Shionogi Study Title:	A Multicenter, Randomized, Double-blind, Parallel-group, Clinical Study of S-649266 Compared with Meropenem for the Treatment of Hospital-acquired Bacterial Pneumonia, Ventilator-associated Bacterial Pneumonia, or Healthcare-associated Bacterial Pneumonia Caused by Gram-negative Pathogens
Shionogi Study Number:	1615R2132
ClinicalTrials.gov Registration No.	NCT03032380
Study Document	Statistical Analysis Plan Version 1.2 09 July 2019

History of Statistical Analysis Plan Amendments

Version 1 (Original)	03 December 2018
Version 1.1	22 February 2019
Version 1.2	09 July 2019
Revisions to Version 1 and 1.1 are document within Version 1.2	

STATISTICAL ANALYSIS PLAN

Study Title:	A phase 3, multicenter, randomized, double-blind, parallel-group, clinical study of S-649266 Compared with meropenem for the treatment of hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, or healthcare-associated bacterial pneumonia caused by gram-negative pathogens
Study Number:	1615R2132
Study Phase:	3
Product Name:	S-649266
Sponsor:	Shionogi Inc.
Version Number:	1.2
Issue Date:	9JUL2019

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SIGNATURE PAGE

Document Title:	Statistical Analysis Plan
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Study Number:	1615R2132
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Issue Date:	9JUL2019

Approved by:

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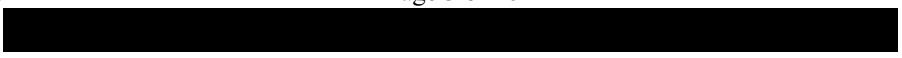
Biometrics, Shionogi Inc.

[redacted]

RECORDS ON REVISIONS

Document History

Version Number	Date
1.0	03 Dec 2018 Added additional analyses • Added analysis for Distribution of Gram-negative pathogens Isolated at Baseline pathogen • Added Analyses for Baseline pathogen per MIC and CLSI interpretation • Added Analyses for Clinical outcome per pathogen • Added Analyses for Clinical outcome per MIC and CLSI interpretation • Added analyses Microbiological outcome per pathogen • Added analyses for Microbiological outcome per MIC and CLSI interpretation • Added analyses for Listing for 4 fold increase of MIC from baseline • Added analyses for Summary for Microbiological Outcome Per Subject whose Gram-Negative Pathogens Isolated from Blood Culture are the Same as Lung at Baseline • Added analyses for Summary of Minimum Inhibitory Concentration of Baseline Gram-negative Pathogens Isolated from the Blood Culture That Are the Same as Lung at Baseline • Summary of All-cause Mortality at Day 28 by Predefined Subgroups • Summary of Microbiological Outcome Per Subject at Test of Cure by Predefined Subgroups • Summary of Clinical Outcome Per Subject at Test of Cure by Predefined Subgroups 22 Feb 2019 • Section 1 :Updated Protocol version to version 4 • Section 9.1 and 9.3.6: changed Day 14 and Day 28 all-cause mortality calculation based on timing of first dose instead of randomization as these two can differ by a day • Section 8.3: changed definition of prior and



	concomitant medication based on first dose date instead of randomization date. • Section 9.2: Added superiority analysis at Day 14 as a key secondary endpoint • Section 9.3.6: Added superiority at Day 28 as a secondary endpoint • Section 9.1.1 : Added that 2 sided p-value will be calculated for non-inferiority and superiority testing. • Table 6-1: Added the text:+1 day for EOT and unexpected EOT analysis window based on protocol amendment. +1 day was added instead of 24 hours as sometimes time of last infusion may not be collected within EDC • Section6.4: Added missing time strategy for classifying prior and concomitant medications. • Section 6.4:Added missing data strategy for missing EOS survival status • Section 8.3 : Added 3 hours grace period for concomitant medications as in CR study • Section 9.1.3: Added supplementary analysis for Day 14 ACM by excluding subjects who are Meropenem resistant. • Section 9.3.1: Clarified presence of colonizer or contaminant of a baseline pathogen will be associated with micro-outcome of eradication • Section 9.3.7.2: Added subgroup analysis for all-cause mortality until EOS visit based on death study day • Section 10.3: Removed PTT from summary of lab parameters. • Section 13: Added Haybittle-Peto alpha spend of 0.0001 will be used for any unplanned looks of the interim efficacy data
1.1	• Section 4.1 : Clarified that for purposes of analysis as randomized strata will be employed.For subgroup analysis the actual strata values will be employed. • Section 5.2 : Corrected the typo in mITT definition • Section 6.4 : Updated missing data strategy for cases all-cause mortality upto EOS endpoint and

	matched definition as in protocol. • Section 9.1.4 : Added post-hoc subgroup categories for Meropenem non-susceptible status and for subjects with MIC value greater than 8 for Meropenem for any baseline gram-negative pathogen. • Section 9.3.7 : Updated definition of all-cause mortality up to EOS to match the protocol definition. • Section 9.1.3: Added sensitivity analysis for missing Day 14 survival status. • Section 9.1.4: Added subgroup analyses for micro outcome per subject by meropenem non-susceptible status and time point • Section 9.1.4: Added subgroup analyses for clinical outcome per subject by meropenem non-susceptible status and time point • Section 9.1.4 : Added post-hoc subgroup category for top 5 baseline pathogens • Section 9.3.7 :Added separate analysis of all-cause mortality by EOS based on time from last dose.
1.2	• Section 6.3 : Added the statement that If a subject is received study drug more than 21 days, Day 21 will be considered as the date of end of last infusion. • Section 6.3 : Clarified that if any visit is flagged as baseline then the corresponding analysis visit will be assigned as a screening/baseline and will not be considered it while deriving the analysis window • Section 6.3: Added that if PK samples are collected just before the 6^{th} dose these will be included in the summary of concentration summary. • Section 10.3 : Added a statement that if the SI units for CRP are available in EDC as a value less than the lower limit then it will be set to the lower limit and then used for analysis. This was added after blinded review of the data during dry run. • Section 8.3: Removed the term respiratory inhalation from the routes of administration considered to be not systemic. • Section 10.2: Added EA and FU visits for summary of vital signs to align with mock-shells.

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	• Section 10.2 : Clarified that prespecified outlier category summarization during post dosing period will include any unscheduled visits for vital signs summary. • Section 10.3: Clarified that prespecified outlier category summarization during post dosing period will include any unscheduled visits for laboratory parameters summary. • Section 4.1 : Clarified that for patient baseline characteristics summaries as well as subgroup analysis the actual values of the stratification factors APACHE II score and clinical diagnosis will be used • Section 6.4 : Clarified that if micro sample collection times are missing the end time of day 23:59PM will be used for imputation.

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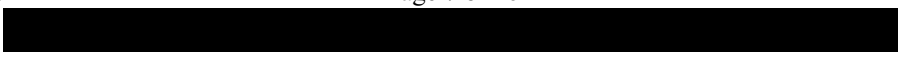

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LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

$\%T_{f>MIC}$	percentage of dosing interval for which free drug concentration in plasma exceeds minimum inhibitory concentration
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARC	augmented renal clearance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BAL	bronchoalveolar lavage
BLA	β-lactamase
BUN	blood urea nitrogen
CABP	community-acquired bacterial pneumonia
CFU	colony-forming unit
CI	confidence interval
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CPIS	Clinical Pulmonary Infection Score
CrCl	creatinine clearance
CRO	contract research organization
CT	computed tomography
DSMB	Data Safety Monitoring Board
EA	early assessment
ECG	electrocardiogram
eCRF	electronic case report form
ELF	epithelial lining fluid
EOS	end of study
EOT	end of treatment
FiO_2	fraction of inspired oxygen
FU	follow-up
GCP	good clinical practice
GCS	Glasgow Coma Scale
HABP	hospital-acquired bacterial pneumonia
HCABP	healthcare-associated bacterial pneumonia
IC_{50}	half maximal inhibitory concentration

ICH	International Council on Harmonisation
ICU	intensive care unit
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
ITT	Intent to treat
IWRS/IVRS	interactive web or voice response system
KPC	*Klebsiella pneumoniae* carbapenemase
MDR	multidrug resistant
MDRD	modification of diet in renal disease
ME-PP	Micro-evaluable Per-protocol
MHRA	Medicines and Healthcare Products Regulatory Agency
MIC	minimum inhibitory concentration
mITT	Modified Intent-to-treat
MRSA	methicillin-resistant *Staphylococcus aureus*
NOAEL	no-observed-adverse-effect level
OAT1 (3)	organic anion transporter 1 (3)
PaO_2	partial pressure of oxygen
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
q6h	every 6 hours
q8h	every 8 hours
q12h	every 12 hours
QTc	corrected QT interval
QTcF	Fridericia's correction formula
SAE	serious adverse event
SAP	statistical analysis plan
SOFA	Sequential Organ Failure Assessment
SPC	summary of product characteristics
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TOC	Test of Cure
ULN	upper limit of normal
VABP	ventilator-associated bacterial pneumonia
WBC	white blood cell
XDR	extensively drug-resistant

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods and data handlings to be employed for the analysis of the study Protocol 1615R2132, Version 4 dated 22 February 2019. Table, listing and figure mock-ups are provided in the TLF shells prepared separately. Details of the analyses of pharmacokinetics/pharmacodynamics are not addressed in this SAP.

All the analyses described in the SAP will be performed in the Biometrics, Shionogi Inc. Any deviations from the SAP will be documented in the clinical study report.

2. OVERVIEW

This clinical trial is performed as a global (North America, South America, Europe, and Asia-Pacific), multicenter, double-blind, parallel-group study with stratified randomization using the infection diagnosis (hospital-acquired bacterial pneumonia [HABP]/ventilator-associated bacterial pneumonia [VABP]/healthcare-associated bacterial pneumonia [HCABP]) and Acute Physiology and Chronic Health Evaluation II (APACHE II) score (≤ 15 and ≥ 16) as allocation factors, using meropenem as a comparator. Study drug is initiated in subjects with documented nosocomial pneumonia caused by Gram-negative bacteria.

Subjects meeting eligibility criteria and assessed by the investigator to require 7 to 14 days of intravenous treatment in the hospital will be randomized (1:1) to either cefiderocol, 2 g, administered intravenously over 3 hours, every 8 hours (q8h) or meropenem, 2 g, administered intravenously over 3 hours q8h. Linezolid will be administered to subjects in both arms to provide coverage for methicillin-resistant *Staphylococcus aureus* (MRSA) and to maintain the study blind and, in the cefiderocol arm, to provide coverage for Gram-positive bacteria.

The study design and study events table are shown in Appendix 1 and Appendix 2, respectively.

3. STUDY OBJECTIVES

3.1 Primary Objective(s)

The primary objective of this study is:

- To compare all-cause mortality at Day 14 of cefiderocol with that of the comparator, meropenem, in adults with HABP, VABP, or HCABP caused by Gram-negative pathogens.

3.2 Secondary Objectives

3.2.1 Key Secondary Objectives

The key secondary objectives of the study are:

- To compare the microbiological outcome of treatment with cefiderocol with that of meropenem per subject at Test of Cure (TOC)[1]
- To compare the clinical outcome of treatment with cefiderocol with that of meropenem per subject at TOC
- To compare Day 14 all-cause mortality of cefiderocol with that of meropenem for superiority of cefiderocol

3.2.2 Other Secondary Objectives

- To compare the microbiological outcome of treatment with cefiderocol with that of meropenem per subject at Early Assessment (EA)[2], End of Treatment (EOT)[3], and Follow-up (FU)
- To compare the clinical outcome of treatment with cefiderocol with that of meropenem per subject at EA, EOT, and FU
- To compare all-cause mortality at Day 28 of subjects treated with cefiderocol with that of meropenem
- To compare Day 28 all-cause mortality of S-649266 with that of meropenem for superiority of S-649266
- To compare the all-cause mortality during treatment and the follow-up period (until EOS) of subjects treated with cefiderocol with that of meropenem

3.3 Safety Objective

- To assess the safety of cefiderocol

4. STUDY DESIGN

4.1 Study Blinding and Randomization

This is a double-blind, parallel-group, randomized, active-controlled study in approximately 300 subjects with documented nosocomial pneumonia caused by Gram-negative bacteria. Subjects meeting eligibility criteria and assessed by the investigator as requiring 7 to 14 days of intravenous treatment in hospital will be randomized (1:1) to either cefiderocol, 2 g, administered intravenously over 3 hours, q8h or meropenem, 2 g, administered intravenously over 3 hours, q8h. Linezolid will be administered to subjects in both arms to provide coverage for MRSA and to maintain the study blind and, in the cefiderocol arm, to provide coverage for Gram-positive bacteria.

The investigator, site personnel, the sponsor, and the sponsor's designees involved in blinded monitoring, data management, or other aspects of the study will be blinded to treatment assignment. The site pharmacist or qualified designee who will prepare the

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

[2] EA is defined as start of treatment + 3 days to 4 days.

[3] EOT is defined as the last day of study treatment.

intravenous infusion solution will be unblinded so that he/she may obtain the assigned drug and prepare the intravenous dosing solutions. The drug supply itself will not be blinded.

Since this is a blinded study, cefiderocol will be prepared and administered within the same timeframe after preparation as meropenem. For comparability of the study drug and the comparator drug meropenem, the dosing solutions will be normal saline and dosed within the time limits established for meropenem. Linezolid will not require blinding.

The treatments will be randomized to subject identification numbers by the interactive response technology (IRT) provider in a 1:1 fashion to cefiderocol or meropenem. The IRT will be used to assign subjects to identification numbers for which treatment has already been randomly assigned. Randomization will be performed by the stratified randomization method using their infection type (HABP, VABP, and HCABP) and APACHE II score (≤ 15 and ≥ 16) as allocation factors.

In the event of cases where incorrect allocations factors for clinical diagnosis and APACHE II scores were used by the IRT provider during treatment randomization, for analysis purposes the as randomized values will be used for the primary and secondary efficacy analyses.

For patient baseline characteristics summaries as well as subgroup analysis the actual values of the stratification factors APACHE II score and clinical diagnosis will be used.

4.2 Sample Size

The study design and the primary objective are based on the hypothesis that cefiderocol is noninferior to meropenem for the treatment of nosocomial pneumonia; this will be established based on a 12.5% noninferiority margin to exclude the possibility that cefiderocol is more than 12.5% inferior to meropenem for the endpoint of all-cause mortality at Day 14. The 12.5% noninferiority margin for a limited use indication was discussed with and agreed to by the US Food and Drug Administration, Division of Anti-Infective Products at a Type C meeting on October 13, 2015 and again with a communication dated April 25, 2016.

A sample size of 244 evaluable subjects (122 evaluable subjects in the cefiderocol group and 122 evaluable subjects in the meropenem group) is required to have 90% power with a 1-sided significance level of 0.025, assuming a 10% all-cause mortality rate at Day 14 in both groups with a 12.5% noninferiority margin. It is further estimated that approximately 20% of randomized subjects will be non-evaluable and therefore excluded from the primary population because they have not received any doses of a study drug treatment or they had a bacterial pneumonia caused by anaerobic and/or Gram-positive aerobic bacteria only. Therefore, it is expected that it will be necessary to randomize up to 300 subjects. The non-evaluable rate will be assessed based on a blinded estimate performed after approximately 150 subjects are enrolled and the randomized population size may be adjusted to meet study requirements. Additionally, the Sponsor will conduct

a blinded evaluation of all-cause mortality after approximately 150 subjects are enrolled and if necessary will perform a blinded re-estimation of sample size.

5. ANALYSIS POPULATIONS

5.1 Intention-to-treat Population

The Intent-to-treat (ITT) population is defined as all randomized subjects who received at least 1 dose of a study drug treatment. This population will be analyzed according to the treatment the subjects were randomized to, regardless of treatment the subjects actually received.

5.2 Modified Intent-to-treat Population

The Modified ITT (mITT) population is defined as all subjects in the ITT population who meet either of the following:

- Those who have evidence of a Gram-negative infection of the lower respiratory tract based on either a culture, Gram stain, or other diagnostic test.
- Those who have evidence of a lower respiratory tract infection, but culture or other diagnostic tests do not provide a microbiological diagnosis.

Note: Subjects with a bacterial pneumonia caused by Gram-positive aerobic or anaerobic (Gram-positive or Gram-negative) bacteria only will be excluded from the mITT Population.

This population will be analyzed according to the treatment the subjects were randomized to, regardless of treatment the subjects actually received.

The primary population for efficacy analysis will be mITT Population.

5.3 Safety Analysis Population

The Safety population is defined as all randomized patients who receive at least 1 dose of the study treatment (ITT population). The population will be analyzed according to the treatment that the subjects actually received, rather than the treatment to which the subjects were randomized. If a wrong treatment is given and later corrected to the appropriate randomized treatment upon discovery of the error, the subject will be classified into the corrected treatment group. This population will be used in all safety analyses.

5.4 Micro-evaluable Per-protocol Population

The Micro-evaluable Per-protocol (ME-PP) population is defined as all subjects in mITT population who do not have major protocol violations and have a culture confirmed diagnosis of a Gram-negative bacterium. These deviations will be determined prior to unblinding of the study.

5.5 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, population PK analyses, PK/PD analyses, and the concentration summary.

6. STATISTICAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLINGS

6.1 Statistical Reporting

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

Subject study data, including data not appearing in tables, will be presented in by-subject data listings. In general, all tables and associated graphics will be presented by treatment group. Individual subject data, PK data and any derived data will be presented by treatment and subject.

All analyses will be performed using SAS Version 9.2 or higher (SAS Institute, Cary, NC, USA).

6.2 Statistical Testing and Multiplicity Strategy

Statistical testing will be performed at the 2-sided significance level of 0.05 unless stated otherwise. A fixed-sequence approach will be applied for multiplicity adjustment with the primary and key secondary efficacy analyses: the primary noninferiority hypothesis will be tested first, and if satisfied, then move to (1) microbiological outcome at TOC, and then (2) the clinical outcome at TOC and (3) Day 14 all-cause mortality rates of S-649266 with meropenem for superiority of cefiderocol

6.3 Analysis Visit Windows

For analysis datasets no records after End of Study visit will be used for TLF purposes.

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

If there are multiple available values in an analysis time window, the following approach will be applied. For the efficacy outcome, the closest value to the scheduled time point captured from a scheduled or unscheduled time point will be used for analysis, and if there are multiple values within same day, the latest value will be used. Also, if 2 visits

are equidistant from the scheduled day, the later visit will be assigned to the windowed visit. For the safety endpoints, the closest value to the scheduled time point will be used for the analysis, and if there are multiple values within same day, the earliest value will be used. Also, if the differences between the observed time point and scheduled time point are the same among values, the earlier will be used.

Measurements that are taken outside the visit window will be considered missing for analysis and will not be imputed.

Table 6-1 Analysis Window

Time Point	Target Day/Time	Analysis Time Window
Blood PK Sampling	After at least 6 doses , before any dosing regimen change according to EA evaluation	Day 3 or Day 4
	• Just prior to the next infusion	-1 to 0 hours
	• 1 hour after the start of infusion	± 15 minutes
	• At the end of infusion	-30 minutes to just before the end of infusion
	• 1 hour after the end of infusion (4 hours after the start of infusion)	± 0.5 hours
EA	Day 3 or Day 4	Not applicable
EOT	End of last infusion	As soon as possible after last dose (same calendar day or +1 day)
Unexpected EOT	Last day of study treatment clinical evaluations, and a blood sample should be obtained if possible	Same calendar day or + 1 day
TOC	EOT + 7	± 2 days
FU	EOT + 14	± 3 days
EOS	EOT + 28	± 3 days

EA = Early Assessment; EOS = End of Study; EOT = End of Treatment; FU = Follow-up;
PK = pharmacokinetic; TOC = Test of Cure

If a subject has received study drug more than 21 days, Day 21 will be considered as the date of end of last infusion.

If any visit is flagged as baseline then the corresponding analysis visit will be assigned as a screening/baseline and will not be considered it while deriving the analysis window.

Subjects who have PK data collected before at least 6 doses will be listed, however they will be excluded from plotting of the concentration-time data and the concentration summary in CSR (Pharmacokinetic samples just prior to the sixth dose will be included)

6.4 Missing Data

For clinical and microbiological outcomes, patients who were lost to follow-up or had missing or had "indeterminate" outcomes will be included in the denominator as indeterminate for cure/eradication rate i.e. considered as non-responders.

For clinical outcome, subjects who died due to pneumonia will be considered as a clinical failure after death.

If a subject dies due to other reasons, they will be considered as "indeterminate" except for the cases when subject is a clinical failure at EA and missing after that or when a subject is a clinical failure at EOT, and missing after that. For these cases clinical failure will be carried forward to the remaining visits.

If subjects withdraw before Day 14 since their first infusion of study drug their survival status at Day 14 would be unknown or missing for the analysis of the primary endpoint of 14 day all-cause mortality. These subjects would not be included in the numerator or denominator in the calculation of all-cause mortality rate at Day 14 since first infusion of study drug. If subjects withdraw before Day 28 since their first infusion their survival status at Day 28 would be unknown or missing for the analysis of 28 day all-cause mortality. These subjects would not be included in the numerator or denominator in the calculation of all-cause mortality rate at Day 28 since first infusion.

If subjects discontinue before their End of study visit and are lost to follow up before End of Study visit their survival status at End of Study would be unknown or missing for the analysis of all-cause mortality during treatment and the follow-up period (until EOS). These subjects would not be included in the numerator or denominator in the calculation of all-cause mortality rate during treatment and the follow-up period (until EOS).

If dates are missing or partial the following strategies will be employed. 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.

For the start date of each AE, the date will be confirmed and recorded and no imputation will be performed.

For classification of prior and concomitant medications, if the medication cannot be classified into concomitant medications or prior medications due to a partial missing date, the rules below will be applied for the classification.

For start date,

- If the year and month are observed but the day is missing, the first day of the month will be used.
- 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, 00:00 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 PM will be used.

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

The imputed dates will not be displayed in the listings.

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. However, in the summary of adverse events (AEs), the AEs that have not been coded will be included as 'Not coded adverse events' in tables or listings.

Measurements for efficacy or safety endpoints will be performed according to the schedule of assessments shown in Appendix 1. The time window, shown in Table 6-1 is acceptable.

6.5 Definition

6.5.1 Study Day

Study Day is defined as the relative day of the observation starting with the reference date as Day 1. Study Day 1 will refer to the date of initial dose of the study drug. In addition, dates prior to the reference date are decremented by 1, with the date preceding Day 1 designated as Study Day -1 (there is no Study Day 0).

6.5.2 Baseline

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 No. 9). 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. 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 rule will be applied:

- In case different Gram-negative pathogens are obtained from different specimens, all of them are considered as baseline pathogens

The appropriate clinical specimen type is sputum, tracheal aspirate, bronchoalveolar lavage (BAL) fluid, protected specimen brush, pleural fluid, or lung biopsy. Specimen that was collected from other site may be considered as appropriate specimen. This will be determined by the medical monitor.

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.

Eligibility of subjects into mITT analysis population will be based on local lab results of baseline pathogens if the microbiological culture results are not sent to central lab for confirmation or if central lab results are missing.

6.6 Handling of 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. However, if the sample sent to IHMA was not tested and reported as “unknown”, the local laboratory name of pathogen will be used for analysis.

7. DEMOGRAPHIC AND OTHER BASELINE CHRACTERISTICS

7.1 Subject Disposition

The number of subjects who failed at Screening Period (ie, screen failure) will be summarized along with the reason for not randomized to treatment with study drug.

A summary table will be produced detailing the number of screened subjects, the number of subjects who screen failed. In addition, the subjects who screen failed will be summarized by respective reasons.

Among the randomized subjects in the ITT population, the mITT population and the safety population, the number and percentage of subjects who complete the study and those who prematurely discontinue from the study will be summarized.

A summary table will be produced detailing the number of subjects randomized, the number of subjects who treated with study drug, the number of subjects who completed the study, and the number of subjects who prematurely discontinued from the study. In addition, the reason for discontinuation from the study will be summarized.

The number and proportion of subjects in each analysis population will be summarized as well as the reasons for exclusion from the ITT Population, mITT Population, the ME-PP Population and the Safety Analysis Population.

7.2 Demographic and Baseline Characteristics

Demographic data and baseline characteristic shown in Table 7-1 will be summarized descriptively as described in Section 6.1 for the ITT population, mITT population and the Safety Analysis population. Categories used in summary of items are shown in Table 14-2.

The baseline pathogen will be summarized for mITT population. The baseline pathogen with the highest minimum inhibitory concentration (MIC) for cefiderocol will also be summarized for the MIC values and susceptibility defined by Clinical and Laboratory Standards Institute (CLSI) 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.

Table 7-1 Demographic and Baseline Characteristics

Continuous variable	Age, height, weight, body mass index, creatinine clearance, MDRD-eGFR, total APACHE II score , number of Gram-negative pathogens from appropriate specimen, CPIS, SOFA score,
Categorical variable	Age, gender, race, ethnicity, region, weight, clinical diagnosis at randomization, severity, empiric treatment failure status, prior therapy, medical history, top baseline gram-negative pathogens, bacteremia pathogens, ICU admission, ventilation status at randomization, type of baseline pathogens, Type of blood culture, CPIS, SOFA ,creatinine clearance renal grading group, Augmented renal clearance

APACHE II = Acute Physiology and Chronic Health Evaluation II; CPIS = Clinical Pulmonary Infection Score; ICU = intensive care unit; MDRD-eGFR = estimated glomerular filtration rate calculated with the modification of diet in renal disease equation; SOFA = Sequential Organ Failure Assessment

Note-See Section 14 for category.

Medical histories will be summarized by treatment group for the mITT and Safety populations for each treatment group by MedDRA system organ class and preferred term (PT). The reported medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1 or higher.

8. STUDY CONDUCT

8.1 Protocol Deviation

For all randomized subjects, major protocol deviations will be listed. Major protocol deviations will be specified in the “Protocol deviation specifications document”

separately. A final list of major protocol deviations will be determined based on the data review prior to database lock.

8.2 Treatment Exposure and Compliance

The duration of treatment in days will be calculated as the last infusion date of study minus the first infusion date of study drug plus 1. It will be summarized for the Safety population by treatment group using descriptive statistics. The number of subjects and its proportion for categorized duration of treatment in each treatment group will be summarized. The category for duration will be presented in Section 14.

In addition, study drug dosing status during the treatment period (from the first infusion to last infusion) will be summarized for each treatment group. The following infusion status will be summarized:

- The number of subjects who had an infusion interruption at least once during treatment period and its proportion
- The percentage of appropriate infusion dose administered
- The number of subjects who had a dose change/adjustment at least once during treatment period and its proportion

All study drug administration data will be listed by subject.

8.3 Prior and Concomitant Medication

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (September 2016).

Prior medications are defined as medications that were taken prior to randomization for the study. During blinded review of the data it was found that a few subjects had randomization date different from first dose of study medication. Hence for purpose of analysis prior medications are defined as medications that were taken before the first dose date and time of the study medication.

Concomitant medications are defined as medications that were taken on or after first dose date and time of study medication.

The number and percentage of subjects taking prior antibiotic medications will be summarized by anatomic therapeutic class (ATC) and preferred term for each treatment group and in total for the Safety population and the mITT population. Although a subject may have taken two or more medications, the subject is counted only once within an ATC classification. The same subject may contribute to two or more preferred terms in the same classification. Concomitant antibiotic medications, concomitant non-antibiotic medications, and prior non-antibiotic medications will be summarized in the same manner.

All prior and concomitant medications will be listed by subject.

[redacted]

Prior therapies are defined as therapies that were taken prior to first dose date for the study drug. Concomitant therapies are defined as therapies administered after first dose date and time of the study drug. Prior and concomitant therapies will be summarized for the Safety population and the mITT population. Subjects for whom a particular therapy name was reported more than once will be counted only once for that therapy.

If the route of administration is subcutaneous, nasal, ophthalmic, rectal, transdermal, topical or vaginal the medication will not be considered as a systemic antibiotic.

The following rules will be used to classify prohibited concomitant medications:

- Systemic antibiotics, other than linezolid, meropenem, and cefiderocol, are not permitted from randomization until TOC
- Aerosolized antibiotics are not permitted from randomization until after TOC
- Probenecid, methotrexate, procainamide, monoamine oxidase inhibitors, and valproic acid are not permitted from screening until EOT
- Inhalation antibiotics are prohibited medication from randomization until EOT

Concomitant medications ending before initial study treatment start date/time plus 3 hours will not be considered as additional antibiotics.

9. EFFICACY

Efficacy analyses will be performed for the mITT Population, unless otherwise specified.

9.1 Primary Endpoint

The primary endpoint is all-cause mortality at Day 14 since first infusion of study drug. All-cause mortality rate at Day 14 since first infusion of study drug will be calculated as the proportion of patients who experienced mortality regardless of the cause at or before Day 14 since first infusion.

9.1.1 Primary Analysis

The study hypothesis to demonstrate noninferiority (NI margin of 12.5%) of cefiderocol to meropenem on all-cause mortality (ACM) at Day 14 can be written as follows:

Null hypothesis H_0: $\pi_1 - \pi_2 > 12.5\%$

Alternative hypothesis H_1: $\pi_1 - \pi_2 \leq 12.5\%$

where π_1 is the ACM rate for cefiderocol and π_2 is the ACM rate on meropenem.

All-cause mortality rate at Day 14 by treatment group will be calculated as the proportion of patients who experienced mortality regardless of the cause at or before Day 14. The adjusted estimates of the difference in the all-cause mortality at Day 14 between cefiderocol and meropenem will be presented along with 95% confidence intervals (CIs) based on a stratified analysis using Cochran-Mantel-Haenszel (CMH) weights. The CI

will be 2-sided. Cochran-Mantel-Haenszel weights will be calculated with APACHE II score (≤ 15 and ≥ 16) as the stratified factor. Since we expect only a limited number of events based on our assumption of 10% mortality in both treatment groups we are likely to see sparse data including zeros in certain 2 x 2 tables based on both stratification factors. APACHE II scores were chosen to stratify data for analysis as studies have shown that APACHE II scores predict mortality well [1,2,3]. Noninferiority can be concluded if the upper bound of a 2-sided 95% CI for the difference in mortality at Day 14 between the 2 treatment groups (cefiderocol – meropenem) is smaller than a noninferiority margin of 12.5%. The associated 2 sided p-value for non-inferiority testing will also be calculated. The all-cause mortality at Day 14 will also be analyzed in ITT and ME-PP populations similarly.

Superiority of cefiderocol over meropenem for the day 14 all-cause mortality endpoint can be concluded if the 2-sided 95% CI for the difference in Day 14 all-cause mortality between the two treatment groups (cefiderocol and meropenem) lies completely below zero. The associated 2 sided p-value for superiority testing will also be calculated.

Let x_{ij} and n_{ij} denote the number of deaths and the total number of subjects in treatment i and stratum j, respectively, where $i = 1, 2$ represents the treatment arm (cefiderocol vs. meropenem) and $j = 1, 2$ represents the stratum based on the stratification factor: acute physiology and chronic health evaluation II (APACHE II) score (≤ 15 and ≥ 16), the following 2 × 2 contingency table shows the total number of subjects and the number of deaths in each treatment arm at stratum j:

Category	cefiderocol	meropenem
Dead	x_{1j}	x_{2j}
Alive	n_{1j}- x_{1j}	n_{2j}- x_{2j}
Total	n_{1j}	n_{2j}

The all-cause mortality rate (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 CMH weights of stratum j are defined as:

$$w_j = \frac{\left(\frac{n_{1j}n_{2j}}{n_{1j}+n_{2j}}\right)}{\sum_{j=1}^{2}\frac{n_{1j}n_{2j}}{n_{1j}+n_{2j}}}$$

The adjusted estimate of the difference in the all-cause mortality rate between the 2 treatment arms (d_{adj}) based on the CMH weights is given as:

$$\hat{d}_{adj} = \sum_{j=1}^{2} w_j d_j$$

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

$$\hat{d}_{adj} \pm z_{\alpha/2}\sqrt{\sum_{j=1}^{2} \hat{w}_j^2 \left(\frac{\hat{\pi}_{1j}(1-\hat{\pi}_{1j})}{n_{1j}} + \frac{\hat{\pi}_{2j}(1-\hat{\pi}_{2j})}{n_{2j}}\right)}$$

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

9.1.2 Sensitivity Analysis

For each of ITT and ME-PP populations primary analyses stated in Section 9.1.1 will be performed as sensitivity analyses.

9.1.3 Missing Day 14 Survival Status Sensitivity Analysis

Primary endpoint sensitivity analysis for missing Day 14 all-cause mortality status will be implemented as follows: subjects with unknown mortality status at Day 14 in the cefiderocol group will be imputed as “Death ” while any subject with unknown mortality status at Day 14 in the Meropenem arm will be imputed as “ Alive “. The data will be then be analyzed in the same way as described in Section 9.1.1.

9.1.4 Supplementary Analysis

Analysis for Day 14 all-cause mortality stated in Section 9.1.1 will be performed by excluding subjects who are meropenem resistant in the mITT analysis population as a supplementary analysis. Subjects who are meropenem resistant will be determined from central laboratory culture results.

9.1.5 Subgroup Analysis

Analyses of all-cause mortality (ACM) at Day 14 will be presented for the following subgroups. The category for each item will be presented in Section 14.

The estimates of the difference in the all-cause mortality rates at Day 14 between cefiderocol and meropenem will be presented along with 95% confidence intervals (CIs) (Wald method) if data warrant. If the number of subjects within a subgroup is less than 10 in any treatment arm, only the difference in the all-cause mortality between the two treatment arms (no CI) will be presented. The CI will be 2-sided. A similar analysis will also be carried out for Day 28 all-cause mortality.

1. Clinical diagnosis
2. Gender
3. Race
4. Age
5. Region
6. Baseline clinical characteristics

Baseline clinical characteristics include:

- APACHE II score
- CPIS score
- Bacteremia status
- Creatinine clearance/MDRD-eGFR
- Empiric treatment failure status
- ICU admission
- Ventilation status at randomization
- Top 5 baseline gram-negative pathogens
- Creatinine Clearance renal grading groups

The top 5 baseline gram-negative pathogens will be based on overall frequency across both groups determined before unblinding.

Subgroup analyses will also be carried out for the key secondary outcomes, per subject microbiological outcome at TOC and per subject clinical outcome at TOC for the subgroups defined above.

For the key secondary endpoints (per subject microbiological outcome at TOC and per subject clinical outcome at TOC) the estimates of the difference in the eradication rate and cure rate respectively between the two treatment arms along with the 95% CIs (Wald method) if data warrant. If the number of subjects within a subgroup is less than 10 in any treatment arm, only the difference in the eradication rate or cure rate between the two treatment arms (no CI) will be presented. The reason we are using 10 as a threshold value for displaying CI is because we are using Wald CI which is appropriate when we have at least 5 successes and at least 5 failures in each sample [5].

Other subgroup analyses may be performed if deemed necessary.

The subgroup analysis category for Meropenem non-susceptible status for Day 14 all-cause mortality, Day 28 all-cause mortality, per subject microbiological outcome at EOT,TOC and FU and per subject clinical outcome at EOT ,TOC and FU , top 5 baseline gram-negative pathogens and creatinine clearance renal grading sub group category was specified after the study team had viewed the aggregate mortality results by treatment group on April 1st , 2019 and is hence is a post-hoc analysis.

The Meropenem non-susceptible status for subjects will be Yes if for any baseline gram-negative pathogens (including stenotrophomonas maltophilia) the CLSI results are non-susceptible to Meropenem. The carbapenem resistant (CR) criteria for Pseudomonas spp. is MIC >= 4µg/mL, for Acinetobacter spp. is MIC >= 8 µg/mL and for Enterobacteriaceae is MIC >= 2 µg/mL.

Subjects who have MIC values > 8 µg/mL for Meropenem for any baseline gram-negative pathogen is another post-hoc subgroup category for Day 14 all-cause mortality,

Day 28 all-cause mortality, per subject microbiological outcome and clinical outcome at EOT, TOC and FU

9.2 Key Secondary Endpoints

The key secondary efficacy endpoints include the following:

- Microbiologic outcome of treatment with cefiderocol or meropenem per subject at Test of Cure (TOC)
- Clinical outcome of treatment with cefiderocol or meropenem per subject at TOC
- To compare Day 14 all-cause mortality of S-649266 with that of meropenem for superiority of S-649266

9.3 Other Secondary Efficacy Endpoints

- To compare the microbiological outcome of treatment with cefiderocol with that of meropenem per subject at Early Assessment(EA),End of Treatment (EOT)[4], and Follow-up (FU)
- To compare the clinical outcome of treatment with cefiderocol with that of meropenem per subject at EA, EOT and FU
- To compare all-cause mortality at Day 28 of subjects treated with cefiderocol with that of meropenem
- To compare all-cause mortality up to EOS visit of subjects treated with cefiderocol with that of meropenem.

9.3.1 Per Subject Microbiological Outcomes

The microbiological outcomes by baseline pathogens will be determined according to the following criteria at EA, EOT and TOC:

- **Eradication:** Absence of the baseline Gram-negative pathogen from an appropriate clinical specimen. Presence of colonizers or contaminants associated with a baseline pathogen will be associated with microbiological outcome of eradication. If it is not possible to obtain an appropriate clinical culture, and the subject has a successful clinical outcome, the response will be presumed as eradication.
- **Persistence:** Continued presence of the baseline Gram-negative pathogen from an appropriate clinical specimen. Persistence at End of Treatment or Test Of Cure will be carried forward.
- **Indeterminate:** No culture obtained from an appropriate clinical specimen or if the microbiological outcome is eradication after additional antibacterial therapy for the treatment of the current infection.

[4] EOT is defined as the last day of study treatment.

The microbiological outcomes by baseline pathogens will be determined according to the following criteria at FU:

- **Sustained Eradication**: Absence of the baseline Gram-negative pathogen from an appropriate clinical specimen after TOC. Presence of colonizers or contaminants associated with a baseline pathogen will be associated with microbiological outcome of sustained eradication. 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 was negative.
- **Persistence:** Persistence of any baseline Gram-negative pathogen from an appropriate specimen
- **Indeterminate**: No culture obtained from an appropriate clinical specimen or if the microbiological outcome is eradication after the subject received additional antibacterial therapy for the treatment of the current infection.

As shown in Table 9-1, subjects who experience eradication of all baseline Gram-negative pathogen(s) at EA, EOT and TOC their per subject microbiological outcome will be considered “eradication” and subjects who experience persistence of any baseline Gram-negative pathogens, their per subject microbiological outcome will be considered “persistent”.” Subjects whose experiences are other than the above will be considered “indeterminate.”

At FU, the per subject microbiological outcome for subjects who experience sustained eradication of all baseline Gram-negative pathogens will be considered as “sustained eradication” and subjects who experience recurrence of any baseline Gram-negative pathogens will have a per subject microbiological outcome of “recurrence”. Subjects who show persistence of any baseline Gram-negative pathogens will have a per subject microbiological outcome of “persistence”. Subjects whose experiences are other than above at FU will be considered “indeterminate”.

[redacted]

Table 9-1 Per Subject Microbiological Outcome at End of Treatment, Test of Cure and Follow-up

Visit	Per Subject Microbiological Outcome	Definition
Early Assessment, End Of Treatment and Test Of Cure	Eradication	Eradication of all baseline Gram-negative pathogens
	Persistence	Persistence of any baseline Gram-negative pathogens
	Indeterminate	Other than those above
Follow-up	Sustained eradication	Absence of baseline Gram-negative pathogens from appropriate clinical specimen after TOC.
	Persistence	Persistence of any baseline Gram-negative pathogen
	Recurrence	Recurrence of any baseline Gram-negative pathogen
	Indeterminate	Other than those above

9.3.1.1 Analysis of the Microbiological Outcome per Subject at Early Assessment, End of Treatment, and Test of Cure

The microbiological response rate at EA, EOT and TOC will be calculated as the proportion of subjects who experience eradication at EA, EOT and TOC respectively by treatment group. The adjusted estimate of the difference in the response rate between the 2 treatment groups will be presented along with the 95% CIs based on a stratified analysis using the CMH weights: infection diagnosis (HABP/VABP/HCABP) and APACHE II score (≤ 15 and ≥ 16). In addition, the number and proportion of subjects having microbiological outcome as persistence and indeterminate will be summarized by treatment group.

9.3.1.2 Analysis of Microbiological Outcome per Subject at Follow-up

The microbiologic response rate at FU will be calculated as the proportion of subjects who experience sustained eradication of all baseline Gram-negative pathogens after documented eradication at the TOC.

The same analysis method as described in Section 9.3.1.1 above for microbiological outcome per subject at EA, EOT and TOC will be performed for the microbiologic outcome per subject at FU. The outcome will be tabulated for each treatment group. The adjusted estimate of the difference in the response rate between the 2 treatments arms along with the adjusted 95% CIs based on the CMH weights will be presented.

9.3.2 Microbiological Outcome per Subject for the Subset where Gram-negative Pathogens Isolated from Blood Culture are the Same as Lung at Baseline

In addition to the analyses described above, the microbiological response rate will be summarized for the subset where gram-negative pathogens isolated from blood culture

are the same as lung at baseline at EA, EOT, TOC and FU. The same analysis method described in Sections 9.3.1.1 and 9.3.1.2 will be implemented for this analysis.

9.3.3 Per pathogen Microbiological Outcomes

The microbiological outcomes by baseline pathogens will be determined according to the criteria defined in Section 9.3.1 above.

For the microbiological outcome per pathogen, the outcomes will be summarized and the eradication rate with 95% CI will be calculated by treatment group at EA, EOT, TOC and FU will be calculated. The estimate of the eradication rate between the two treatment arms along with the 95% CIs will be presented for pathogens with a frequency of at least 10 in each treatment arm. In case of baseline pathogens with a frequency less than 10 in any treatment arm, only the difference in the eradication rate between the two treatment arms (no CI) will be presented.

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 CLSI 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 summarized.

A listing of per pathogen microbiological assessment for emergence resistance will be provided for the cefiderocol arm. The emergence of resistance will be determined by assessing for at least 4-fold increases in MICs from baseline value for baseline pathogens that persist at EA, EOT, TOC or recurrence at FUP.

9.3.4 Per Subject Clinical Outcomes

The clinical outcomes will be assessed by the investigator according to the following criteria at EA, EOT and TOC:

- **Clinical Cure:** Resolution or substantial improvement of baseline signs and symptoms of pneumonia, including a reduction in Sequential Organ Failure Assessment (SOFA) and Clinical Pulmonary Infection (CPIS) scores, and improvement or lack of progression of chest radiographic abnormalities such that no additional antibacterial therapy is required for the treatment of current infection at the EA and EOT visits, and no antibacterial therapy is required for the treatment of the current infection at the TOC.
- **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.

The clinical outcome at FU will be assessed by the investigator according to the following criteria:

- **Sustained Clinical Cure:** Continued resolution or substantial improvement of baseline signs and symptoms of pneumonia, such that no antibacterial therapy has been 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.
- **Clinical Failure:** Clinical failure at TOC will be carried forward regardless of lost to follow-up.
- **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.

9.3.4.1 Analysis of Clinical Outcome per Subject at Early Assessment, End of Treatment and Test of Cure

The clinical response rate at Early Assessment, End of Treatment and Test of Cure will be calculated as the proportion of subjects who have a clinical outcome of cure. The adjusted estimate of the difference in the cure rate between the 2 treatment groups will be presented along with the adjusted 95% CIs based on the CMH weights: diagnosis and APACHE II score. In addition, the number and proportion of subjects having clinical outcome as failure and indeterminate will be summarized by treatment group.

9.3.4.2 Analysis of Clinical Outcome per Subject at Follow-up

The cure rate at FU will be calculated as the proportion of subjects with clinical outcome of sustained clinical cure. In addition, the number and proportion of subjects having clinical outcome as relapse, clinical failure and indeterminate will be summarized by treatment group.

The same analysis method as described in Section 9.3.4.1 above for clinical outcome per subject at EA, EOT and TOC will be performed for the clinical outcome per subject FU. The outcome will be tabulated for each treatment group. The adjusted estimate of the difference in the response rate between the 2 treatments arms along with the adjusted 95% CIs based on the CMH weights will be presented.

9.3.5 Clinical Outcome per Pathogen

For the clinical outcome per pathogen, the outcomes will be summarized and the cure rate and its 95% CI at EA, EOT, TOC and FU will be calculated by treatment group for each time point. The 95% CIs (2-sided) are calculated using a normal approximation to the difference between 2 binomial proportions (Wald method). For baseline pathogens with a frequency less than 10 in any treatment arm, the 95% CIs are not presented.

[redacted]

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 will be summarized.

9.3.6 All-cause Mortality at Day 28

All-cause mortality rate at Day 28 since first infusion of study drug will be calculated as the proportion of patients who experienced mortality regardless of the cause at or before Day 28 since first infusion.

Superiority of cefiderocol over meropenem for the day 28 all-cause mortality endpoint can be concluded if the 2-sided 95% CI for the difference in Day 28 all-cause mortality between the two treatment groups (cefiderocol and meropenem) lies completely below zero.

9.3.6.1 Analysis of All-cause Mortality at Day 28

All-cause mortality at Day 28 will be analyzed in a similar way to the primary efficacy endpoint described in Section 9.1.1

9.3.7 All-cause Mortality during treatment and follow-up period (until EOS)

All-cause mortality rate during treatment and follow-up period (until EOS) will be calculated as the proportion of patients who experienced mortality regardless of the cause at or before EOS since the first infusion. If a subject discontinues from the study before this period and survival information was not available, then the survival status for this endpoint for the subject will be unknown.

9.3.7.1 Analysis of All-cause Mortality during treatment and follow-up period (until EOS)

All-cause until EOS visit will be analyzed in a similar way to the Primary Efficacy endpoint described in Section 9.1.1

9.3.7.2 Subgroup Analysis for All-cause Mortality until EOS

9.3.7.2.1 From Time of First Dose

Analyses of all-cause mortality during treatment and follow-up period (until EOS) will be presented for the subgroup associated with time period of death: ≤ 3 days after start of study treatment, 4 – 28 days of start of study treatment and > 28 days since start of study treatment.

The estimates of the difference in the all-cause mortality rates between cefiderocol and meropenem will be presented along with 95% confidence intervals (CIs) (Wald method) if data warrant. If the number of subjects within a subgroup is less than 10 in any

treatment arm, only the difference in the all-cause mortality between the two treatment arms (no CI) will be presented. The CI will be 2-sided.

9.3.7.2.2 From Time of Last Dose

Analyses of all-cause mortality during treatment and follow-up period (until EOS) will also be presented for the subgroup associated with the timing of last dose to death: 0 day (on the same day as last dose) , 1-7 days after last dose of study treatment, 8 – 14 days after last dose of study treatment and >= 15 days after last dose of study treatment. The time will be calculated as death day – last dose of study drug day.

The estimates of the difference in the all-cause mortality rates between cefiderocol and meropenem will be presented along with 95% confidence intervals (CIs) (Wald method) if data warrant. If the number of subjects within a subgroup is less than 10 in any treatment arm, only the difference in the all-cause mortality between the two treatment arms (no CI) will be presented. The CI will be 2-sided.

9.3.7.3 Survival Time Up to End of Study

For the survival time up to 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 since their last visit day.

9.4 Sequential Organ Failure Assessment Score

Sequential Organ Failure Assessment score at Baseline and at each postbaseline visit (early assessment, end of treatment, test of cure and follow-up) will be summarized. Change from baseline for each postbaseline visit will also be summarized.

9.5 Clinical Pulmonary Infection Score

Clinical Pulmonary Infection Score at Baseline and at each postbaseline visit (early assessment, end of treatment, test of cure and follow-up) will be summarized by treatment group. Change from baseline for each postbaseline visit will also be summarized.

10. SAFETY

Safety assessments included AEs, clinical laboratory safety tests (hematology, chemistry, endocrinology, and urinalysis), vital sign measurements, and 12-lead electrocardiograms (ECGs). 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 administered a pharmaceutical product (including investigational drug) during the course of a clinical investigation. An AE can therefore be any unfavorable and unintended sign (including an

abnormal laboratory finding), symptom, or disease temporarily associated with the use of an investigational product, whether or not considered related to the investigational product. Where symptoms or signs form part of a diagnosis, the diagnosis should be reported as AE instead of the individual symptoms and signs.

Adverse events will be collected from the time of informed consent through EOS for randomized subjects. Adverse events will be classified by System Organ Class (SOC) and Preferred Term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1 or higher

Adverse events that started 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, 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 incidence proportion of treatment-emergent adverse events (TEAEs) will be calculated by treatment group. The incidence proportion will be calculated as the proportion of subjects experiencing TEAEs to total subjects in the safety population. Difference in the incidence proportion between cefiderocol and meropenem, and its 95% CI will be calculated using Wilson (score) method. Deaths due to AEs, serious adverse events (SAEs), AEs leading to discontinuation of study drug, treatment related AEs, treatment related SAEs, and treatment-related AEs leading to discontinuation of study drug will be analyzed in a similar way.

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. Difference in the incidence proportions between cefiderocol and meropenem, and its 95% CI will be calculated using the Wilson's (score) method. Treatment-related AEs, SAEs, treatment-related SAEs, AEs leading to discontinuation of the study drug 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.

10.2 Vital Signs

Vital sign measurements, including diastolic blood pressure (mm Hg), systolic blood pressure (mm Hg), body temperature, pulse rate (beats per minute), and respiration rate (breaths/minute) will be measured at Screening and at specified times.

Summary statistics for vital sign measurements will be presented for EA, EOT, TOC, FU and for the change from baseline to each time point. Baseline will be the last value obtained before first dose of study drug.

For postbaseline measurements, if multiple readings (ie, 3 readings) of vital sign measurements are obtained within a visit, the maximum body temperature within that visit 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.

In addition, the number and percentage of subjects with the following prespecified outlier category given in Table 10-1 during the post dosing period including unscheduled will be presented by treatment group.

Table 10-1 Outliers 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

10.3 Clinical Laboratory Evaluations

Summary statistics for laboratory test data (hematology, blood chemistry, and other specialized tests) will be presented for each scheduled time point measured after first infusion and for the change from baseline to each time point. Since PTT and APTT were collected in the same data field a meaningful data summary cannot be made for PTT. 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. All central clinical laboratory data and local clinical laboratory data will be listed. If the SI units for CRP are available in EDC as a value less than the lower limit then it will be set to the lower limit and then used for analysis.
Scheduled laboratory parameters shown in Table 10-2 include the following:

Table 10-2 Routine Laboratory Tests

Category	Evaluation Items
Hematology tests	Hematocrit, hemoglobin, platelet count, RBC, WBC with differential and morphology indices, INR
Blood chemistry tests	ALP, ALT, AST, GGT, LDH, CPK, CRP, and amylase, BUN, creatinine, TBL, sodium, potassium, bicarbonate, chloride, calcium, magnesium, glucose, total protein, albumin, uric acid, and total cholesterol
Urinalysis	Glucose, blood, protein, ketones, bilirubin, urobilinogen, leukocyte esterase, and microscopic[a] (WBC, RBC, crystals, and casts)
Specialized tests	Iron, total iron-binding capacity, transferrin iron saturation, and hepcidin at Screening and Test of Cure
Others	Serum or urine pregnancy test at screening CrCl and eGFR: at Screening and EA (Section 7.6.4.4 in the protocol) CrCl determined from a timed urine collection at EA[b] (Section 7.6.4.4 in the protocol)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; CrCl = creatinine clearance; CRP = C-reactive protein; EA = Early Assessment; eGFR = estimated glomerular filtration rate; GGT = gamma-glutamyl transferase; INR = international normalized ratio; LDH = lactate dehydrogenase; PTT = partial thromboplastin time; RBC = red blood cell; TBL = total bilirubin; WBC = white blood cell

a If sediment is present.

b For subject with eGFR $\geq$ 90 mL/min/1.73 m^2 at Screening.

The number and percentage of subjects with the following prespecified outlier category listed in Table 10-3 below each postbaseline visit (Early assessment, End of Treatment, Test of Cure and Follow-up) including unscheduled visits will be presented by treatment group.

Table 10-3 The Outlier for Each Parameter in Laboratory Test

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

10.4 Electrocardiograms

All ECG measurements and the overall interpretation will be listed by subject.

11. PHARMACOKINETIC ANALYSES

Individual plasma concentrations of cefiderocol will be listed and summarized by nominal sampling time window, and if possible, by dosing group based on renal function. 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 = $[\exp(sd^2) - 1]^{1/2}$ × 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. The time course of individual and mean plasma concentrations will be presented by appropriate graphics.

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.

12. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

The pharmacokinetics/pharmacodynamics 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

After about 50 and 150 subjects have been randomized, completed treatment and follow-up, the interim analysis to review un-blinded safety and efficacy data will be performed by the DSMB. After the first unblinded review of the first 50 subjects by the DSMB, a request was made to have an additional unblinded review of safety and efficacy data after 100 subjects were randomized into the study.

An alpha spend of 0.0001 based on Haybittle-Peto will be used for the two formal unblinded looks of the data related to the primary endpoint at ~ 50 patients and ~ 150 patients . The same Haybittle-Peto alpha spend of 0.0001 will be used for any unplanned looks of the data.

In the event of unplanned looks of the efficacy data for the entire study, a Haybittle-Peto alpha spend of 0.0001 will be used for every unplanned look of the data.

14. PROGRAMMING CONVENTIONS

14.1 Formatting and Programming Rule

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.

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	One more decimal place than raw data.
Maximum, minimum	Same number of decimal places as raw data.
Percentage (%)	Round off to 1 decimal place.
P value	Round off to 4 decimal places. Note: $p < 0.0001$ is displayed as "< .0001".
Summary statistics for pharmacokinetics analysis	Three significant digit

Handling of Outliers

Possible outliers will not be omitted from analyses.

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
Gender	Male, female
Race	American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other
Ethnicity	Hispanic or Latino, Not Hispanic or Latino, Unknown
Age (years)	< 65, ≥ 65 and <75, ≥ 75
Weight (kg)	< 70, ≥ 70
Clinical Diagnosis	HABP, VABP, and HCABP
APACHE II score	≤ 15, 16-19, ≥ 20
CPIS	< 6, 6-7, 8-9, > 9
Bacteremia	Yes, No
Medical History	Yes, No
Prior Therapy	Yes, No
Creatinine clearance renal grading	>120mL/min, > 80-120mL/min, > 50-80mL/min, 30-50mL/min, < 30mL/min
Type of Baseline pathogen	Gram-negative pathogens only, Gram-positive pathogens only, Mixed pathogens ,Fungal pathogens only, No respiratory sample, Culture negative, Others
Type of Blood Culture	Positive, Negative, Blood culture not done
Augmented renal clearance	MDRD-eGFR >= 90 mL/min/1.73 m^2 and CrCl >=120 mL/min, MDRD-eGFR >= 90 mL/min/1.73 m^2 and CrCl < 120 mL/min, MDRD-eGFR 60 to < 90 mL/min/1.73 m^2,MDRD-eGFR 15 to < 30 mL/min/1.73 m^2 ESRD(MDRD-eGFR < 15 mL/min/1.73 m^2)
Severity of disease	Mild, Moderate, Severe
Ventilation status at randomization	Ventilated, Non-Ventilated
ICU admission	Yes, No
Empiric therapy failure status	Yes, No
Number of Gram-negative pathogens isolated at baseline	0,1, 2, 3, >3
Duration of treatment (days)	< 7,>= 7 to <= 14,> 14 to <= 21, > 21
Country (region)	North America, Asia-Pacific, Europe
Meropenem non-susceptible status*	Yes, No
MIC > 8 µg/mL for Meropenem	Yes, No

* Non-susceptible by CLSI criteria (Pseudomonas spp. is MIC >= 4µg/mL, for Acinetobacter spp. is MIC >= 8 µg/mL and for Enterobacteriaceae is MIC >= 2 µg/mL) APACHE II = Acute Physiology and Chronic Health Evaluation II; eGFR = estimated glomerular filtration rate; HABP = hospital-acquired bacterial pneumonia; HCABP = healthcare-associated bacterial pneumonia; VABP = ventilator- associated bacterial

15. CHANGES FROM PROTOCOL SPECIFIED ANALYSES

- Added analysis for Distribution of Gram-negative pathogens Isolated at Baseline pathogen
- Added Analyses for Baseline pathogen per MIC and CLSI interpretation
- Added Analyses for Clinical outcome per pathogen
- Added Analyses for Clinical outcome per MIC and CLSI interpretation
- Added analyses Microbiological outcome per pathogen
- Added analyses for Microbiological outcome per MIC and CLSI interpretation
- Added analyses for Listing for 4 fold increase of MIC from baseline
- Added analyses for Summary for Microbiological Outcome Per Subject whose Gram-Negative Pathogens Isolated from Blood Culture are the Same as Lung at Baseline
- Added analyses for Summary of Minimum Inhibitory Concentration of Baseline Gram-negative Pathogens Isolated from the Blood Culture That Are the Same as Lung at Baseline
- Summary of All-cause Mortality at Day 28 by Predefined Subgroups
- Summary of Microbiological Outcome Per Subject at Test of Cure by Predefined Subgroups
- Summary of Clinical Outcome Per Subject at Test of Cure by Predefined Subgroups
- Summary of all-cause mortality until EOS visit based on study day of death
- Added a post-hoc subgroup category for Meropenem non-susceptible status
- Added a post-hoc subgroup category for subjects with MIC values greater than 8 for Meropenem for any baseline gram-negative pathogen
- Added a post hoc subgroup for top 5 baseline gram-negative pathogens.

16. REFERENCE

1. Guidance for Clinical Trial Sponsors. Establishment and Operation of Clinical trial Data Monitoring Committees. March 2006.
2. Wiskirchen DE, Kuti JL, Nicolau DP. Acute physiology and chronic health evaluation II score is a better predictor of mortality than IBMP-10 in patients with ventilator-associated pneumonia.SurgInfect (larchmt). 2011 Oct;12(5):385-90.
3. Mirsaeidi M, Peyrani P, Ramirez JA; Improving Medicine through Pathway Assessment of Critical Therapy of Hospital-Acquired Pneumonia(IMPACT-HAP) Investigators. Predicting mortality in patients with ventilator-associated pneumonia: The APACHE II score versus the new IBMP-10 score. Clin Infect Dis. 2009 Jul; 49(1):72-7.
4. Zhou XY, ben SQ, Chen HL, Ni SS. A comparison of APACHE II and CPIS scores for the prediction of 30-day mortality in patients with ventilator-associated pneumonia. Int J Infect Dis. 2015 Jan;30:144-7.
5. Agresti A. *Categorical Data Analysis 2nd ed.*, New York: John Wiley & Sons, 2002.

17. APPENDIX 1 STUDY SCHEMATIC

<table>
<tr><td colspan="3">D −2 to D 1</td><td colspan="2">D 3 to D 4</td><td>EOT[a]</td><td>EOT
+ 7
(±2)</td><td>EOT
+ 14
(±3)</td><td>EOT
+ 28
(±3)</td></tr>
<tr><td rowspan="4">Screening\Baseline</td><td rowspan="4">Randomization</td><td colspan="3">Treatment Period</td><td rowspan="4">Up to D 14[a]</td><td rowspan="4">Test of Cure (TOC)</td><td rowspan="4">Follow-up (FU)</td><td rowspan="4">End of Study (EOS)</td></tr>
<tr><td>D 1</td><td colspan="2">Early Clinical/Micro Assessment (EA)
Pharmacokinetic blood sampling</td></tr>
<tr><td colspan="3">S-649266 daily 2-g intravenous dosing at 8-hour intervals[b] as a 3-hour infusion</td></tr>
<tr><td colspan="3">Meropenem daily 2-g intravenous dosing at 8-hour intervals[b] as a 3-hour infusion</td></tr>
</table>

D = Day; EOT = End of Treatment

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.

b. Dosing adjustments for renal impairment (see Tables 5-1 and 5-2 in the protocol).

18. APPENDIX 2 TIME AND EVENTS SCHEDULE

Evaluation	Screening/ Baseline		Treatment Period				Test of Cure (TOC)		Follow-up (FU)	End of Study (EOS)
	Day −2 to Same Day Prior to Randomization[a]		Day 1	EA Day 3 to 4	Day 14[b]	EOT[c]	EOT + 7 (± 2)	Day 28[b]	EOT + 14 (± 3)	EOT + 28 (± 3)
Informed Consent	X									
I/E Criteria	X									
Demographics	X									
Medical History[d]	X									
Physical Examination	X[e]			X[f]	X[f]	X[f]	X[f]		X[f]	X[f, g]
GCS	X			X	X	X	X		X	
APACHE II Score	X									
SOFA Score	X			X	X	X	X		X	
Clinical Assessment of Signs and/or Symptoms	X			X	X	X	X		X	
Oxygenation Status	X	Randomization	X	X	X	X	X		X	
Chest Radiographs	X			X[h]	X	X	X		X[h]	
CPIS Parameters[i]	X		X	X	X	X	X		X[i]	
Pregnancy Test[j]	X									
Hematology Tests, Blood Chemistry Tests, and Urinalysis (see Table 7-1)	X			X	X	X	X		X	X[g]
Specialized Tests (see Table 7-1)	X						X			
CrCl from Serum[k] Creatinine and MDRD-eGFR	X			X						
CrCl from Urinary Creatinine[k]	X			X						
Vital Signs[l]	X		X	X	X	X	X		X	X[g]

[redacted]

Evaluation	Screening/ Baseline		Treatment Period				Test of Cure (TOC)		Follow-up (FU)	End of Study (EOS)
	Day −2 to Same Day Prior to Randomization[a]		Day 1	EA Day 3 to 4	Day 14[b]	EOT[c]	EOT + 7 (± 2)	Day 28[b]	EOT + 14 (± 3)	EOT + 28 (± 3)
12-lead ECG	X									
Drug Administration[m]			X	X	X	X				
Assess Clinical Outcome				X	X	X	X		X	
Microbiological Outcome				X	X	X	X		X	
Lower Respiratory Specimens for Microbiologic Cultures[n]	X			X	X	X	X		X	
Blood Cultures[o]	X			X	X	X	X		X	
Blood PK Samples[p]				X[p]		X[p]				
AE Assessment	X ←								→	X
Concomitant Therapy	X ←								→	X
Hospitalization (see Section 7.2.1 in the protocol)	X ←								→	X
Survival[q]	X ←								→	X

AE= adverse event; APACHE II = Acute Physiology and Chronic Health Evaluation II; CPIS = Clinical Pulmonary Infection Score; CrCl = creatinine clearance; EA = Early Assessment; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = End of Study; EOT = End of Treatment; FU = Follow-up; GCS = Glasgow Coma Scale; I/E = inclusion/exclusion; MDRD = modification of diet in renal disease, PK = pharmacokinetics; q8h = every 8 hours; q12h = every 12 hours; SOFA = Sequential Organ Failure Assessment; TOC = Test of Cure

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 Additional assessment will be conducted on Day 14, if treatment duration is extended beyond 14 days to up to 21 days; survival will be recorded on Day 14 and Day 28.

c EOT evaluations occur on the last day of study treatment; EOT can be any time after the subject had at least 1 dose of study treatment, duplication of assessments for a given day and EOT is not necessary.

d Include a review of prior/concomitant therapies.

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

f A limited physical examination relevant to the subject's current condition will be performed.

g If EOS evaluation is by phone, physical examination, laboratory tests, and vital signs will not be performed.

[redacted]

h Chest radiographs will be performed if clinically indicated. Applicable only to Germany due to local requirements: 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.

i Most recent chest radiograph is used for the CPIS calculation.

j Urine or serum pregnancy test only for females who are not postmenopausal or surgically sterile.

k The CrCl (the Cockcroft-Gault equation) and eGFR (the MDRD equation) will be calculated from the serum creatinine. For subjects with eGFR $\geq$ 90 mL/min/1.73 m^2 and CrCl $\geq$ 120 mL/min at baseline and EA, urine samples will be collected a time interval as short as 2 hours or up to 8 hours.

l Blood pressure (systolic/diastolic pressures), body temperature, pulse rate, and respiratory rate. Once a day during screening, and 3 times a day during treatment in hospital.

m Drug administration is q8h daily for S-649266 and meropenem unless change is made because of renal function. Linezolid is dosed q12h daily for at least 5 days.

n Lower respiratory tract specimens for microbiologic cultures must be obtained at specified times. When subjects are recovering from pneumonia and produce little respiratory secretion, at least an attempt to collect respiratory specimen needs to be made (eg, ask subjects to cough, cough up sputum, or conduct suction from endotracheal tube).

o 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 or Day 4 of study drug treatment;1 draw just prior to the infusion of the dose, 1 hour after start of infusion, before the end of infusion, and at 1 hour after the end of infusion. Subjects with nonstable renal function resulting in a dosage adjustment after EA will undergo another blood PK sampling 24 to 72 hours after their dosing adjustment. If possible, a single blood draw should be performed as soon as possible (within 24 hours of last dose) in the case of premature EOT, which is defined as receiving < 7 days of intravenous treatment.

q Survival is confirmed daily and continuously during the study. Mortality at Days 14 and 28 are study endpoint

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