- **Recurrence:** Recurrence of the baseline Gram-negative pathogen from a blood culture or other primary source after TOC and the TOC culture is negative or death due to BSI/sepsis.
- **Indeterminate:** Lost to follow-up due to death not related to current infection, withdrawal, no assessment, or additional antibacterial therapy for the treatment of the current infection.
- **Persistence:** Persistence at TOC will be carried forward.

9.2.6 Per Subject Microbiological Outcomes

As shown in Table 9-1, subjects who experience eradication of all baseline Gram-negative pathogens at EOT and TOC will be considered " eradication" and subjects who experience persistence of any baseline Gram-negative pathogen will be considered "persistence." Subjects whose experiences are other than above will be considered "indeterminate." At FU, subjects who experience sustained eradication of all baseline Gram-negative pathogens after documented eradication at the TOC will be considered "sustained eradication" and subjects who experience persistence or recurrence of any baseline Gram-negative pathogen or subjects who are considered as "persistence" at TOC will be "persistence." Subjects whose experiences are other than above will be considered "indeterminate."

9.3 Primary Efficacy Endpoint

The primary endpoints in subjects with HABP/VABP/HCABP or BSI/sepsis and in subjects with cUTI are the following:

- For subjects with HABP/VABP/HCABP or BSI/sepsis, clinical outcome per subject at TOC.
- For subjects with cUTI, microbiologic outcome (for Gram-negative pathogen) per subject at TOC.

9.3.1 Primary Analyses for the Primary Efficacy Endpoint

For the CR Micro-ITT population, the following analysis will be performed.

The clinical outcomes at TOC will be summarized and clinical cure rates and its 95% CIs will be calculated by treatment group (cefiderocol or BAT) for subjects with HABP/VABP/HCABP or BSI/sepsis, separately. The clinical response rate will be calculated as the proportion of subjects whose clinical outcome is clinical cure at TOC.

The microbiological outcomes at TOC will be summarized and microbiological eradication rates and its 95% CIs will be calculated by treatment group (cefiderocol or BAT) for the subjects with cUTI. The microbiological response rate will be calculated as the proportion of subjects whose all of baseline Gram-negative uropathogen(s) are eradicated at TOC.

9.3.2 Supplementary Analyses for the Primary Efficacy Endpoint

9.3.2.1 Supplementary Analyses for the Primary Efficacy Endpoint Using Different Population

For the CR-ME population and Micro-ITT population, the primary analyses stated in Section 9.2.1 will be performed as supplementary analyses.

9.3.2.2 Supplementary Analyses for the Microbiological Outcome Changing Eradication Criteria for cUTI

For the subjects with cUTI in the CR Micro-ITT population, CR-ME population and Micro-ITT population based on the definition of microbiological outcomes below, the outcomes at each time point will be summarized and its 95% CIs will be calculated by treatment group.

For EOT and TOC:

- **Eradication:** A urine culture shows the baseline Gram-negative uropathogen found at entry at $\geq 10^5$ CFUs/mL are reduced to $< 10^4$ CFUs/mL.
- **Persistence:** A urine culture shows that the baseline Gram-negative uropathogen found at entry at $\geq 10^5$ CFUs/mL grows $\geq 10^4$ CFUs/mL.
- **Indeterminate:** No urine culture obtained or additional antibacterial therapy for the treatment of the current infection.

For FU:

- **Sustained Eradication:** A culture taken any time after documented eradication at TOC, and a urine culture obtained at FU shows that the baseline uropathogen found at entry at $\geq 10^5$ CFUs/mL remains $< 10^4$ CFUs/mL.
- **Recurrence:** A culture taken any time after documented eradication at TOC, up to and including FU that grows the baseline uropathogen $\geq 10^4$ CFUs/mL.
- **Indeterminate:** No urine culture or subject received additional antibacterial therapy for the treatment of the current infection. Indeterminate at TOC will be carried forward.
- **Persistence:** Persistence at TOC will be carried forward.

9.3.3 Subgroup Analyses

Clinical outcome and microbiological outcome per subject at TOC will be summarized by age group, gender, race, and infection site, type of baseline CR pathogen, APACHE II score (≤ 15 and ≥ 16), and region (North America, South America, Europe, and Asia-Pacific) for the CR Micro-ITT population. The same analysis will be applied for microbiological outcome, and 28 days all-cause mortality.

Other subgroup analyses may be performed if deemed necessary.

9.4 Secondary Endpoints

The secondary endpoints of this study are the following:

- Clinical outcome per subject at EOT and FU (HABP/VABP/HCABP or BSI/sepsis)
- Clinical outcome per pathogen at EOT,TOC, and FU(HABP/VABP/HCABP, BSI/sepsis or cUTI)
- Clinical outcome per subject/pathogen at EOT, TOC, and FU (cUTI)
- Clinical outcome per subject/pathogen at EOT, TOC, and FU (HABP/VABP/HCABP + BSI/sepsis, overall)
- Clinical outcome per CR pathogen at EOT, TOC, and FU (HABP/VABP/HCABP, BSI/sepsis, cUTI, HABP/VABP/HCABP + BSI/sepsis, overall)
- Microbiological outcome (for baseline Gram-negative pathogens) per subject/pathogen at EOT, TOC, and FU (HABP/VABP/HCABP or BSI/sepsis)
- Microbiological outcome (for baseline Gram-negative pathogens) per subject at EOT and FU (cUTI)
- Microbiological outcome (for baseline Gram-negative pathogens) per pathogen at EOT, TOC, and FU (cUTI)
- Microbiological outcome (for baseline Gram-negative pathogens) per subject/pathogen at EOT, TOC, and FU (HABP/VABP/HCABP + BSI/sepsis, overall)

- Microbiological outcome (for baseline CR Gram-negative pathogens) per subject at EOT, TOC and FU (HABP/VABP/HCABP, BSI/sepsis, cUTI, HABP/VABP/HCABP + BSI/sepsis, overall)
- Microbiological outcome (for baseline CR Gram-negative pathogens) per pathogen at EOT, TOC, and FU (HABP/VABP/HCABP, BSI/sepsis, cUTI, HABP/VABP/HCABP + BSI/sepsis, overall)
- Microbiological outcome with documented carbapenem-resistant Gram-negative bacteremia (overall) at EOT, TOC, and FU
- Composite clinical and microbiological outcome at EOT, TOC, and FU (HABP/VABP/HCABP, BSI/sepsis, cUTI)
- All-cause mortality at Day 14 and Day 28
- Composite endpoint of survival and no change in antibiotic treatment due to either lack of therapeutic benefit or drug-related toxicity at TOC
- Survival time (HABP/VABP/HCABP, BSI/sepsis)
- CPIS parameters at EOT, TOC, and FU (HABP/VABP/HCABP only)
- SOFA score at EOT, TOC, and FU

9.4.1 Analyses for Secondary Efficacy Endpoints

The following analyses of the secondary efficacy endpoints will be performed for the CR Micro-ITT population.

9.4.1.1 Clinical Outcome

For the clinical outcome per subject, the outcomes will be summarized and the cure rate and its 95% CI at EOT,TOC (only for cUTI) and FU will be calculated by treatment group per infection site (HABP/VABP/HCABP, cUTI, and BSI/sepsis). The clinical response rate will be calculated as the proportion of subjects whose clinical outcome is clinical cure at each point. In addition, the clinical outcome per subject for HABP/VABP/HCABP + BSI/sepsis and overall will be analyzed in a similar manner. For Micro-ITT, CR-MITT2 and CR-ME population, same analysis will be applied.

In addition, the outcomes will be summarized and the cure rate at TOC will be calculated by treatment group per study drug regimen and antibacterial treatment regimen at Day 1 and Day 2.

For the clinical outcome per pathogen, the outcomes will be summarized and the cure rate and its 95% CI at EOT, TOC and FU will be calculated by treatment group per infection site. In addition, the clinical outcome per subject for HABP/VABP/HCABP + BSI/sepsis and overall will be analyzed in a similar manner. Clinical outcome per CR pathogen will also be summarized. For the CR-MITT2 population, the same analysis will be applied.

In addition to the analyses described above, the clinical cure rate per pathogen at TOC will also be tabulated by the MIC values and susceptibility defined by CLSI of the

baseline pathogen. For this analysis, MIC for cefiderocol, amikacin, aztreonam, ceftazidime-avibactam, meropenem, ceftolozane-tazobactam, ciprofloxacin, imipenem, cefepime, colistin, and tigecycline. For European Medicines Agency (EMA), the same analysis will be performed with the susceptibility defined by EUCAST.

9.4.1.2 Microbiological Outcome

For the microbiological outcome per subject, the outcomes will be summarized and the eradication rate with 95% CI by treatment group per infection site at EOT, TOC (only for HABP/VABP/HCABP and BSI/sepsis) and FU will be calculated. The eradication rate is the proportion of subjects whose all of baseline Gram-negative pathogen(s) are eradicated at each time point. In addition, the microbiological outcome per subject for HABP/VABP/HCABP + BSI/sepsis and overall will be analyzed in a similar manner. For Micro-ITT, CR-MITT2 and CR-ME population, same analysis will be applied.

In addition, the outcomes will be summarized and the cure rate at TOC will be calculated by treatment group per study drug regimen and antibacterial treatment regimen at Day 1 and Day 2.

For the microbiological outcome per subject with documented carbapenem-resistant Gram-negative bacteremia at baseline, the outcomes will be summarized and the eradication rate with 95% CI by treatment group at EOT, TOC and FU will be calculated as the proportion of subjects who have documented carbapenem-resistant Gram-negative bacteremia at baseline to subjects who experience eradication of baseline documented carbapenem-resistant Gram-negative bacteremia. For this analysis, the same criteria of 9.2.4.3 and 9.2.5.3 will be used but only considering blood sample.

For the microbiological outcome per pathogen, the outcomes will be summarized and the eradication rate with 95% CI will be calculated per infection site by treatment group at EOT, TOC and FU will be calculated. The microbiological outcome per pathogen only including baseline carbapenem-resistant pathogen will also be summarized. For the CR-MITT2 population, the same analysis will be applied.

In addition to the analyses described above, the eradication rate per pathogen at TOC will also be tabulated by the MIC) values and susceptibility defined by EUCAST of the baseline pathogen. For this analysis, MIC for cefiderocol, amikacin, aztreonam, ceftazidime-avibactam, imipenem, ceftolozane-tazobactam, ciprofloxacin, meropenem, cefepime, colistin, and tigecycline.

For supplementary analysis, the eradication rate, defined in Section 9.3.2, per pathogen at TOC will also be tabulated by the MIC values and susceptibility defined by CLSI.

Super infections caused by a Gram-negative pathogen will be summarized and tabulated by the MIC values and susceptibility. Earliest MIC data for each super infection will be used for the analysis.

9.4.1.3 Supplementary Clinical Outcomes

For the supplementary clinical outcome per subject, the outcomes will be summarized and the cure rate and its 95% CI at EOT, TOC and FU will be calculated by treatment group per infection site (HAP/VAP/HCAP, cUTI, BSI/sepsis, HAP/VAP/HCAP plus BSI/sepsis and overall). The clinical response rate will be calculated as the proportion of subjects whose clinical outcome is clinical cure at each point. For Micro-ITT population, the same analysis will be applied.

In addition, the outcomes will be summarized and the cure rate at TOC will be calculated by treatment group per study drug regimen and antibacterial treatment regimen at Day 1 and Day 2.

For the clinical outcome per pathogen, the outcomes will be summarized and the cure rate at EOT, TOC and FU will be calculated by treatment group. The clinical response rate will be calculated as the proportion of subjects whose clinical outcome is clinical cure at each point. Supplementary clinical outcome per CR pathogen will also be summarized.

9.4.1.4 Supplementary Microbiological Outcomes

For the supplementary microbiological outcome per subject, the outcomes will be summarized and the microbiological eradication rate and its 95% CI at EOT, TOC and FU will be calculated by treatment group per infection site (HAP/VAP/HCAP, cUTI, BSI/sepsis, HAP/VAP/HCAP plus BSI/sepsis and overall). The supplementary microbiological eradication rate will be calculated as the proportion of subjects whose supplementary microbiological outcome is microbiological eradication at each point. For Micro-ITT population, same analysis will be applied.

In addition, the outcomes will be summarized and the eradication rate at TOC will be calculated by treatment group per study drug regimen and antibacterial treatment regimen at Day 1 and Day 2.

For the supplementary microbiological outcome per pathogen, the outcomes will be summarized and the eradication rate at EOT, TOC and FU will be calculated by treatment group. The eradication rate will be calculated as the proportion of subjects whose microbiological outcome is eradication at each point.

The supplementary microbiological outcome per pathogen only including baseline carbapenem-resistant pathogen will also be summarized.

9.4.1.5 Composite Outcome

For the composite clinical and microbiological outcome, the outcomes will be summarized and the response rate with 95% CI at EOT, TOC, and FU will be calculated per infection site by treatment group as the proportion of subjects who have both clinical cure and microbiological eradication.

9.4.1.6 All-cause Mortality and Survival Time

All-cause mortality rate with 95% CI at Day 14, Day 28 and overall by treatment group will be calculated as the proportion of subjects who experienced mortality regardless of the cause at or before Day 14 and Day 28, respectively. In this analysis, deaths occurring after EOS will not be used for analysis and any subject who does not have vital status information at Day 14 and 28 will not be included in the analysis. This analysis will be performed for both CR MITT and ITT Population.

In addition, for CR MITT Population, subgroup analysis regarding all-cause mortality at Day 28 will be performed. For the survival time up to End of Study (EOS), the survival curve using Kaplan-Meier method by treatment group will be presented. For the subjects whose vital status is survival at EOS, the subjects will be treated as right-censored at EOS. For the subjects whose vital status is not collected or unknown, the subjects will be treated as right-censored at last visit day.

All-cause mortality rate at Day 14, Day 28 and overall incuding death after EOS will be calculated by treatment group for ITT population.

9.4.1.7 Sequential Organ Failure Assessment Score

Sequential Organ Failure Assessment score (SOFA) and its change from baseline will be summarized by treatment group per infection site at Baseline, EOT, TOC, and FU. Change from baseline will also be summarized. In addition, SOFA score regardless of primary infection diagnosis will be analyzed in a similar manner.

9.4.1.8 Clinical Pulmonary Infection Score

For the HABP/VABP/HCABP subjects, CPIS at EOT, TOC, and FU will be summarized by treatment group.

9.4.1.9 Composite of Survival and No Change in Antibiotic Treatment

For the composite of survival and no change in antibiotic treatment due to either lack of therapeutic benefit or drug-related toxicity at TOC, the response rate with 95% CI by treatment group per infection site will be presented. This composite endpoint will be assessed by Shionogi medical expertise internally. The response rate in the cefiderocol treatment group will be compared with that in the BAT group using Cochran Mantel-Haenszel Method stratified by infection site. The 95% CI will be calculated by Wald method (see Appendix 2).

10. SAFETY

Safety assessments included adverse events (AEs), clinical laboratory safety tests (hematology, chemistry, and specialized test), vital sign measurements. All safety summaries and analyses will be performed based on the Safety population.

10.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject received a pharmaceutical product (including investigational drug) during the course of a clinical investigation.

Adverse events will be collected from the time of signed informed consent through EOS. If adverse events onset after EOS were reported, the events will not be used for analysis. Adverse events will be classified by SOC and PT using MedDRA Version 18.1 or higher.

Adverse events that started on or after the first dose of the study drug and up to "End of Study" are defined as treatment-emergent.

Unless otherwise noted, the summary of AEs will be performed for events of treatment-emergent. An overview of AEs will be provided that summarizes subject incidence and the number of AEs, treatment-related AEs, serious adverse events (SAEs), treatment-related SAEs, death due to AEs, AEs leading to discontinuation of study drug, and treatment-related AEs leading to discontinuation of study drug.

The number and percentage of subjects with AEs will be summarized for each treatment group by SOC and PT. Subjects with more than 1 AE in the same SOC will be counted once for the SOC. Similarly, subjects with more than 1 AE in the same PT will be counted once for the PT. Treatment-related AEs, SAEs, treatment-related SAEs, AEs leading to discontinuation of study drug, and treatment-related AEs leading to discontinuation of study drug, death due to AEs will be summarized in the same manner.

Summaries will be provided by maximum severity for the number and percentage of subjects with AEs by SOC and PT. For the summary of AEs by maximum severity, missing severity will be assumed as "severe." For these summaries, subjects with multiple AEs will be counted only once by the maximum severity within an SOC and PT.

All AEs including AEs not considered treatment-emergent, which have occurred before or after the first dose of the study drug, will be listed by subject.

10.1.1 Analysis of Adverse Events Changing Treatment Group for a Subject Who Received Cefiderocol after BAT Administration

As this is an open-label study, it has been observed that one subject received cefiderocol after completion of the randomization assigned study drug regimen of BAT. Therefore, an limited set of key safety analyses which consider this subject as assigned to the cefiderocol arm will be performed for an overview of AEs. These analyses are: the number and percentage of subjects with AEs, SAEs and death due to AEs by SOC and PT.

10.2 Clinical Laboratory Evaluations

Summary statistics for laboratory test data (hematology and serum chemistry parameters, and other specialized tests) will be presented for each scheduled time point measured

after randomization and for the change from baseline to each time point. If a site reports a laboratory value including sign for numeric value (i.e. "<", "'>") , the value removing sign will be used for analysis.

The number and percentage of subjects with the following prespecified outlier category (Table 10-1) during the postdosing period including unscheduled will be presented by treatment group.

Table 10-1 Outlier for Each Parameter in Laboratory Test

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

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; LLN = lower limit of normal; PT-INR = prothrombin time-international normalized ratio; ULN = upper limit of normal

All clinical laboratory summaries other than specialized tests will be based on the local laboratory measurements, and only the data that can be converted into standard units will be included in analysis. Summaries for specialized tests will be based on the central

laboratory measurements. Within the laboratory parameters, PTT will not be analyzed since during the study monitoring, study team found PTT was reported mixed with APTT.

All central clinical laboratory data and local clinical laboratory data will be listed. Values outside the normal ranges will be flagged for the central laboratory measurements.

10.3 Vital Sign Measurements

Summary statistics for vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) will be presented for baseline, EOT and TOC and for the changes from baseline to postbaseline.

Baseline vital sign measurements are defined as the last measurement obtained prior to the first infusion of the study drug. For postbaseline measurements, if multiple readings (ie, 3 readings) of vital signs are obtained in a day, the maximum body temperature within a study day and the associated systolic and diastolic blood pressure, pulse rate, and respiratory rate measured at the same time point will be used for the summary. If the multiple maximum body temperatures are obtained in a day, the first result among them will be used for the summary.

In addition, the number and percentage of subjects with the following prespecified outlier category (Table 10-2) during the postdosing period including unscheduled will be presented by treatment group.

Table 10-2 Outlier for Each Parameter in Vital Sign Measurements

Parameter (Unit)	Outlier Category
Systolic blood pressure (mm Hg)	Value ≥ 160 or increase from baseline ≥ 20
	Value ≤ 90 or decrease from baseline ≥ 20
Diastolic blood pressure (mm Hg)	Value ≥ 105 or increase from baseline ≥ 15
	Value ≤ 50 or decrease from baseline ≥ 15
Heart rate (beats per minute)	Value ≥ 120 or increase from baseline ≥ 15
	Value ≤ 50 or decrease from baseline ≥ 15

A listing of all vital sign measurements will be provided by subject.

11. Pharmacokinetic Analyses

Individual plasma concentrations of cefiderocol will be listed and summarized by nominal sampling time window. Individual plasma concentrations of cefiderocol will also be summarized by nominal sampling time window and dosing group based on renal function (augmented renal function, normal renal function, mild renal impairment, moderate renal impairment, severe renal impairment, end-stage renal disease, subjects with intermittent hemodialysis, continuous venovenous hemofiltration, continuous venovenous hemodialysis, and continuous venovenous hemodiafiltration). The summary statistics will include the number of nonmissing observations (N), arithmetic mean (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 CV% Geometric Mean = $[\exp(sd^2)-1]^{1/2} \times 100$, where sd is the SD for natural log (ln)-transformed data. If the number of nonmissing observations at a time point is less than 3, the data at the time point will not be summarized.

Individual plasma 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 study report along with justification for exclusion.

For the summary of plasma concentrations, plasma concentrations below the limit of quantification (BLQ) will be treated as 0 for calculations of Mean, SD, CV%, median, minimum, and maximum values and treated as missing for the calculation of geometric mean value and CV% Geometric Mean.

Population PK analyses will be planned and reported separately by the Clinical Pharmacology & Pharmacokinetics of Shionogi & Co., Ltd.

12. Pharmacokinetic/Pharmacodynamic Analyses

The pharmacokinetic/pharmacodynamic analyses will be planned and reported separately by the Clinical Pharmacology & Pharmacokinetics of Shionogi & Co., Ltd.

For each subject randomized to cefiderocol with an identified Gram-negative pathogen, the percentage of the dosing interval for free-drug plasma concentration to be above the minimum inhibitory concentration ($\%T_{f>MIC}$) will be calculated and the relationship between $\%T_{f>MIC}$ and clinical and microbiological outcome will be described.

13. INTERIM ANALYSES

A data safety monitoring board (DSMB) will periodically review the efficacy and safety. Interim analysis for DSMB is specified in SAP for DSMB. The sponsor reserves the option to submit preliminary data to competent regulatory authorities.

14. PROGRAMMING CONVENTIONS

Unless otherwise stated, TFLs will be made in accordance with the following specifications on programming:

1) Display Digit of Various Statistics

The display digit of various tests (such as laboratory tests) is as specified for each respective test, in principle. Display digits of statistics for efficacy and safety analyses are defined in Table 14-1. For variables calculated from raw data like creatinine clearance, we will consider raw data is 1 decimal space.

Table 14-1 Display Digit of Statistics for Efficacy and Safety

Statistics	Display Digit
Number of subjects	Displayed as integer
Mean, median, first quartile, least-square mean, 95% confidence interval, standard deviation, standard error	One more decimal place than raw data
Maximum, minimum	Same number of decimal places as raw data
Percentage (%)	Round off to 1 decimal place
Summary statistics for pharmacokinetics analysis	Three significance digit

2) Handling of Outliers

Possible outliers will not be omitted from analyses.

3) Categories Used in the Summarization

Categories used in the summarization of items are shown in Table 14-2. The breakdown of categories may be changed with blind inspection of distribution as needed.

Table 14-2 Subject Characteristics and Items of Therapeutic Process

Items	Categories
Age (years)	< 65, ≥ 65
Gender	Male, Female
Weight (kg)	< 70, ≥ 70
Ethnicity	Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown
Race	American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other
Region	North America, South America, Europe, and Asia-Pacific
Extent of exposure (days)	< 5, ≥ 5 to < 7, ≥ 7 to ≤ 14, > 14
Infection site	HABP/VABP/HCABP, cUTI, and BSI/sepsis
CrCl renal grading group	>= 120, > 80 - < 120, > 50 - 80, 30 - 50, < 30
Type of CR baseline pathogen	Enterobacteriaceae, nonfermenters, mixed
Severity of disease	Mild, Moderate, Severe
APACHE II score	≤ 15, ≥ 16

APACHE II = Acute Physiology and Chronic Health Evaluation II; BSI = bloodstream infections; CR = Carbapenem-resistant; CrCl = creatinine clearance; cUTI = complicated urinary tract infection; HABP = hospital-acquired bacterial pneumonia; HCABP = healthcare-associated bacterial pneumonia; VABP = ventilator-associated bacterial pneumonia

15. CHANGES FROM PROTOCOL

- Add analysis for HABP/VABP/HCABP + BSI/sepsis subgroup for efficacy endpoint
- Add analysis by initial study drug regimen for clinical and microbiological outcome
- Add analysis for supplementary clinical and microbiological outcome
- Add subgroup analysis for all-cause mortality
- Add analysis for microbiological outcome by MIC and interpretation
- Add analysis for all-cause mortality for subjects with cUTI
- Add analysis for new infectionChange target timepoint of analysis window for premature EOT (PK data), from end date/time of last infusion to start date/time of last infusion since EDC does not capture end of infusion date/time for premature EOT.
- The reference point of prior/concomitant medication has been changed from randomication date to first drug infusion
- If BSI, also allowed to consider presumed eradication.
- Add imputation rule if date/time is missing (section 6.4)

Appendix 1 Time and Events Schedule

Evaluation	Screening\Baseline	Randomization	Treatment					Test of Cure (TOC)	Follow-up (FU)	End of Study (EOS)
	Day −2 to Same Day Prior to Randomization[a]		Day 1	Day 3	Early Asses. (EA) Day 3 to 4	(Day 14)[b]	End of Treatment (EOT)[c]	EOT + 7 (± 2)	EOT + 14 (± 3)	EOT + 28 (± 3)
Rapid Diagnostic for the Presence of a Carbapenemase	X[d]									
Informed Consent	X									
Inclusion/Exclusion Criteria	X									
Demographics	X									
Medical History[e]	X									
Physical Examination	X[f]				X[g]	X[g]	X[g]	X[g]	X[g]	X[g,h]
Glasgow Coma Scale	X				X	X	X	X	X	
APACHE II	X									
SOFA Score	X				X	X	X	X	X	
Clinical Assessment of Signs and/or Symptoms	X				X	X	X	X	X	
Oxygenation Status[i]	X				X	X	X	X	X	
Ventilator Parameters (ventilated subjects treated with cefiderocol				X[j]	X[j]					
Chest Radiographs[k] (HABP/VABP/HCABP)	X				X	X	X	X	X	
CPIS Parameters (HABP/VABP/HCABP)	X				X	X	X	X	X	
Pregnancy Test[l]	X									

[redacted]

Evaluation	Screening\Baseline	Randomization	Treatment					Test of Cure (TOC)	Follow-up (FU)	End of Study (EOS)
	Day −2 to Same Day Prior to Randomization[a]		Day 1	Day 3	Early Asses. (EA) Day 3 to 4	(Day 14)[b]	End of Treatment (EOT)[c]	EOT + 7 (± 2)	EOT + 14 (± 3)	EOT + 28 (± 3)
Hematology Tests, Blood Chemistry Tests, and Urinalysis	X				X	X	X	X	X	X[h]
TIBC, Transferrin Iron Saturation, Hepcidin	X							X		
CrCl from Serum Creatinine[m]	X	Randomization			X					
CrCl from Urinary Creatinine[m]					X					
Vital Signs[n]	X		X ←				→ X	X	X	X[h]
12-lead ECG	X									
Drug Administration			X ←				→ X			
Clinical Outcome					X	X	X	X	X	
Biologic Tissue or Fluids for Microbiologic Cultures[o]	X				X	X	X	X	X	
Microbiological Outcome					X	X	X	X	X	
Blood PK Samples (cefiderocol group)				X[p]	X[p]					
AE Assessment	X ←								→	X
Concomitant Therapy	X ←								→	X
Hospitalization	X ←								→	X
Vital Status	X ←								→	X

AE = adverse event; APACHE = Acute Physiology and Chronic Health Evaluation II; CrCl = creatinine clearance; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HACP = healthcare-associated bacterial pneumonia; HABP = hospital-acquired bacterial pneumonia; MDRD =

[redacted]

Evaluation	Screening\Baseline	Randomization	Treatment					Test of Cure (TOC)	Follow-up (FU)	End of Study (EOS)
	Day −2 to Same Day Prior to Randomization[a]		Day 1	Day 3	Early Asses. (EA) Day 3 to 4	(Day 14)[b]	End of Treatment (EOT)[c]	EOT + 7 (± 2)	EOT + 14 (± 3)	EOT + 28 (± 3)

modification of diet in renal disease; PK= pharmacokinetic; SOFA = Sequential Organ Failure Assessment; TIBC = total iron-binding capacity; VABP = ventilator-associated bacterial pneumonia

a If Screening and Randomization (Day 1) occur on the same day, the activities of Screening and Day 1 should be completed, without duplication of assessments.

b In case treatment duration is extended beyond 14 days, an additional assessment will be conducted on Day 14.

c EOT evaluations occur on the last day of study treatment. EOT can be any time after the patient had at least one dose of study treatment, duplication of assessments for a given day and EOT is not necessary.

d The use of investigational diagnostics or diagnostics that are not the local standard of care for determination of carbapenem resistance will require that the investigational diagnostics section of the informed consent be signed by the patient or legally authorized representative.

e Include a review of prior/concomitant therapies.

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

g A limited physical examination relevant to the patient's current condition will be performed.

h If end of study evaluation is by phone, physical examination, laboratory tests, and vital signs will not be performed.

i Patients receiving an oxygen inhalation treatment.

j For ventilated patients treated with cefiderocol specified ventilator parameters will be captured at the start of the infusion (acceptable time window; 0 hours to end of infusion) which PK sampling will be taken.

k **At German sites,** in sites where chest radiographs after screening are part of the standard of care, ie, a chest radiograph is clinically indicated by the treating physicians, it can be performed as usual without a special informed consent. If a chest radiograph is not standard of care (no clinical indication), and is planned based on the study protocol, an informed consent from a conscious patient is mandatory. Chest radiographs without clinical indication cannot be performed in unconscious patients.

l Urine or serum pregnancy test only for females who are not diagnosed as postmenopausal or surgically sterile.

m The CrCl (the Cockcroft-Gault equation) and eGFR (the MDRD equation) will be calculated from the serum creatinine. For patients with eGFR $\geq$ 90 mL/min/1.73 m^2 at baseline, urine samples will be collected a time interval as short as 2 hours or up to 8 hours.

n Blood pressure (systolic/diastolic pressures), body temperature, pulse rate, and respiratory rate.

[redacted]

o Biologic tissue or fluids (including blood regardless of the infection site) for microbiologic cultures will be obtained with 48 hours of the start of treatment, at specified times and at the investigator's discretion. Two blood samples from separate venipunctures will be collected within 48 hours prior to start of the first dose of study treatment. Subsequent blood cultures are to be completed only if the first culture is positive.

p PK blood samples will be drawn on Day 3 after at least the sixth dose of study drug; one draw just prior to the infusion of the dose, 1 hour after start of infusion, at the end of infusion, and at 1 hour after the end of infusion. Patients with nonstable renal function resulting in a dosage adjustment at EA will undergo another blood PK sampling (4 samples at the above specified time points) within 24 to 72 hours after their dosing adjustment. If possible, a single blood draw should be performed as soon as possible at EOT in case of premature EOT.

[redacted]

Appendix 2 Calculation Confidence Interval for Cochran-Mantel-Haenzel Test

Let x_{ij} and n_{ij} denote the number of responders and the total number of patients in treatment i and stratum j, respectively, where i=1,2 represents the treatment group (cefiderocol or BAT) and $j = 1,2,3$ represents the stratum, the following 2 × 2 contingency table shows the total number of subjects and the number of responders in each treatment arm at stratum j.

Category	cefiderocol	BAT
Response	x_{1j}	x_{2j}
No Response	$n_{1j} - x_{1j}$	$n_{2j} - x_{2j}$
Total	n_{1j}	n_{2j}

The proportion of patients with response (π_{ij}) in treatment i and stratum j can be estimated by:

$$\hat{\pi}_{ij} = x_{ij}/n_{ij}$$

and the stratum-specific proportion difference (d_j) is estimated by:

$$\hat{d}_j = \hat{\pi}_{1j} - \hat{\pi}_{2j}.$$

The adjusted estimate of the difference in the rate of responders between the two treatment groups (d_{adj}) is given as:

$$\hat{d}_{adj} = \sum_{j=1}^{3} w_j \hat{d}_j$$

using the CMH weights defined as $w_j = \left(\frac{n_{1j}n_{2j}}{n_{1j}+n_{2j}}\right) \Big/ \sum_{j=1}^{3} \frac{n_{1j}n_{2j}}{n_{1j}+n_{2j}}$.

Hence, the 2-sided stratified 95% Wald-type confidence intervals of d_{adj} based on the CMH weights is constructed as:

[redacted]

$$\hat{d}_{adj} \pm z_{\alpha/2}\mathrm{Var}(\hat{d}_{adj}),$$

where the variance of d_{adj} is given as:

$$\mathrm{Var}(\hat{d}_{adj}) = \sqrt{\sum_{j=1}^{3} \hat{w}_j^2 \left(\frac{\hat{\pi}_{1j}(1-\hat{\pi}_{1j})}{n_{1j}} + \frac{\hat{\pi}_{2j}(1-\hat{\pi}_{2j})}{n_{2j}}\right)},$$

and $z_{\alpha/2}$ is the 97.5th percentile of the standard normal distribution.

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