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	Protocol Version 4 (Amendment 3) 22 Feb 2019

History of Protocol Amendments

Version 1 (Original)	02 Aug 2016
This version of the protocol was not used to enroll participants	
Version 2	21 Dec 2016
This version of the protocol was not used to enroll participants	
Version 3	24 Jul 2017
• Changed the concomitant use of Linezolid to at least 5 days rather than full treatment term • Contraceptive inclusion criteria added • Added inclusion criteria for patients who had failed previous empiric antibiotic therapy both clinically and microbiologically • Valproic acid was excluded as a concomitant therapy because of meropenem dosing instructions • Clarification of PK blood sampling times was added • Added rescreening criteria for previously screen-failed patients • A new appendix provided a flow chart to help investigators determine the eligibility of patients failing empiric antibiotic treatment	
Version 3.1	14 Aug 2017
• The Time and Events Table was edited to better display the relationship between columns and foot notes	
Version 3.2 RUS:	19 Dec 2017
• Adds a requirement for only Russian study sites	
Version 3.3 EU	21 Dec 2018
• Adds BREXIT required changes to protocol	
Version 3.4 RUS	11 Jan 2019
• Adds BREXIT required changes to protocol and phone number change	

Version3.5 EU	11 Jan 2019
• Adds change in phone number for BREXIT required changes	
Version 4	22 Feb 2019
• Adds address changes required for BREXIT • Clarifies that Middle Eastern study sites are under the purview of SEU personnel • Adds a superiority analysis in a fixed sequence for secondary endpoints • Notes that resource utilization will be reported outside of the CSR • Removes probenecid, methotrexate, and procainamide from the list of prohibited medications • Specifically allows metronidazole or clindamycin to cover anaerobic bacteria and vancomycin for *C. difficile* • Removes the requirement for urinalysis for anuric patients • Adds major nonfatal events to the list of items to be reviewed at the prespecified times for other evaluations	

CLINICAL STUDY PROTOCOL: 1615R2132

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
Study Number:	1615R2132
EudraCT Number:	2016-003020-23
Study Phase:	3
IND Number:	116,787
Product Name:	S-649266 (INN name: cefiderocol)
Sponsor* for North America, South America:	Shionogi Inc. 300 Campus Drive, Florham Park, NJ 07932 USA
Sponsor* for Europe/Middle East:	Shionogi B.V. Kingsfordweg 151, 1043 GR Amsterdam Netherlands
Sponsor* for Asia-Pacific:	Shionogi & Co., Ltd. (Head Office) 1-8 Doshomachi, 3 Chrome, Chuo-ku, Osaka 541-0045, Japan (Development Office) 12F, Hankyu Terminal Bldg., 1-4, Shibata 1-chome, Kita-ku, Osaka 530-0012, Japan
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Medical Monitor CRO:	[redacted]
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Version 1: (Original)	02 Aug 2016
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Version 3.1: (Amendment 2.1)	14 Aug 2017
Version 3.2 RUS: (Amendment 2.2)	19 Dec 2017
Version 3.3 EU (Amendment 2.3)	21 Dec 2018
Version 3.4 RUS (Amendment 2.4)	11 Jan 2019
Version3.5 EU (Amendment 2.5)	11 Jan 2019
Version 4: (Amendment 3)	22 Feb 2019

* The study sponsor may be 1 or more of the above companies. Throughout the protocol, the term "sponsor" represents the various legal entities identified in the "Sponsor List of the Study Administrative Structure" in the protocol. The above companies are referred to as Shionogi.

SYNOPSIS

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

Study Number: 1615R2132

Study Phase: 3

Primary Objective:

- To compare all-cause mortality at Day 14 of subjects who receive S-649266 with that of subjects who receive the comparator, meropenem, in adults with hospital-acquired bacterial pneumonia (HABP),ventilator-associated bacterial pneumonia (VABP), or healthcare-associated bacterial pneumonia (HCABP) caused by Gram-negative pathogens

Secondary Objectives:

Key Secondary Objectives:

- To compare the clinical outcome of treatment with S-649266 with that of meropenem in subjects at Test of Cure (TOC)[1]
- To compare the microbiologic outcome of treatment with S-649266 with that of meropenem at TOC
- To compare Day 14 all-cause mortality of S-649266 with that of meropenem for superiority of S-649266

Other Secondary Objectives:

Efficacy:

- To compare the clinical outcome of treatment with S-649266 with that of meropenem in subjects at Early Assessment (EA)[2], End of Treatment (EOT)[3], and Follow-up (FU)
- To compare the microbiologic outcome of treatment with S-649266 with that of meropenem at EA, EOT, and FU
- To compare the all-cause mortality at Day 28 of subjects treated with S-649266 with that of subjects treated with meropenem
- To compare the all-cause mortality during treatment and the follow-up period (until End of Study [EOS])[4] of S 649266 with that of meropenem

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.

4 EOS is defined as the last day of the study

- To compare the resource utilization required for the 2 study treatments for the study-qualifying infection. This end point will not be included in the CSR, but it will be analyzed based upon a separate analytical plan after the conclusion of the study.

Safety:

- To assess the safety of S-649266

Study Design:

This is a Phase 3, multicenter (multinational), 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 the hospital will be randomized (1:1) to either S-649266, 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 for at least 5 days to subjects in both arms to provide coverage for methicillin-resistant *Staphylococcus aureus* (MRSA) and to maintain the study blind and, in the S-649266 arm, to provide coverage for Gram-positive bacteria.

Study Population:

Subjects with documented nosocomial pneumonia caused by a suspected Gram-negative pathogen(s) will be enrolled.

Key Inclusion Criteria:

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

1. Subjects 18 years or older at the time of signing informed consent
2. Subjects who have provided written informed consent or their informed consent has been provided by a legally authorized representative (Note: Country-specific rules and local ethics committee approval for legally authorized representative informed consent will determine whether or not and how a subject unable to comprehend or sign the informed consent is allowed to be enrolled in the study)
3. Subjects who meet the clinical diagnosis criteria for HABP/VABP/HCABP
4. All subjects must fulfill at least 1 of the following clinical criteria at Screening:
    a. New onset or worsening of pulmonary symptoms or signs, such as cough, dyspnea, tachypnea (eg, respiratory rate > 25 breaths/minute), expectorated sputum production, or requirement for mechanical ventilation
    b. Hypoxemia (eg, a partial pressure of oxygen [PaO_2] < 60 mm Hg while the subject is breathing room air, as determined by arterial blood gas [ABG], or worsening of the ratio of the PaO_2 to the fraction of inspired oxygen [PaO_2/FiO_2])
    c. Need for acute changes in the ventilator support system to enhance oxygenation, as determined by worsening oxygenation (ABG or PaO_2/FiO_2) or needed changes in the amount of positive end-expiratory pressure

d. New onset of or increase in (quantity or characteristics) suctioned respiratory secretions, demonstrating evidence of inflammation and absence of contamination

5. All subjects must have at least 1 of the following signs:
   a. Documented fever (ie, core body temperature [tympanic, rectal, esophageal] ≥ 38°C [100.4°F], oral temperature ≥ 37.5°C, or axillary temperature ≥ 37°C)
   b. Hypothermia (ie, core body temperature [tympanic, rectal, esophageal] ≤ 35°C [95.0°F], oral temperature ≤ 35.5°C and axillary temperature ≤ 36°C)
   c. Leukocytosis with a total peripheral white blood cell (WBC) count ≥ 10,000 cells/mm^3
   d. Leukopenia with total peripheral WBC count ≤ 4500 cells/mm^3
   e. Greater than 15% immature neutrophils (bands) noted on peripheral blood smear
6. All subjects must have a chest radiograph during Screening or have a previous chest radiograph within 48 hours prior to randomization showing the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia. A computed tomography (CT) scan in the same time window showing the same findings could also be acceptable.
7. All subjects must have a suspected Gram-negative infection involving the lower respiratory tract by 1 or more of the following:
   a. Gram stain of lower respiratory secretions showing Gram-negative bacteria, either alone or mixed with Gram-positive bacteria at or within 72 hours prior to randomization
   b. Microbiologic culture of respiratory tract secretions within 72 hours prior to randomization identifying Gram-negative aerobic bacteria
   c. Other diagnostic tests, including molecular tests, which provide evidence of Gram-negative bacterial infection of the lower respiratory tract
   d. Pneumonia highly suspected to be due to Gram-negative bacteria based on prior antibiotic use or local epidemiologic evidence of Gram-negative infection outbreak
8. Subject is male (no contraception required) or female and meets 1 of the following criteria:
   a. Surgically sterile (has had a hysterectomy and/or bilateral oophorectomy, or a bilateral salpingectomy or tubal ligation for the purpose of contraception for at least 6 weeks with appropriate documentation of such surgery)
   b. Postmenopausal (defined as older than 45 years of age with cessation of regular menstrual periods for at least 6 months and a follicle-stimulating hormone level of > 40 mIU/mL, or amenorrhea for at least 12 months)
   c. Of childbearing potential and using combined (estrogen and progestogen) or progestogen-only hormonal contraception associated with inhibition of ovulation (including oral, intravaginal, injectable, implantable, and

transdermal contraceptives), or an intrauterine device, or intrauterine hormone-releasing system for the entire duration of the study

d. Of childbearing potential and practicing abstinence as a preferred and usual life style and agrees to continue practicing abstinence from screening for the entire duration of the study
e. Of childbearing potential and whose sole heterosexual partner has been successfully vasectomized and agrees to not have other heterosexual partners for the entire duration of the study

9. Subjects who failed empiric therapy will be allowed in this study. However, confirmation of both clinical and microbiological failure is necessary.
   a. Clinical failure: An investigator needs to confirm clinical failure of empiric treatment by clinically available information such as vital signs, physical examinations, laboratory data, and/or imaging
   b. Microbiological failure: Respiratory specimens from a subject need to meet either i OR ii:
      i. The lower respiratory tract specimen taken at the time of or before empiric therapy shows that the pathogen cultured is a Gram-negative aerobic bacteria, and the pathogens are resistant or intermediate to all the empiric antibiotics used
      ii. The pathogen from a specimen obtained after at least 2 calendar days of the empiric antibiotic regimen demonstrates that it is a Gram-negative aerobe, or shown in Gram stain as Gram-negative bacteria

Exclusion Criteria

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

1. Subjects who have known or suspected community-acquired bacterial pneumonia, atypical pneumonia, viral pneumonia, or chemical pneumonia (including aspiration of gastric contents, inhalation injury)
2. Subjects who have a history of any hypersensitivity to cephalosporins or to carbapenems, or severe hypersensitivity to any other type of β-lactams other than cephalosporins and carbapenems (eg, penicillins, monobactams), or hypersensitivity to linezolid (Note: For β-lactams, a history of a mild rash followed by uneventful re-exposure is not a contraindication to enrollment)
3. Subjects with a Gram-negative infection caused by a carbapenem-resistant pathogen, if known at the time of randomization (Note: Subjects who have a carbapenem-resistant pathogen identified after randomization should be evaluated clinically before discontinuation of study treatment.)
4. Subjects with coinfection caused by invasive aspergillosis, mucormycosis or other highly lethal mold
5. Subjects who have central nervous system infection (eg, meningitis, brain abscess, shunt infection)
6. Subjects with cystic fibrosis

7. Subjects in refractory septic shock, defined as persistent hypotension despite adequate fluid resuscitation or despite vasopressive therapy at the time of randomization
8. Subjects with neutropenia (ie, polymorphonuclear neutrophils < 500 cells/μL)
9. Female subjects who have a positive pregnancy test at Screening, who are lactating, or who refuse to use 1 of the previously specified methods of contraception
10. Subjects with an Acute Physiology and Chronic Health Evaluation II (APACHE) II score of > 35
11. Subjects who have received potentially effective antibiotic therapy for a continuous duration of more than 24 hours during the previous 72 hours prior to randomization (Note: Subjects failing empiric therapy as defined in inclusion criterion 9 may be eligible for inclusion.)
12. Subjects with any condition or circumstance that, in the opinion of the investigator, would compromise the safety of the subject or the quality of the study data
13. Subjects receiving peritoneal dialysis (hemofiltration and hemodialysis are permitted)
14. Subjects requiring continued treatment with methotrexate, procainamide, probenecid, monoamine oxidase inhibitors, or valproic acid (see Section 5.2)
15. Subjects who have received another investigational drug or device within 30 days prior to study entry
16. Subjects who have previously been randomized in this study or have previously received S-649266
17. Subjects with 1 or more of the following laboratory abnormalities in baseline specimens: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, or total bilirubin level > 3 times the upper limit of normal (ULN), platelet count < 40,000/μL
18. Subjects with bronchiectasis with symptoms of persistent or recurrent bronchial infection related to irreversibly damaged and dilated bronchi; namely, subjects with clinical bronchiectasis
19. Subjects with lung abscesses

Test Drug, Dose, and Mode of Administration:

S-649266 (cefiderocol), 2 g, is to be administered intravenously q8h as a 3-hour infusion in subjects with normal renal function. Dose adjustment for renal function or dialysis is required, and the dosages established by clinical testing are presented in the protocol. The solution volume for infusion must be at least 100 mL.

Control Treatment, Dose, and Mode of Administration:

The control population will be treated with meropenem. The dosing regimen will be 2 g as a 3-hour infusion q8h. Dosage adjustment for renal function is required. The solution volume for infusion must be at least 100 mL.

Concomitant Linezolid Treatment, Dose, and Mode of Administration:

Linezolid 600 mg will be administered intravenously every 12 hours (q12h) over 30 minutes to 2 hours concomitantly to provide coverage for Gram-positive bacteria in the S-649266 arm, to provide coverage for MRSA in both study arms, and to maintain the study blind. Linezolid can be discontinued after 5 days if a subject's lower respiratory tract specimens do not provide evidence of Gram-positive infection when appropriate lower respiratory tract specimens have been obtained, and the subject is not at high risk for MRSA infection (eg, no prior known MRSA colonization in the lower airway, no prior MRSA pneumonia in the past 6 months, or low prevalence (< 10% to 20%) of MRSA in the healthcare facility, etc). If a subject's lower respiratory tract specimens demonstrate Gram-positive infection, if respiratory specimens have not been obtained, or if a subject is at high risk for MRSA infection, then linezolid should be administered for the entire treatment period of 7 to 14 days along with S-649266 or meropenem.

Duration of Treatment:

The treatment duration for S-649266 or meropenem is anticipated to be 7 to 14 days, which is consistent with published treatment guidelines for HABP/VABP/HCABP infections. Based on the investigator's clinical assessment of the subject and a clear reason being documented in the electronic case report form, treatment may be extended up to 21 days. All study treatments are to be administered in the hospital.

Prohibited Concomitant Therapy:

- Systemic antibiotics, other than linezolid, meropenem, and S-649266, 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

Efficacy Assessment:

In addition to the 14-day all-cause mortality (primary efficacy endpoint), both clinical and microbiological outcomes will be assessed by the investigator at EA, EOT, TOC, and FU. If case study treatment duration is extended beyond 14 days, an additional clinical and microbiological outcome will be assessed on Day 14.

Pharmacokinetic Assessments:

All subjects will have blood drawn for sparse sampling of plasma concentrations of S-649266 for pharmacokinetic assessment. Pharmacokinetic blood sampling will preferably be performed on Day 3 or 4. The following is the schedule for the sampling time points:

(1) Just prior to the start of the 3-hour infusion

(2) 1 hour after the start of infusion

(3) Before the end of infusion

(4) 1 hour after the end of infusion

The actual sampling date and time will be recorded.

The pharmacokinetic sampling will be repeated when/if the drug dosage was changed due

to changes in renal function determined at EA; this should occur 24 to 72 hours after the change in dosing regimen.

In the case of premature EOT, a single blood sampling should be performed, if possible, as soon as possible at EOT (within 24 hours), which is defined as receiving < 7 days of intravenous treatment with either S-649266 or meropenem.

Safety Assessments:

Subject safety will be assessed from the time of having signed informed consent to the end of the study by identifying adverse events (AEs) with the addition of physical and laboratory evaluations, which include multiple electrocardiograms obtained early in the treatment with study drug.

In case treatment duration is extended beyond 14 days, additional safety assessments will be conducted on Day 14. Safety surveillance will extend up to 28 days after the last dose of the drug treatment.

Statistical Methods:

For the primary efficacy endpoint, the adjusted estimates of the difference in the all-cause mortality at Day 14 between S-649266 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. The CMH weights will be calculated with the stratification factor: APACHE II score (≤ 15 and ≥ 16).

Sample Size:

The study design and the primary objective are based on a 12.5% noninferiority margin to exclude the possibility that S-649266 is more than 12.5% inferior to meropenem for the endpoint of all-cause mortality at Day 14.

A sample size of 244 evaluable subjects (122 evaluable subjects in the S-649266 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 nonevaluable, 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 nonevaluable 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 may perform a blinded re-estimation of sample size if deemed necessary.

Stratification at Randomization:

Randomization will be performed by the stratified randomization method using the infection diagnosis (HABP/VABP/HCABP) and APACHE II score (≤ 15 and ≥ 16) as allocation factors.

Safety and Efficacy Evaluation:

When approximately 50 and 150 subjects have completed treatment and the FU visit, an evaluation of safety and efficacy data will be performed by the Data Safety Monitoring Board (DSMB) according to the DSMB charter. After the review, the DSMB will communicate their recommendation(s) to the sponsor.

Number of Study Sites/Countries:

It is estimated that approximately 135 study sites from around the world will participate in this clinical study.

Study Duration:

Study duration for individual subjects: approximately 5 to 7 weeks

Planned duration of the study: approximately 26 months (24 months for enrollment and 5 to 7 weeks to complete the study)

Date of Original (Version 1): 02 Aug 2016

Date of Latest Amendment: 22 Feb 2019

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LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

$\%fT_{>MIC}$	percentage of the dosing interval for which the free-drug concentration in plasma exceeds the minimum inhibitory concentration
ΔΔQTcF	baseline and placebo corrected QTc interval(s) calculated using Fridericia's correction
ABG	arterial blood gas
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
C_0	concentration at the end of infusion
CI	confidence interval
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CPIS	Clinical Pulmonary Infection Score
CrCl	creatinine clearance
CRO	contract research organization
CT	computed tomography
cUTI	complicated urinary tract infection
DDI	drug-drug interaction
DMPK	drug metabolism and pharmacokinetics
DSMB	Data Safety Monitoring Board
EA	Early Assessment
ECG	electrocardiogram/electrocardiography
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELF	epithelial lining fluid
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
ETA	endotracheal aspiration
FDA	Food and Drug Administration

FiO_2	fraction of inspired oxygen
FU	Follow-up evaluation at end of treatment + 14 days
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
HABP	hospital-acquired bacterial pneumonia
HCABP	healthcare-associated bacterial pneumonia
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IEC	Institutional Ethics Committee
IgM	immunoglobulin M
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous
KPC	*Klebsiella pneumoniae* carbapenemase
LS	least squares
MATE	multidrug and toxin extrusion transporter
MATE2-K	multidrug and toxin extrusion protein 2
MDR	multidrug resistant
MDRD	modification of diet in renal disease
ME-PP	microbiological-evaluable per-protocol
MIC	minimum inhibitory concentration
mITT	modified intent-to-treat
MRSA	methicillin-resistant *Staphylococcus aureus*
NOAEL	no-observed-adverse-effect-level
OAT1	organic anion transporter 1
OAT3	organic anion transporter 3
OATP1B1	organic anion transporting polypeptide 1B1
OATP1B3	organic anion transporting polypeptide 1B3
OCT1	organic cation transporter 1
OCT2	organic cation transporter 2
P-gp	P-glycoprotein
PaO_2	partial pressure of oxygen
PD	pharmacodynamic
PK	pharmacokinetic
PT-INR	prothrombin time-international normalized ratio
PSB	protected specimen brush

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
sCR	serum creatinine concentration
SOFA	Sequential Organ Failure Assessment
SmPC or SPC	Summary of Product Characteristics
TBL	total bilirubin level
TEAE	treatment-emergent adverse event
TOC	Test of Cure
TQT	thorough QT
TQTc	corrected thorough QT/QTc
uCr	urinary creatinine concentration
ULN	upper limit of normal
VABP	ventilator-associated bacterial pneumonia
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary
XDR	extensively drug-resistant

GLOSSARY

Augmented renal clearance (ARC)	Augmented renal clearance describes a hyperdynamic cardiovascular state as a consequence of systemic inflammatory response associated with increased perfusion of the kidneys resulting in increases in the glomerular filtration rate and enhanced renal elimination of circulating solutes, including antibiotics. This phenomenon is known as renal hyperfiltration, or ARC. In this protocol, ARC is defined as estimated glomerular filtration rate ($\geq$ 90 mL/min/1.73 m^2) and a creatinine clearance (CrCl > 120 mL/min).
Carbapenem resistance	Carbapenem resistance is defined by the in vitro susceptibility phenotype (minimum inhibitory concentration [MIC], E-test, disc diffusion) and subject to the approved breakpoints for carbapenems in the respective countries. For this study, intermediate breakpoints to imipenem/cilastatin, doripenem, or meropenem are classified as carbapenem-susceptible.
Comparator drug	Comparator drug refers to meropenem, which is an antibiotic approved by regulatory agencies for the treatment of bacterial infections.
Concomitant antibiotic	A concomitant antibiotic is an antibiotic added to the primary Gram-negative antibiotic treatment regimen to treat Gram-positive bacterial infections. Only linezolid will be allowed and used in both treatment arms.
Effective antibiotic	The term “effective antibiotic” refers to an antibiotic to which the specific pathogen is susceptible based on in vitro susceptibility test methods performed by the local microbiology laboratory.
Nosocomial infection	A nosocomial infection is an infection that is contracted from the environment or staff of a healthcare facility. It can be spread in the hospital environment, nursing home environment, rehabilitation facility, clinic, or other clinical settings.
Study drug	Study drug refers to S-649266
Study treatment	Study treatment refers to either S-649266 or meropenem therapy and includes the use of linezolid in both treatment groups.

1. INTRODUCTION

1.1 Background and Rationale

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

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

Although most reports of β-lactam resistance focus on hydrolyzing enzymes, 2 other mechanisms of resistance are important when considering the overall phenotype of Gram-negative resistance among the β-lactam classes and other classes of antibiotics. These include porin channel mutants (entrance channels for antibiotics and important bacterial nutrients) and efflux pumps (exit channels with active excretion mechanisms for removal of antibiotics from the bacterial cells). They are particularly prevalent among XDR *P. aeruginosa* [2, 3]. Not infrequently, more than 1 β-lactam resistance mechanisms exist in the same bacterial strain.

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

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

S-649266 has an approved international nonproprietary name: cefiderocol. For purposes of this protocol, S-649266 will be used to refer to the study drug.

S-649266 is being developed to address the unmet medical need to treat carbapenem-resistant infections caused by Gram-negative bacteria, including Enterobacteriaceae, *Pseudomonas, Stenotrophomonas*, and *Acinetobacter* species independent of the underlying mechanism of carbapenem resistance. Although S-649266 was designed to have bacterial-killing ability for carbapenem-resistant species of Gram-negative bacteria, it also has improved bacterial-killing ability for common community-acquired Gram-negative infections, as demonstrated by reduced minimum inhibitory concentration (MIC) values (for additional information refer to the current Investigator's Brochure).

1.2 Biological Features of S-649266 for Injection

S-649266 is an injectable siderophore cephalosporin discovered and being developed by Shionogi & Co., Ltd., Osaka, Japan. The antibacterial activity of S-649266 is based on the inhibition of Gram-negative bacterial cell wall synthesis.

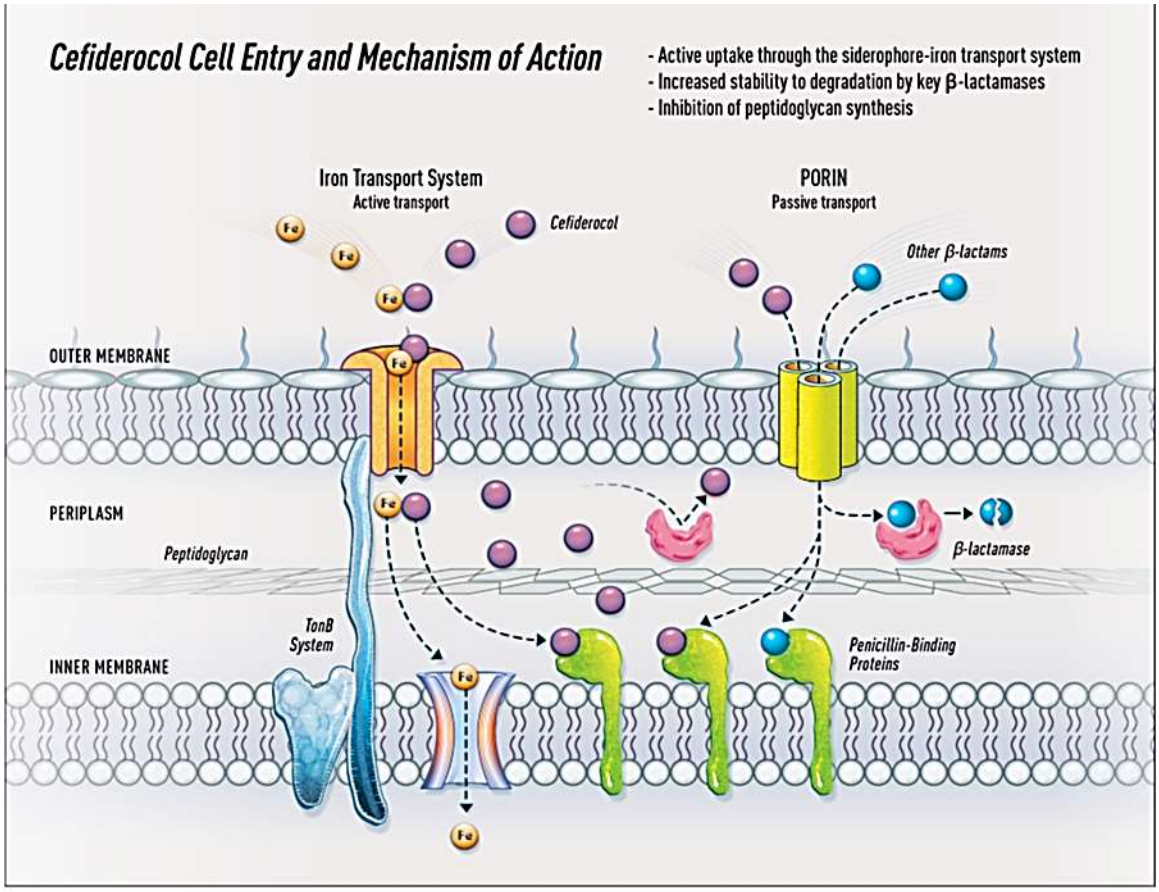
The chemical structure of S-649266 is similar to cefepime, which is a fourth-generation cephalosporin with an extended spectrum of activity against Gram-positive and Gram-negative bacteria with greater activity against both types of organisms than third-generation agents. The major difference in the chemical structure of S-649266 compared with cefepime is the presence of a catechol group on the side chain at position 3. S-649266 also has a pyrrolidinium group in the side chain at position 3 and a carboxypropanoxyimino group in the side chain at position 7 of the cephem nucleus. As a consequence of its structure, S-649266 has the following features in addition to the basic mechanism of action to inhibit cell wall synthesis:

1. A unique mode of action, which enhances entry into the periplasmic space of Gram-negative aerobic bacteria through the outer cell membrane. S-649266 forms complexes with trivalent iron and is transported via the active iron transport system common to Gram-negative bacteria. In this way, it also overcomes other mechanisms of resistance such as porin channel loss and efflux pumps.
2. Enhanced stability against BLA enzymes, including carbapenemases of the serine or metallo-BLA classes.
3. Enhanced activity against aerobic Gram-negative bacteria, especially Enterobacteriaceae, particularly *K. pneumoniae* and *E. coli*, and the nonfermenters *P. aeruginosa, S. maltophilia*, and *A. baumannii*.
4. No activity against Gram-positive bacteria and anaerobic bacteria.

The host's innate immune response to bacterial infection is to remove or severely limit the available free iron, an essential cation for bacterial growth [6]. In response, bacteria upregulate the production of extracellular molecules called siderophores that scavenge for available free iron [7]. S-649266 is a siderophore compound that binds free iron, and this antibiotic-iron complex is transported through the outer membrane of Gram-negative

bacteria into the periplasmic space using the bacteria's active siderophore transport system [2, 6-11]. A graphic depiction of this process is presented in Figure 1-1. This process achieves bactericidal concentrations at relatively low blood concentrations of S-649266. Once inside the periplasmic space of the Gram-negative bacteria, S-649266 is resistant to the usual mechanisms of degradation of β-lactam or carbapenem antibiotics by bacterial BLAs. The primary bactericidal activity is due to inhibition of bacterial cell wall synthesis.

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



Source: Shionogi Inc.

The greatest current unmet medical need is in the treatment of bacterial infections caused by MDR aerobic Gram-negative bacilli, broadly including the Enterobacteriaceae and the nonfermenters *P. aeruginosa, S. maltophilia,* and *A. baumannii*. Multidrug resistant bacteria, defined as > 3 class antibiotic resistance, include most Enterobacteriaceae producing AmpC, extended-spectrum BLAs, and serine BLAs. While they may be resistant to penicillins, cephalosporins, fluoroquinolones, and aminoglycosides, they have, for the most part, remained susceptible to carbapenems [2, 10, 11]. More recently, these same Enterobacteriaceae, particularly *K. pneumoniae* and *E. coli*, have acquired serine KPCs, oxacillinases, and metallo-BLAs (eg, Verona integron-encoded

metallo-BLA, imipenemase, and New Delhi metallo-BLA-1) capable of hydrolyzing carbapenems [12-14]. Most of these bacteria remain susceptible only to polymyxins (polymyxin B or colistin), and thus should be considered XDR, not just MDR. The nonfermenters *P. aeruginosa, S. maltophilia,* and *A. baumannii* have also acquired carbapenemases and are also considered XDR bacteria [15]. Rarely, these XDR pathogens may also be resistant to polymyxins, and, therefore, can be considered pandrug resistant organisms, defined as resistant to all classes [15, 16].

The principal objective for S-649266 clinical development is to demonstrate efficacy for the treatment of serious, life-threatening infections caused by Gram-negative bacteria, including Enterobacteriaceae and nonfermenters, such as *P. aeruginosa, S. maltophilia,* and *A. baumannii*. One of the most serious of these infections is pneumonia. Gram-negative pneumonia is almost always nosocomial, meaning it is associated with prior or current hospitalization or other contact with healthcare services [17]. Variably defined as hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), or healthcare-associated bacterial pneumonia (HCABP), when the infection is caused by Gram-negative bacteria, the outcomes are especially dire, with mortality rates approaching 60% [17-21]. Increasing antibiotic resistance among Gram-negative organisms, particularly that to aminoglycosides, fluoroquinolones, and cephalosporins, has limited therapeutic options to carbapenems and polymyxins [17-25]. Clinical trials in HABP/VABP/HCABP are particularly challenging due to the severity of illness, preexisting comorbidities, and controversies over study endpoints [26]. Recent clinical trials have failed to meet predefined endpoints for noninferiority (tigecycline, doripenem). Despite these setbacks, the need for new antibiotic treatments for Gram-negative infections has resulted in renewed interest in HABP/VABP as an important area for clinical investigation. Both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have updated their clinical trial guidelines for these indications [27, 28].

1.3 Nonclinical Experience

In vitro, S-649266 showed potent antibacterial activity against carbapenem-resistant Enterobacteriaceae, including metallo-BLA producing isolates, MDR *A. baumannii*, and MDR *P. aeruginosa*. S-649266 also showed more robust antibacterial activity than other β-lactam antibiotics in systemic, lung, urinary tract, and subcutaneous animal models of infection due to MDR *P. aeruginosa*, carbapenem-resistant *A. baumannii*, or enteric bacteria, such as extended-spectrum BLA-producing *E. coli* and *K. pneumoniae*.

The safety and drug metabolism and pharmacokinetics (DMPK) profiles of S-649266 have been evaluated in toxicity studies (general toxicity, reproductive and developmental toxicity, genotoxicity, and antigenicity), safety pharmacology studies, and DMPK studies. No severe toxic changes were observed in the rat and monkey 2-week and 1-month intravenous toxicity studies, the monkey 3-month intravenous toxicity study, the safety pharmacology studies, and the antigenicity study.

In the rat 3-month intravenous toxicity study (doses levels: 0, 300, 1000, and 1500 mg/kg/day), convulsions and subsequent deaths were noted at 1000 and

1500 mg/kg/day. In order to assess more in depth the dose-response relationship of convulsions between 300 and 1000 mg/kg/day, a supplemental 3-month intravenous toxicity study was conducted in rats with intermediate dose levels at 500 and 750 mg/kg/day. The study showed neither convulsion nor death at either dose level. Overall, the no-observed-adverse-effect-level (NOAEL) was judged to be 750 mg/kg/day in rat 3-month toxicity studies. The concentration at the end of infusion (C_0) value at 750 mg/kg (1500 or 1610 µg/mL, values of the last day of dosing in the supplemental 3-month toxicity study) was approximately 17-fold of the maximum plasma concentration (C_{max}) value in humans (89.7 µg/mL from the thorough QT [TQT] study [R2116] at the intended clinical dosing regimen (2 g, infused over 3 hours, 3 times daily).

In the monkey cardiovascular safety pharmacology study and 2-week, 1-month, and 3-month intravenous toxicity studies, an increase in the corrected QT interval (QTc) was observed at the highest doses of 600 or 1000 mg/kg; no QTc interval prolongation was observed at the next lower dose of 300 mg/kg in any of these studies, which was considered to be the study's NOAEL, and provides approximately a 9- to 10-fold margin relative to the C_{max} of S-649266 in the currently proposed study (eg, C_0 of 770 to 876 µg/mL, values on the last day of dosing in the repeat-dose toxicity studies vs the C_{max} of 89.7 µg/mL at the intended clinical dose of 2 g, infused over 3 hours, from the TQT study [R2116]). No dose-dependent increases in the QTc interval were observed in these studies. The TQT study, which was subsequently performed, was negative (ie, without any clinically significant increase in the QTc interval of regulatory concern [refer to Section 1.4.])

In a fertility and early embryonic development study in rats treated intravenously with up to 1000 mg/kg/day of S-649266, no adverse findings were observed.

In studies for effects on embryo-fetal development in rats (dose levels: 0, 100, 300, and 1000 mg/kg/day, intravenous injection) and mice (dose levels: 0 , 500, 1000, and 2000 mg/kg/day [0, 250, 500, or 1000 mg/kg/injection, twice a day]; 6 hours apart subcutaneous injection), there were no deaths in dams and no treatment-related changes in fetal viability, including external, visceral, or skeletal morphology of fetuses. As described above, there was no evidence of embryo-fetal lethality or teratogenicity in mice or rats.

In a pre- and postnatal development study in rats treated intravenously with up to 1000 mg/kg/day of S-649266, no effects on parturition and nursing on dams, and pre- and postnatal development of offspring were observed and the NOAEL was judged to be 1000 mg/kg/day for pre- and postnatal development in offspring.

Positive reactions were observed in the in vitro chromosomal aberration tests and mouse lymphoma cell line (L5178Y tk+/− 3.7.2C) assay at high drug concentrations, but genotoxicity risk of S-649266 in humans was judged to be low, because the results of the bacterial reverse mutation test and the hypoxanthine-guanine phosphoribosyltransferase gene mutation assay were negative. In addition, the results of the in vivo rat micronucleus test and the rat comet assay were negative.

In the rat micronucleus test, death and acute symptoms, including convulsions, occurred only at the highest single dose (2000 mg/kg). Because death and these acute symptoms did not occur at 1000 mg/kg twice a day (total 2000 mg/kg), they were judged to be caused by high plasma concentration immediately after administration rather than total drug exposure represented by area under the concentration-time curve (AUC).

Based on the DMPK studies in rats and monkeys, S-649266 is rapidly and widely distributed in the whole body and is mainly excreted in urine as unchanged drug. In addition, S-649266 did not inhibit major cytochrome P450 drug metabolizing enzymes. S-649266 is not an inhibitor of P-glycoprotein (P-gp).

As S-649266 is not a substrate for human P-gp, organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3), organic cation transporter 2 (OCT2), multidrug and toxin extrusion 1 (MATE1), or multidrug and toxin extrusion protein 2 (MATE2-K), the risk for drug-drug interactions (DDIs) with S-649266 mediated by these transporters is low. Since S-649266 is not an inhibitor for human P-gp or bile salt export pump, the risk of a DDI with S-649266 as a perturbator of these transporters is low. S-649266, in a concentration-dependent manner, reduced the uptake and transcellular transport activity of each typical substrate via breast cancer resistance protein, organic anion transporting polypeptide 1B1, organic anion transporting polypeptide 1B3 (OATP1B3), organic cation transporter 1 (OCT1), MATE1, MATE2-K, OAT1, OAT3, and OCT2. The half maximal inhibitory concentration values for OAT1, OAT3, OCT1, OCT2, OATP1B3, and MATE2-K were calculated to be 141, 292, 1550, 2170, 2570, and 1230 μmol/L. The free concentration of C_{max} value at the intended clinical dose (2 g, 3 times daily) was calculated to be 57.4 μmol/L (43.2 μg/mL) by multiplying the C_{max} (119 μmol/L [89.7 μg/mL]) and the in vitro free fraction ratio of S-649266 in human at 100 μg/mL (48.2%). S-649266 was suggested to have DDI potential on OAT1, OAT3, OCT1, OCT2, OATP1B3, and MATE2-K from the evaluation conducted in accordance with FDA draft guidance [29] and EMA guideline [30] of drug interaction, and therefore, a clinical DDI study was performed (R2115). Topline data from that DDI study showed no significant effects on the pharmacokinetics of furosemide (an OAT1 and OAT3 substrate) or metformin (an OCT1, OCT2, and MATE2-K substrate). Coadministration of S-649266 and rosuvastatin (an OATP1B3 substrate) increased the AUC for rosuvastatin by 21%, but because it is unlikely that oral medications such as rosuvastatin, other statins, or medications that are OATP1B3 substrates will occur during a treatment course requiring intravenous antibiotics, the potential for a clinically meaningful outcome in the clinically setting is considered to be low.

1.3.1 Pharmacokinetics/Pharmacodynamics

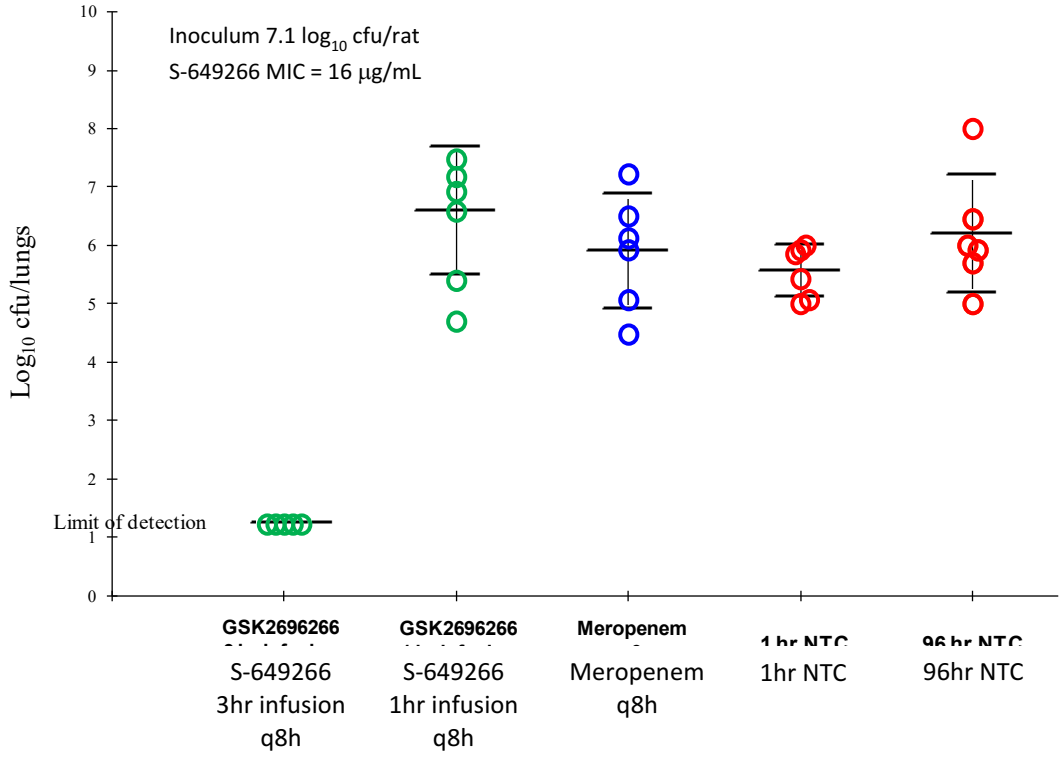
1.3.1.1 Animal Models of Efficacy

As with all β-lactams that target penicillin-binding proteins, the controlling pharmacodynamic (PD) parameter for S-649266 is the percentage of the dosing interval for which the free-drug concentration in plasma exceeds the minimum inhibitory concentration ($\%fT_{>MIC}$), and while the plasma pharmacokinetic measurements can

determine the drug exposure over time, corrected for protein binding, the MIC remains the key variable in determining %$fT_{>MIC}$.

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

Figure 1-2 Efficacy of S-649266 (Human 3- and 1-hr Infusion of 2 g IV q8h) Compared with Meropenem (Human 1 g IV q8h) Against *K. pneumoniae* VA-384 in a Respiratory Tract Infection Model in Cannulated Rats



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

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

The pharmacokinetics/pharmacodynamics (PK/PD) parameter required for efficacy was determined in a murine thigh model of infection caused by 16 strains of Gram-negative bacteria with widely divergent MICs. The %$fT_{>MIC}$ values of S-649266 required for a static effect and 1-$\log_{10}$ reduction were approximately 60% to 70% and 70% to 80%, respectively. The %$fT_{>MIC}$ values required for efficacy were similar among bacterial species (for additional information refer to the current version of Investigator's Brochure).

In summary, the nonclinical data support the clinical development of S-649266 as a potential human therapeutic agent against serious bacterial infections. The target PK/PD parameter is 70% to 80% $fT_{>MIC}$.

1.4 Clinical Experience

1.4.1 Phase 1

The safety and tolerability of S-649266 has been assessed in a total of 212 healthy adult subjects who participated in 6 clinical pharmacology studies (a single-and multiple-ascending dose study [Study 1203R2111], an intrapulmonary pharmacokinetic study [Study 1214R2112], a renal impairment study [Study 1222R2113], a mass balance study [Study 1516R2114], a thorough QT/QTc study [Study 1603R2116], and a 3-part drug interaction study [Study 1521R2115]). In these studies, healthy adult subjects or subjects with impaired renal function received single doses of S-649266 ranging from 100 to 4000 mg (4 g) or multiple doses of up to 2000 mg (2 g) for up to 10 days, infused intravenously over 1 or 3 hours. In general, S-649266 was safe and well tolerated in the clinical pharmacology studies. There were no treatment-related or dose-dependent trends in vital sign measurements, electrocardiogram/electrocardiography (ECG) parameters, or clinical laboratory test results. There were no deaths or serious adverse events (SAEs) reported in any study. Adverse events (AEs) occurred relatively infrequently, were mostly mild in severity, and almost all resolved spontaneously without intervention. There were no dose-dependent trends in the frequency or type of AEs reported.

S-649266 is primarily excreted unchanged (approximately 90%) in the urine (Study R2114), has a plasma half-life of 2.75 hours, and is associated with linear pharmacokinetics in the therapeutic dose range with little accumulation after multiple-dose administration. After administration of single 100- to 2000-mg (2 g) doses, infused over 1 hour (single ascending dose study [R2111]) and single 2- to 4-g doses, infused over 3 hours (thorough QT/QTc [TQTc] study [R2116]), the C_{max} and AUC of S-649266 increased in proportion to the dose. After administration of multiple 2-g doses of S-649266 q8h infused over 1 hour (once daily doses on Days 1 and 10 and q8h doses from Days 2 to 9), only a slight accumulation (1.05- to 1.16-fold) for the C_{max} and AUC of S-649266 was observed, and plasma concentrations of S-649266 reached steady state within 1 day of repeated administration [Study R2111]. After administration of a single 1000-mg (1-g) dose of [^{14}C]-S-649266, S-649266 was the major component in plasma, accounting for 92.27% of the plasma AUC for total radioactivity. A degradation product, pyrrolidine chlorobenzamide, accounted for 4.70% of the plasma AUC for plasma total radioactivity, with all other metabolites each accounting for < 2% of the plasma AUC for plasma total radioactivity [Study R2114]. The majority (98.6%) of total radioactivity was excreted unchanged in urine, with negligible amounts (2.8%) excreted in feces (Study R2114).

A Phase 1 study to assess the repolarization effects of S-649266 on the human heart was conducted as a TQTc study (Study R2116) in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E14 Guidance and subsequent Questions & Answers. The first part of the study

consisted of a sequential-group safety and tolerability study in which the safety of the supratherapeutic dose of S-649266 was confirmed. The second part of the study consisted of a thorough QTc study in which single 2-g (therapeutic) and 4-g (supratherapeutic) doses of S-649266 administered as 3-hour infusions were assessed along with placebo (to S-649266) and moxifloxacin (active control) in a double-blinded, crossover design in a total of 48 subjects.

The point estimates of the least squares (LS) means of baseline and placebo-corrected QTc intervals (ΔΔQTcF) calculated using Fridericia's correction for the 2- and the 4-g doses of S-649266 were < 5 msec and the upper bounds of the 1-sided 95% CI were < 10 msec at all postinitiation of the infusion time points. For the moxifloxacin treatment, a prolongation of the QTcF interval was observed for all time points from 1 to 10 hours postdose, confirming that a positive effect on the QTcF interval could be detected in the study (the lower bound of 1-sided 95% CI of LS means in the ΔΔQTcF > 5 msec). The results indicate that single 2- and 4-g doses of S-649266 did not prolong the ΔΔQTcF interval to a level of regulatory concern and met the criteria stipulated in the ICH E14 guideline associated with a negative TQT study.

1.4.2 Phase 2 and Phase 3

1.4.2.1 Phase 2 Complicated Urinary Tract Infections

A Phase 2 study of the safety and efficacy of S-649266 administered at a 2-g dose over a 1-hour infusion to 300 subjects with complicated urinary tract infections (cUTIs) has been completed (Study R2121). The results support the safety profile of S-649266 in a subject population using the same dose (2 g, q8h) proposed for this study.

1.4.2.2 Phase 3

A Phase 3 study of the safety and efficacy of S-649266 administered at a 2-g dose over a 3-hour infusion at 8-hour intervals in subjects with infections caused by carbapenem-resistant Gram-negative pathogens is ongoing (Study R2131). This randomized study (NCT02714595) is enrolling subjects with pneumonia, blood stream infections, or cUTIs determined to be resistant to carbapenems to compare S-649266 with best available therapy as selected by the investigator.

Refer to the current Investigator’s Brochure for additional details of completed studies.

2. STUDY OBJECTIVES

Hypothesis:

- All-cause mortality at Day 14 in subjects who receive S-649266 will not be inferior to subjects who receive meropenem if the upper bound of a 2-sided 95% CI for the difference in all-cause mortality at Day 14 between the 2 treatment groups (S-649266 and meropenem) is smaller than a noninferiority margin of 12.5%.

2.1 Primary Objective

- To compare all-cause mortality at Day 14 of subjects who receive S-649266 with that of subjects who receive the comparator, meropenem, in adults with hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), or healthcare-associated bacterial pneumonia (HCABP) caused by Gram-negative pathogens

2.2 Secondary Objectives

2.2.1 Key Secondary Objectives

- To compare the clinical outcome of treatment with S-649266 with that of meropenem in subjects at Test of Cure (TOC)[1]
- To compare the microbiologic outcome of treatment with S-649266 with that of meropenem at TOC
- To compare Day 14 all-cause mortality of S-649266 with that of meropenem for superiority of S-649266

2.2.2 Other Secondary Objectives

Efficacy:

- To compare the clinical outcome of treatment with S-649266 with that of meropenem in subjects at Early Assessment (EA)[2], End of Treatment (EOT)[3], and Follow-up (FU)
- To compare the microbiologic outcome of treatment with S-649266 with that of meropenem at EA, EOT, and FU
- To compare the all-cause mortality at Day 28 of subjects treated with S-649266 with that of subjects treated with meropenem
- To compare the all-cause mortality during treatment and the follow-up period (until End of Study [EOS])[4] of S-649266 with that of meropenem

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

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

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

4 EOS is defined as the last day of the study

- To compare the resource utilization required for the 2 study treatments for the study-qualifying infection. This end point will not be included in the CSR, but it will be analyzed based upon a separate analytical plan after the conclusion of the study.

Safety:

- To assess the safety of S-649266

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 3, multicenter (multinational), 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 the hospital will be randomized (1:1) to either S-649266, 2 g, administered intravenously over 3 hours, q8h or meropenem, 2 g, administered intravenously over 3 hours, q8h. Linezolid will be administered for at least 5 days to subjects in both arms to provide coverage for methicillin-resistant *Staphylococcus aureus* (MRSA), to maintain the study blind and, in the S-649266 arm, to provide coverage for Gram-positive bacteria.

Sequential oral antibiotic (step-down) therapy is not permitted by this protocol.

A subject's clinical status will be reviewed daily and will be formally evaluated at specified intervals for clinical assessment and safety during hospitalization and periodically during follow-up for approximately 28 days from EOT (ie, End of Study [EOS]). The end of the trial for this study is defined as the last visit of the last subject and is 28 days (± 3 days) after the EOT for that subject.

The study design is shown in Figure 3-1. The study time and events table is shown in Appendix 1.

Figure 3-1 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 Table 5-1 and Table 5-2)

3.2 Rationale for Study Design and Control Group

3.2.1 Rationale for Subject Population

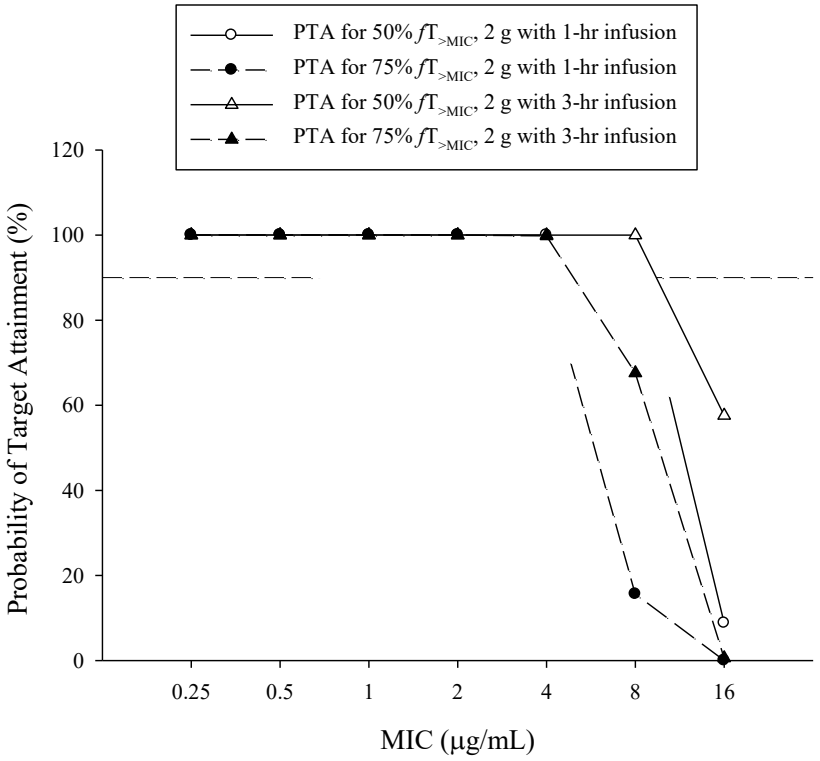
This study is designed to show that S-649266 is noninferior to the carbapenem, meropenem, which has a similar spectrum of Gram-negative activity and a similar dosing interval, in the treatment of subjects with HABP/VABP/HCABP caused by Gram-negative aerobic pathogens. The target pathogens do not include Gram-positive or anaerobic bacteria. Concomitant treatment with linezolid will be administered to subjects in both arms to provide coverage for MRSA and to maintain the study blind and, in the S-649266 arm, to provide coverage for Gram-positive bacteria.

3.2.2 S-649266 Dose Regimen

The dose and dosage regimen for this study were developed from extensive PK/PD analyses of treatment of infections in appropriate animal models and pharmacokinetic modeling based on human pharmacokinetics. The controlling PD parameter for S-649266 is $\%fT_{>MIC}$. Although the plasma pharmacokinetic measurements corrected for protein binding determines the drug exposure over time, the MIC remains the key variable in determining $\%fT_{>MIC}$. The dosage for this study was chosen to provide concentrations of plasma free drug sufficient to maintain the $\%fT_{>MIC}$ that had been established in the animal infection models to be bactericidal for Gram-negative bacteria, including carbapenem-resistant Enterobacteriaceae and carbapenem-resistant strains of *P. aeruginosa* and *A. baumannii* (see Section 1.3.1.1).

Monte Carlo simulations using a population pharmacokinetic model, which was developed with data from the ascending dose Phase 1 study (Study R2111), were performed to assess the dose regimens that would attain the PD target of 50% or 75% $fT_{>MIC}$ as free plasma concentrations over a dosing interval for at least 90% of the population. The probability of target attainment for the percentage of dosing interval over MIC with administration of 2 g q8h with 1- or 3-hour infusions is shown in Figure 3-2.

Figure 3-2 Probability of Target Attainment for 50% or 75% $fT_{>MIC}$



hr = hour; MIC = minimum inhibitory concentration; PTA = probability of target attainment; T = the length of the dosing interval in hours; % $fT_{>MIC}$ = percentage of the dosing interval for which the free-drug concentration in plasma exceeds the minimum inhibitory concentration

The results indicated that with administration of 2 g q8h with 1- or 3-hour infusions, more than 90% of subjects with normal renal function would achieve 50% $fT_{>MIC}$ at a MIC of 8 µg/mL and 75% $fT_{>MIC}$ at a MIC of 4 µg/mL. A 2-g q8h dosage regimen with a 3-hour infusion could be considered a potential treatment for > 90% of the target Gram-negative pathogens (each MIC_{90}: ≤ 4 µg/mL, for additional information refer to the current Investigator's Brochure).

A 2-g q8h 1-hour infusion dose was the maximum dose regimen administered for 10 days. The 2-g dose of S-649266 was well tolerated in Study R2111, and no significant AEs occurred. The 2-g q8h 1-hour infusion of S-649266 was administered to subjects in the recently completed cUTI study.

The proposed S-649266 dosage regimen for the treatment of HABP/VABP/HCABP with Gram-negative pathogens is 2 g q8h over a 3-hour infusion. Dosage adjustments for either impaired renal function or augmented renal clearance (ARC) are required in this study to allow for enrollment of subjects with significant comorbidities while maintaining the target drug exposure (Table 5-1).

A 2-g every 6 hours (q6h) dosage regimen with a 3-hour infusion is proposed for subjects with ARC, in which > 90% probability of target attainment would be expected against pathogens requiring an MIC of 4 µg/mL, as shown in Table 3-1.

Table 3-1 Probability of Target Attainment for Subjects with Augmented Renal Clearance

Dose Regimen	CrCl: 120 to 150 mL/min	CrCl: 150 to 200 mL/min
2 g, q8h, 3-hour infusion	82.0%	72.7%
2 g, q6h, 3-hour infusion	96.4%	94.1%

CrCl = creatinine clearance (calculated by Cockcroft-Gault equation); q6h = every 6 hours; q8h = every 8 hours
Interindividual variability of 40% was assumed.

3.2.3 Meropenem Dose Regimens

Because of the life-threatening nature of the protocol specified infections, a placebo-controlled study is not appropriate. Meropenem was chosen as the comparator given that it is listed by the American Thoracic Society/Infectious Disease Society guidelines of 2004 as an option for initial combination empiric therapy at a dosage of 1 g intravenously q8h in subjects with late-onset disease or risk factors for MDR pathogens [17].

The dosage of meropenem administered and the duration of treatment should take into account the type and severity of infection to be treated, and the clinical response to treatment. A dosage of up to 2 g given 3 times daily in adults and adolescents may be particularly appropriate when treating some types of infections, such as infections due to less susceptible bacterial species (eg, Enterobacteriaceae, *P. aeruginosa*, *S. maltophilia,* and *Acinetobacter spp*.) or very severe infections [18].

The efficacy of an antibiotic agent is dependent on its pharmacokinetic and pharmacodynamic properties [19,20]. The β-lactams are characterized by time-dependent bactericidal activity, which means that $\%fT_{>MIC}$ must be maintained for efficacy. For these agents, increasing the concentration does not necessarily increase the rate or extent of killing; best results are achieved by optimizing the duration of exposure to effective concentrations. Several investigations of carbapenem (eg, meropenem, ertapenem, and imipenem) bactericidal activity in animal models of infection have suggested that the PD target for maximal bactericidal activity is a $\%fT_{>MIC}$ of free drug of ~ 40% [21-24].

Monte Carlo simulation of the effects of other dosages of meropenem administered as a 3-hour infusion, compared with the standard 30-minute infusion, showed that prolonged

infusion increased the probability of conservative bactericidal target attainment (50% $fT_{>MIC}$) for *Acinetobacter* species and *P. aeruginosa.* For those pathogens, the highest target-attainment rates were obtained with a 3-hour infusion of 2 g of meropenem q8h.

The dosage of meropenem will be 2 g q8h infused intravenously over 3 hours to ensure the highest probability of bactericidal target attainment (40% $fT_{>MIC}$), which is important especially in less susceptible bacterial species. This approach is most appropriate especially when using meropenem as monotherapy in subjects with HABP/VABP/HCABP and risk factors for MDR pathogens or caused by less susceptible species, eg, Enterobacteriaceae, *P. aeruginosa*, *S. maltophilia,* and *Acinetobacter spp*.

Dosage adjustment for renal impairment will be done per label (see Table 5-2).

3.2.4 Linezolid Dose Regimens

Linezolid will be administered for at least 5 days to subjects in both arms to provide coverage for MRSA and to maintain the study blind and, in the S-649266 arm, to provide coverage for Gram-positive bacteria. The dosage is 600 mg intravenously every 12 hours (q12h). No dosage adjustment is required for impaired renal function as per the approved label. Linezolid can be discontinued after 5 days if the subject's lower respiratory tract specimens do not provide evidence of Gram-positive infection when appropriate lower respiratory tract specimens have been obtained, and the subject is not at high risk for MRSA infection (eg, no prior known MRSA colonization in the lower airway, no prior MRSA pneumonia in the past 6 months, low prevalence [< 10% to 20%] of MRSA in the healthcare facility, etc). If a subject's respiratory specimens demonstrate Gram-positive infection, if respiratory specimens have not been obtained, or if a subject is at high risk for MRSA infection, then linezolid should be administered for the entire treatment period of 7 to 14 days along with S-649266 or meropenem.

Linezolid should be administered by intravenously infusion over a period of 30 minutes to 2 hours, q12h. If linezolid is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each product.

3.2.5 Duration of Study Treatment

The treatment duration for S-649266 or meropenem is anticipated to be 7 days to 14 days, which is consistent with published treatment guidelines for serious infections [17, 25-28]. Treatment with linezolid will be the same as that for S-649266 or meropenem when a Gram-positive infection has been demonstrated in subject's lower respiratory tract specimens. Linezolid can be discontinued after 5 days when appropriate lower respiratory tract specimens have been obtained that do not provide evidence of Gram-positive infection and if the subject is not at high risk for MRSA infection. Based on the investigator's clinical assessment of the subject, treatment may be extended up to 21 days. The reason for the extension should be clearly documented in the electronic case report form (eCRF). All study treatments will be performed in the hospital.

3.3 Study Duration

3.3.1 Study Duration in Individual Subjects

The approximate timing for the subject-related activities during the study is up to 2 days for screening, 7 days to 14 days for treatment, and 28 days for post-treatment testing and safety follow-up. This gives a total study participation time from treatment initiation to EOS of approximately 5 weeks to 7 weeks for each subject.

3.3.2 Planned Study Duration for the Study

It is anticipated that it will take approximately 24 months to complete enrollment and an additional 5 to 7 weeks for the last subject to complete the study.

4. STUDY POPULATION SELECTION

4.1 Study Population

Male or female subjects 18 years of age or older who have a documented nosocomial pneumonia (HABP/VABP/HCABP) caused by an aerobic Gram-negative pathogen only, or in combination with an aerobic Gram-positive or anaerobic pathogen, and who require hospitalization for the parenteral (intravenous) treatment of the infection may be enrolled in the study. The sponsor will monitor the blinded mortality rate when 50 subjects have completed the study, and if the mortality rate is deemed too low (≤ 8%) compared with the assumption of 10%, the lower limit of the acceptable Acute Physiology and Chronic Health Evaluation II (APACHE II) score will be set to ≥ 8 (see Exclusion Criterion 10).

HABP/VABP/HCABP Definitions

HABP is defined as an acute bacterial pneumonia in a subject hospitalized for more than 48 hours or developing within 7 days after discharge from a hospital. Subjects may experience acute respiratory failure and require mechanical ventilation for HABP (ventilated-HABP).

VABP is defined as an acute bacterial pneumonia in a subject receiving mechanical ventilation via an endotracheal (or nasotracheal) tube for a minimum of 48 hours.

HCABP is defined as an acute bacterial pneumonia in a subject who meets any of the following criteria:

- hospitalized in an acute care hospital for 2 or more days within 90 days of the HCABP
- residing in a nursing home or long-term care facility
- received intravenous antibiotic therapy or chemotherapy
- received wound care within the past 30 days of the current infection
- attended a hospital clinic or hemodialysis clinic

4.2 Inclusion Criteria

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

1. Subjects 18 years or older at the time of signing informed consent
2. Subjects who have provided written informed consent or their informed consent has been provided by a legally authorized representative (Note: Country-specific rules and local ethics committee approval for legally authorized representative informed consent will determine whether or not and how a subject unable to comprehend or sign the informed consent is allowed to be enrolled in the study)
3. Subjects who meet the clinical diagnosis criteria for HABP/VABP/HCABP (see above)
4. All subjects must fulfill at least 1 of the following clinical criteria at Screening:
   a. New onset or worsening of pulmonary symptoms or signs, such as cough, dyspnea, tachypnea (eg, respiratory rate > 25 breaths/minute), expectorated sputum production, or requirement for mechanical ventilation
   b. Hypoxemia (eg, a partial pressure of oxygen [PaO_2] < 60 mm Hg while the subject is breathing room air, as determined by arterial blood gas [ABG], or worsening of the ratio of the PaO_2 to the fraction of inspired oxygen [PaO_2/FiO_2])
   c. Need for acute changes in the ventilator support system to enhance oxygenation, as determined by worsening oxygenation (ABG or PaO_2/FiO_2) or needed changes in the amount of positive end-expiratory pressure
   d. New onset of or increase in (quantity or characteristics) suctioned respiratory secretions, demonstrating evidence of inflammation and absence of contamination
5. All subjects must have at least 1 of the following signs:
   a. Documented fever (ie, core body temperature [tympanic, rectal, esophageal] ≥ 38°C [100.4°F], oral temperature ≥ 37.5°C, or axillary temperature ≥ 37°C)
   b. Hypothermia (ie, core body temperature [tympanic, rectal, esophageal] ≤ 35°C [95.0°F], oral temperature ≤ 35.5°C and axillary temperature ≤ 36°C)
   c. Leukocytosis with a total peripheral white blood cell (WBC) count ≥ 10,000 cells/mm^3
   d. Leukopenia with total peripheral WBC count ≤ 4500 cells/mm^3
   e. Greater than 15% immature neutrophils (bands) noted on peripheral blood smear
6. All subjects must have a chest radiograph during screening or have a previous chest radiograph within 48 hours prior to randomization showing the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia. A computed tomography (CT) scan in the same time window showing the same findings could also be acceptable.
7. All subjects must have a suspected Gram-negative infection involving the lower respiratory tract by 1 or more of the following:

a. Gram stain of lower respiratory secretions showing Gram-negative bacteria, either alone or mixed with Gram-positive bacteria at or within 72 hours prior to randomization
b. Microbiologic culture of respiratory tract secretions within 72 hours prior to randomization identifying Gram-negative aerobic bacteria
c. Other diagnostic tests, including molecular tests, which provide evidence of Gram-negative bacterial infection of the lower respiratory tract
d. Pneumonia highly suspected to be due to Gram-negative bacteria based on prior antibiotic use or local epidemiologic evidence of Gram-negative infection outbreak

8. Subject is male (no contraception required) or female and meets 1 of the following criteria:
   a. Surgically sterile (has had a hysterectomy and/or bilateral oophorectomy, or a bilateral salpingectomy or tubal ligation for the purpose of contraception for at least 6 weeks with appropriate documentation of such surgery)
   b. Postmenopausal (defined as older than 45 years of age with cessation of regular menstrual periods for at least 6 months and a follicle-stimulating hormone level of > 40 mIU/mL, or amenorrhea for at least 12 months)
   c. Of childbearing potential and using combined (estrogen and progestogen) or progestogen-only hormonal contraception associated with inhibition of ovulation (including oral, intravaginal, injectable, implantable, and transdermal contraceptives), or an intrauterine device, or intrauterine hormone-releasing system for the entire duration of the study
   d. Of childbearing potential and practicing abstinence as a preferred and usual life style and agrees to continue practicing abstinence from screening for the entire duration of the study
   e. Of childbearing potential and whose sole heterosexual partner has been successfully vasectomized and agrees to not have other heterosexual partners for the entire duration of the study
9. Subjects who failed empiric therapy will be allowed in this study. However, confirmation of both clinical and microbiological failure is necessary (see flow chart in Appendix 7):
   a. Clinical failure: An investigator needs to confirm clinical failure of empiric treatment by clinically available information such as vital signs, physical examinations, laboratory data, and/or imaging
   b. Microbiological failure: Respiratory specimens from a subject need to meet either i OR ii:
      i. The lower respiratory tract specimen taken at the time of or before empiric therapy shows that the pathogen cultured is Gram-negative aerobic bacteria and the pathogens are resistant or intermediate to all the empiric antibiotics used

ii. The pathogen from a specimen obtained after at least 2 calendar days of the empiric antibiotic regimen demonstrates that it is a Gram-negative aerobe, or shown in Gram stain as Gram-negative bacteria

4.3 Exclusion Criteria

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

1. Subjects who have known or suspected community-acquired bacterial pneumonia, atypical pneumonia, viral pneumonia, or chemical pneumonia (including aspiration of gastric contents, inhalation injury)
2. Subjects who have a history of any hypersensitivity to cephalosporins or to carbapenems, or severe hypersensitivity to any other type of β-lactams other than cephalosporins and carbapenems (eg, penicillins, monobactams), or hypersensitivity to linezolid (Note: For β-lactams, a history of a mild rash followed by uneventful re-exposure is not a contraindication to enrollment)
3. Subjects with a Gram-negative infection caused by a carbapenem-resistant pathogen, if known at the time of randomization (Note: Subjects who have a carbapenem-resistant pathogen identified after randomization should be evaluated clinically before discontinuation of study treatment.)
4. Subjects with coinfection caused by invasive aspergillosis, mucormycosis or other highly lethal mold
5. Subjects who have central nervous system infection (eg, meningitis, brain abscess, shunt infection)
6. Subjects with cystic fibrosis
7. Subjects in refractory septic shock, defined as persistent hypotension despite adequate fluid resuscitation or despite vasopressive therapy at the time of randomization
8. Subjects with neutropenia (ie, polymorphonuclear neutrophils < 500 cells/μL)
9. Female subjects who have a positive pregnancy test at Screening, who are lactating, or who refuse to use 1 of the previously specified methods of contraception
10. Subjects with an APACHE II score of > 35

    Note: Sponsor may limit to subjects with an APACHE II score < 8 (see Section 4.1). This restriction will be communicated to investigators via a sponsor's notification letter.
11. Subjects who have received potentially effective antibiotic therapy for a continuous duration of more than 24 hours during the previous 72 hours prior to randomization (Note: Subjects failing empiric therapy as defined in inclusion criterion 9 may be eligible for inclusion.)
12. Subjects with any condition or circumstance that, in the opinion of the investigator, would compromise the safety of the subject or the quality of the study data

13. Subjects receiving peritoneal dialysis (hemofiltration and hemodialysis are permitted)
14. Subjects requiring continued treatment with methotrexate, procainamide, probenecid, monoamine oxidase inhibitors, or valproic acid (see Section 5.2)
15. Subjects who have received another investigational drug or device within 30 days prior to study entry
16. Subjects who have previously been randomized in this study or have previously received S-649266
17. Subjects with 1 or more of the following laboratory abnormalities in baseline specimens: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), or total bilirubin level (TBL) > 3 times the upper limit of normal (ULN), platelet count < 40,000/μL
18. Subjects with bronchiectasis with symptoms of persistent or recurrent bronchial infection related to irreversibly damaged and dilated bronchi; namely, subjects with clinical bronchiectasis
19. Subjects with lung abscesses

4.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the study but are not subsequently randomized/administered the study drug. Minimal information collected will include informed consent date, baseline subject characteristics, all eligibility criteria violated, reason(s) for screen failure, and AEs that lead to screen failure, including any SAEs. Rescreening is allowed for the following situations:

1. If a screen failed subject has a relapse or new HCABP/HABP/VABP
2. If a screen failed subject's respiratory specimen grows Gram-negative aerobic causative pathogen(s) that are not covered by empiric therapy in addition to lack of clinical improvement with that therapy

5. STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 Test Drug

S-649266 (1 g/vial): as a powder for solution for intravenous administration, manufactured by Shionogi & Co., Ltd., Japan

5.1.2 Control Treatment

Meropenem (500/1000 mg/vial): as a powder for solution for injection or infusion, as commercially available

5.1.3 Linezolid Treatment

Linezolid for intravenous injection is supplied as a ready-to-use sterile isotonic solution for infusion with a concentration of 2 mg/mL of linezolid, as commercially available.

5.2 Treatments to Be Administered

Each subject who is qualified for entry in the study will be randomized into 1 of 2 treatment groups according to the method of treatment assignment specified in Section 5.4.

S-649266 will be administered intravenously over 3 hours, q8h. Meropenem will also be administered intravenously over 3 hours, q8h. Linezolid will be administered intravenously over 30 minutes to 2 hours, q12h.

The study treatment duration is anticipated to be 7 to 14 days, which is consistent with published treatment guidelines for HABP/VABP/HCABP and serious infections [17,25-29]. Linezolid will be administered for at least 5 days, but will be extended if a Gram-positive pathogen or MRSA is present in addition to the Gram-negative pathogen.

It is recommended that dosing not exceed 14 calendar days or the equivalent of 14 full days of dosing. However, treatment may be extended up to 21 days based on the investigator's clinical assessment of the subject and a clear reason being documented in the eCRF. All study treatments will be administered in the hospital in a manner that preserves the blinded nature of the study.

If a subject needs to be treated for longer than 21 days, the subject should be discontinued from the study treatment, an EOT visit should be performed after last dose (same calendar day or within 24 hours), and antibiotic treatment should be instituted per local clinical practice. These subjects are still considered to be in the study and should be followed through to the completion of all study activities (ie, TOC, FU, and EOS).

The latest recommendations in the drug labelling should be followed in regard to precautions, contraindications, warnings, and DDIs with other medication that is or might be added as concomitant medication so that it does not interact adversely with the study antibiotics. The latest drug labelling can be found at the local regulatory agency’s website.

5.2.1 S-649266 Group

The preparation of the dosing solutions for S-649266 is described in the pharmacy manual. The solution volume for infusion must be at least 100 mL. Dilution volumes > 100 mL may be used, if deemed necessary by the investigator, to reduce any emerging symptoms related to nausea or infusion site issues (eg, pain, swelling).

5.2.2 Meropenem Group

The control population will be treated with meropenem, supplied by the sponsor. The solution volume for infusion must be at least 100 mL. The preparation of the dosing solutions for meropenem is described in the pharmacy manual. To be comparable with the S-649266 dosing solution, the meropenem dosage will be prepared in normal saline and will be the same volume as the S-649266 dose.

5.2.3 Linezolid

All subjects will be treated with linezolid for the duration of treatment if Gram-positive pathogens are identified in the subject's respiratory specimens. If no Gram-positive pathogens are identified, and the subject is not at high risk for a MRSA infection, linezolid can be discontinued after 5 days. Linezolid will be supplied by the sponsor.

5.3 Selection and Timing of Dose for Each Subject

Both study treatments, S-649266 and meropenem, are renally excreted and require dosage adjustment based on renal function estimated from serum creatinine concentration. Dosage adjustment based on reduced renal function will be made by the investigator or a qualified designee in a blinded manner, and then the dosage of randomized antibiotic will be prepared by an unblinded pharmacist or qualified designee. Dosage adjustments for S-649266 for subjects with various degrees of renal function and ARC are found in Table 5-1. Dosage adjustments for meropenem for subjects with various degrees of renal function are found in Table 5-2.

5.3.1 S-649266 Dosing

The proposed S-649266 dosage regimen for the treatment of serious or life-threatening infections is 2 g q8h infused over 3 hours.

The initial dosage for each subject will be adjusted based on estimated glomerular filtration rate (eGFR) calculated by modification of diet in renal disease (MDRD) equation [32,33] and creatinine clearance (CrCl) by Cockcroft-Gault equation [34] as per Table 5-1.

Renal function for all subjects will be assessed at EA to determine if there are changes in renal function for which the dosage of the study drug needs to be adjusted. The main purpose for this is to ensure that drug levels remain in a safe and therapeutic range. If renal function is changed at EA from Screening, dosage adjustment will be required as per Table 5-1.

For subjects with eGFR $\geq$ 90 mL/min/1.73 m^2 and CrCl $\geq$ 120 mL/min by Cockcroft-Gault equation at Screening or at EA, a CrCl measured by urinary excretion with urine collection of 2 to 8 hours duration will be determined (see Section 7.6.4.4) in order to determine if an additional dosing adjustment is required.

During treatment period other than at EA, dosage adjustment will be required on review of renal function conducted per local clinical practice.

5.3.2 Meropenem Dosing

The dosage for meropenem of 2 g q8h with infusion over 3 hours was selected to provide an appropriate target MIC for Gram-negative bacteria that are associated with nosocomial pneumonia. In order to maintain the blinding during the treatment of a subject, it will be necessary to use the same dosing procedure for both of the study drugs, S-649266 and the comparator drug, meropenem; therefore, the volume of solution will be the same, and the

length of the infusion will be the same. The solutions will be made in saline for injection for either drug.

Renal function for all subjects will be assessed at EA to determine if there are changes in renal function for which the dosage of the study drug needs to be adjusted. The main purpose for this is to ensure that drug levels remain in a safe and therapeutic range. If renal function is changed at EA from Screening, dosage adjustment will be required as per Table 5-2.

During treatment period other than at EA, dosage adjustment will be required on review of renal function conducted per local clinical practice.

5.3.3 Linezolid Dosing

Linezolid will be administered by infusion over 30 minutes to 2 hours q12h to both treatment groups. If no evidence of Gram-positive infection is identified, and the subject is not at high risk for MRSA infection, linezolid can be discontinued after 5 days in both treatment groups. The linezolid dose does not have to be administered at the same time as the Gram-negative antibiotic. If needed, the infusions of the antibiotics could be overlapped or separated to accommodate the difference in the timing of the infusions. Linezolid does not require dosage adjustment in subjects with reduced renal function according to label prescribing information.

Table 5-1 S-649266 Dosing Adjustments for Various Degrees of Renal Function and Augmented Renal Clearance

Creatinine Clearance	Dosage
Augmented renal function (MDRD-eGFR ≥ 90 mL/min/1.73 m^2 and CrCl ≥ 120 mL/min)[a]	2 g, q6h, 3-hour infusion
Normal renal function (MDRD-eGFR ≥ 90 mL/min/1.73 m^2 and CrCl < 120 mL/min)	2 g, q8h, 3-hour infusion
Mild renal impairment (MDRD-eGFR 60 to < 90 mL/min/1.73 m^2)	2 g, q8h, 3-hour infusion
Moderate renal impairment (MDRD-eGFR 30 to < 60 mL/min/1.73 m^2)	1.5 g, q8h, 3-hour infusion
Severe renal impairment (MDRD-eGFR 15 to < 30 mL/min/1.73 m^2)	1 g, q8h, 3-hour infusion
ESRD (MDRD-eGFR < 15 mL/min/1.73 m^2)	0.75 g, q12h, 3-hour infusion
Subject with intermittent HD	0.75 g, q12h, 3-hour infusion[b]
CVVH	1 g, q12h, 3-hour infusion[c]
CVVHD or CVVHDF	1.5 g, q12h, 3-hour infusion[c]

CrCl = creatinine clearance; CVVH = continuous venovenous hemofiltration; CVVHD = continuous venovenous hemodialysis; CVVHDF = continuous venovenous hemodiafiltration; EA = Early Assessment, eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HD = hemodialysis; MDRD-eGFR = estimated glomerular filtration rate calculated with the modification of diet in renal disease (MDRD) equation; q6h = every 6 hours; q8h = every 8 hours; q12h = every 12 hours

a Creatinine clearance will be calculated by Cockcroft-Gault equation at Screening and at EA. A urine measured CrCl will be calculated by using timed urine collections of 2 hours to 8 hours at Screening and EA in order to determine if an additional dosing adjustment is required.

b S-649266 is hemodialyzable, thus a supplemental dose of 0.75 g will be administered after the completion of intermittent HD as a 3-hour infusion on dialysis days. If the supplemental dose overlaps with the next regular dose, the investigator can consider skipping either a next regular q12h dose or the supplemental dose to avoid excessive exposure and complexity of clinical operation.

c The dose will be determined based on MDRD-eGFR on nondialysis days.

The dosage of meropenem should be adjusted per label on review of renal function tests, whether part of required study assessments or conducted per local clinical practice (see Table 5-2) [18, 35]. Neither the US package insert nor the UK Medicines and Healthcare products Regulatory Agency Summary of Product Characteristics (SPC or SmPC) makes any recommendations for ARC. Dosing recommendations are made for hemodialysis and hemofiltration [18].

Table 5-2 Meropenem Dosing Adjustments for Various Degrees of Renal Function

Creatinine Clearance (mL/min)[a]	Dosage
CrCl > 50	2 g, q8h, 3-hour infusion
CrCl 26-50	2 g, q12h, 3-hour infusion
CrCl 10-25	1 g, q12h, 3-hour infusion
CrCl < 10	1 g, q24h, 3-hour infusion

CrCl = creatinine clearance; q8h = every 8 hours; q12h = every 12 hours; q24h = every 24 hours

a Creatinine clearance calculated by Cockcroft-Gault equation at Screening, early assessment, and at other times as needed. Meropenem is cleared by hemodialysis and hemofiltration. The required dose should be administered after completion of the hemodialysis cycle. There are no established dosage recommendations for subjects receiving peritoneal dialysis. There are no established dosage recommendations for subjects with augmented renal clearance.

Source: Meropenem Medicines and Healthcare products Regulatory Agency Summary of Product Characteristics dosing information [18]

The administration schedule of study treatment after initial administration may be adjusted gradually, within reason, and based on the clinical judgment of the investigator to fit the routine treatment schedules of the investigator's hospital, as long as the dosing intervals and infusion durations indicated by the protocol are maintained following adjustment.

5.4 Randomization to Treatment Groups

The treatments will be randomized to subject identification numbers by the Interactive Response Technology (IRT) provider in a 1:1 fashion to S-649266 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 diagnosis (HABP, VABP, and HCABP) and APACHE II score (≤ 15 and ≥ 16) as allocation factors. The number of ventilated subjects in the study is anticipated to be approximately 50%. This would include subjects with VABP, as well as subjects with HABP and HCABP who are ventilated.

When the centralized IRT has accepted and randomized the subject to either treatment group, the dispensing pharmacist will prepare for administration of the allocated treatment according to the pharmacy manual.

The process for subject number assignment and treatment assignment are described in the IRT procedure documents.

The person or organization responsible for randomization will prepare and complete the randomization procedures/processes.

5.5 Blinding

This is a randomized, double-blind study. The investigator, site personnel, sponsor, and 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 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, S-649266 will be prepared and administered within the same timeframe after preparation as meropenem. The infusion bag containing a reconstituted study or comparator drug will be identified with the study number and subject's identification number, but will not identify the specific drug product. 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, and it will be labeled with the study number, subject's identification number, and drug name.

Unblinding by request of an investigator should occur only in the event of an SAE assessed by the investigator to possibly be drug-related and for which it is necessary to know the study treatment to determine an appropriate course of therapy for the subject. Subjects who are unblinded due to a treatment-related SAE should be withdrawn from study treatment. If the investigator must identify the treatment assignment to an individual subject, an investigator or qualified designee should request the medication information from the IRT. They should not attempt to get this information from the site unblinded pharmacist or qualified designee. The documentation received from the IRT indicating the code break must be retained with the subject's source documents in a secure manner so as not to unblind the treatment assignment to other site or sponsor personnel. The investigator is also advised not to reveal the study treatment assignment to other site or sponsor personnel.

Prior to unblinding, and if the situation allows it, the investigator should try to contact the site monitor or the sponsor's medical monitor in order to get additional information about the investigational product. If this is impractical, the investigator must notify the site monitor or the sponsor's medical monitor as soon as possible, without revealing the treatment assignment of the unblinded subject. The investigator must document the subject's number, the date, and the time for breaking the blind and must clearly explain the reasons for breaking the code. For subjects withdrawing consent, EOT procedures should be completed.

Plasma concentrations of S-649266 will be reported to the sponsor by the analytical laboratory only after the database is locked in order to maintain the blind.

5.6 Packaging and Labeling

Study treatments, S-649266 and meropenem, will be supplied to the study sites in containers that identify the contents (ie, not blinded). The individual vials of both study treatments will be labeled with the name of active ingredient, protocol number, lot number, dosage form, strength, dosing instructions, medication identification number, storage conditions, caution statements, name, and address of the manufacturer or sponsor as appropriate for a given country labeling requirements.

5.7 Storage and Accountability

5.7.1 S-649266 Treatment Arm

S-649266 vials will be stored in a tight, light-resistant container at 2°C to 8°C (36°F to 46°F), and must be protected from light.

The investigator/site pharmacist will ensure that all study drugs are stored and dispensed in accordance with local health regulations concerning the storage and administration of investigational drugs. All drug supplies must be kept in a secure locked, temperature-controlled area with access limited to those authorized by the investigator.

The unblinded pharmacist or designee will maintain accurate records of the following information: receipt and condition of all study drugs, date of the receipt, when and how much study drug is dispensed and administered to each subject in the study, date and time of reconstitution, and any reasons for departure from the protocol-dispensing regimen.

The drug accountability records and the spent dosage vials will be available for verification by the unblinded sponsor monitor, unblinded contract research organization (CRO), or designee at each monitoring visit as specified in the unblinded monitoring plan. If the local procedures at a site require immediate disposal of spent vials, an alternative process for drug accountability will be made with the site and the process will be documented in the study files. At the completion of the study, a final reconciliation of all study drugs will be performed. Study drugs must not be used for any purpose other than the present study.

5.7.2 Meropenem Treatment Arm

Meropenem will be stored as specified by the label.

5.7.3 Linezolid Treatment

Linezolid will be stored as specified by the label.

5.8 Investigational Product Retention at Study Site

All unused study drug supplies will be held in the medical institution; although, those supplies will not be required to be stored under the storage conditions defined above. At the completion of the study, all of the unused drug supplies must be returned to the sponsor (or designee) as per the sponsor’s written instructions or destroyed as per the

CRO's or local standard operating procedures upon agreement and written approval of the sponsor.

5.9 Treatment Compliance

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

5.9.1 Changes in Treatment Regimen

Subjects, who have their treatment regimen altered for reasons such as, but not limited to, lack of therapeutic response, possible drug-related toxicity, or de-escalation, will be identified, and the reason for the change in treatment regimen will be recorded in the eCRF.

Alteration of treatment dosage or dosing regimen for any reason will be reported in the eCRF.

6. RESTRICTIONS

6.1 Prior Therapy

Prior therapies are defined as therapies that were taken prior to randomization of the subject into the study.

Systemic antibiotic treatment or prophylaxis for Gram-negative pathogens, including aerosolized antibiotics, must be stopped before administration of study drug treatments.

Any prior systemic antibiotic therapy and the reason for its use within 2 weeks prior to randomization of the study will be recorded in the eCRF, and the information will include:

- Name of used drug
- Dose, dosing frequency, and route of administration (if a drug is administered)
- Duration of treatment
- Reason for use

6.2 Concomitant Therapy during the Study

6.2.1 Antibiotic Therapies

Concomitant antibiotic therapies are defined as therapies administered after randomization in the study. No concomitant systemic antibiotics except for linezolid are permitted from randomization until after TOC. Topical antibiotics, excluding aerosolized antibiotics, are permitted.

The investigator, subinvestigator, or designee will record the following information for all therapies (prescription drugs, over-the-counter drugs, and herbal preparations) used during the study (from randomization to completion of EOS) in the eCRF:

- Name of used drug
- Dose, dosing frequency, and route of administration (if a drug is administered)
- Duration of treatment
- Reason for use

6.2.2 Nonantibiotic Therapies and Procedures

Concomitant nonantibiotic therapies are defined as therapies including concomitant medication to support blood pressure or renal output, antiviral agents, or antifungal therapy that are administered after randomization in the study.

Concomitant procedures are defined as procedures including surgical procedures, mechanical blood pressure device, and intravenous or urinary catheters, which are performed after randomization in the study.

The investigator, subinvestigator, or designee will record all Prior Therapy (including all types of antibiotics, prescription drugs, over-the–counter drugs and procedures) used from 2 weeks prior to randomization in the eCRF.

The investigator, subinvestigator, or designee will record the following information for all therapies (prescription drugs, over-the-counter drugs, herbal preparations, and procedures without any medication) used during the study (from Screening to completion of EOS) in the eCRF.

- Name of used drug or used procedures
- Dose, dosing frequency, and route of administration (if a drug is administered)
- Duration of treatment
- Reason for use

It is not required to record the following concomitant medications: intravenous fluids, nutrition, mineral supplements (potassium, sodium, etc), nonantibiotic herbal supplements, ointments, or ocular drops.

6.2.3 Prohibited Therapy

- Systemic antibiotics for Gram-negative infections, other than meropenem and S-649266, are not permitted from randomization until TOC. Systemic antibiotics for Gram-positive infections other than linezolid are not permitted from randomization until TOC.
- Aerosolized antibiotics are not permitted from randomization until after TOC.

- Monoamine oxidase inhibitors and valproic acid are not permitted from Screening until EOT.

Metronidazole or clindamycin to cover anaerobes is permitted. Oral vancomycin or metronidazole for *C. difficile* infection is permitted.

6.2.4 Rescue Therapy

Alternative systemic antibacterial treatment should be administered when a subject has been deemed a treatment failure. Subjects determined as treatment failure and needing rescue therapy should be considered as EOT, and EOT procedures should be completed. All antibiotics drugs will continue to be recorded in the eCRF until the completion of the EOS assessment.

7. STUDY PROCEDURES AND METHODS OF ASSESSMENTS

In the case that a subject is screened and randomized on the same day, the information requirements for Screening (Day −2 to Day 1) and for Randomization (Day 1) are to be completed, but only 1 set of screening tests/results for the complete physical examination, vital signs, and laboratory tests are needed.

7.1 Informed Consent

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

Informed consent will be obtained for all subjects. A subject cannot be entered in the study until he/she or his/her guardian or holder of an appropriate medical power of attorney has signed and dated the consent form. The subject who can only be enrolled with the consent of his/her legally authorized representative should be informed about the study when the subject is able to sign a consent during the study and, if capable, the subject should sign and personally date the written informed consent. (Note: Country-specific rules and local ethics committee approval for legally authorized representative informed consent will determine whether or not a subject unable to comprehend or sign the informed consent is allowed to be enrolled in the study).

The investigator or subinvestigator is responsible for ensuring that the subject understands the risks and benefits of participating in the study, including answering any questions the subject may have throughout the study and sharing any new information in

a timely manner that may be relevant to the subject's willingness to continue his/her participation in the study.

7.2 Baseline Subject Characteristics and Medical History

The following baseline subject characteristics will be obtained upon entering into the study and entered in the eCRF: age, sex, ethnicity, race, onset of infection, severity of infection, prior/concomitant therapies, and medical history with time of onset. Medical history will include previous significant medical conditions (eg, cancer, stroke, and myocardial infarction), any concurrent medical conditions, surgical history, history of diagnosis, and history of treatment of current infection or other infections requiring antibiotic therapy. All subjects must receive a clinical diagnosis of nosocomial pneumonia (HABP/VABP/HCABP) presumably caused by a Gram-negative pathogen at the time of randomization.

7.2.1 Hospitalization

Additional information to be entered into the eCRF to assist in the pharmacoeconomic evaluation is the date of any hospitalization from 90 days prior to enrollment through the study, admission source (home, clinic, skilled nursing facility, acute care treatment facility, etc), admission type (elective, urgent, emergent, other), date of discharge, discharge status (expired, home, hospice, transferred, etc), main location of care, initial/end date of intensive care unit (ICU) admission or isolation, initial/end date of treatment with ventilator, and status at EOS.

7.3 Enrollment in the Study and Dispensing Study Drug Treatments

After a subject is determined to be eligible according to the inclusion/exclusion criteria, the investigator, designee or study site pharmacist will contact the IRT for an identification number and specify the:

- Clinical diagnosis (HABP, VABP, or HCABP)
- Calculated APACHE II score

If the registration is accepted, the subject will be randomized to either treatment group. The number of ventilated subjects in the study is anticipated to be approximately 50%. This would include subjects with VABP, as well as subjects with HABP and HCABP who are ventilated.

7.4 Efficacy Assessments

7.4.1 Specific Evaluations

Several of the assessments used in this study are considered to be both efficacy assessments and safety assessments (eg, survival and vital signs). These evaluations will be collected in the eCRF. The specific evaluations will then be incorporated into the appropriate analysis according to the Statistical Analysis Plan (SAP) for the respective evaluation.

7.4.1.1 Survival

The investigator or qualified designee will enter survival status (survival or death) in the eCRF, including the date and cause of death if the subject dies during this study up to the EOS. Survival will be assessed on a continuous basis and will be evaluated as an endpoint on Days 14 and 28 after the initiation of study treatment.

In case there is no other requirement for a study visit on Day 14, such as EOT, or if dosing will go beyond Day 14, the survival of the subject will be confirmed by designated study staff and recorded in the eCRF. If the Day 28 survival determination does not coincide with a planned study visit, such as the FU visit, the survival of the subject will be confirmed by designated study staff and recorded in the eCRF. If the subject is no longer in the hospital at the time of the Day 14 or 28 survival determination, a phone call to the subject or caregiver to confirm survival will be sufficient, and the result will be recorded in the eCRF.

7.4.1.2 Sequential Organ Failure Assessment

The Sequential Organ Failure Assessment (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 (see Appendix 4). The investigator or qualified designee will collect and enter the SOFA scores in the eCRF at the specified evaluation points based on Appendix 1. In nonventilated subjects, a respiration score of 0 may be assigned.

7.4.1.3 Oxygenation Status

The subject's oxygenation status, including PaO_2, partial pressure of carbon dioxide, FiO_2, and O_2 saturation, will be determined by ABG measurements (ABG measurement is preferable but not mandatory), and peripheral capillary oxygen saturation will be measured by pulse oximetry as relevant at the specified evaluation points and entered in the eCRF. The oxygen inhalation devices, ie, a ventilation device, and the flow rate also will be identified and entered in the eCRF. If a subject is on a ventilation device, the start date and time of initiation of ventilation will be recorded in the eCRF. If the subject is taken off ventilation, the date and time of the end of ventilation will be recorded in the eCRF. If the subject was on ventilation during the time of the PK blood sampling, the FiO_2 should be recorded.

7.4.1.4 Clinical Assessment of Signs and/or Symptoms

Signs and symptoms specific to HABP/VABP/HCABP, such as expectorated sputum production, worsening of tracheal secretions, cough, dyspnea (including retractions), chest pain, wheezing, rales, rhonchi, egophony, dullness to percussion, and bronchial breath sounds will be assessed at baseline as absent, mild, moderate, severe, or unknown. Signs and symptoms present at baseline will similarly be assessed at the specified subsequent evaluation points. Any new sign or symptom of the underlying infection, which may occur in any specific subject during the course of the study, will also be assessed. The results will be entered in the eCRF.

7.4.1.5 Vital Signs

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

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

For subjects treated in ICU, vital signs obtained through continuous monitoring methods, including intra-arterial catheters, may be used to record blood pressure, temperature, and heart rate.

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

7.4.1.6 Clinical Pulmonary Infection Score

Clinical Pulmonary Infection Score (CPIS) is a surrogate for diagnosis and treatment response. Points (0, 1, or 2) will be assigned for observed findings for 5 variables: body temperature, WBC count, tracheal secretion, PaO_2/FiO_2, and chest radiograph. The investigator or qualified designee will collect and enter the points in the eCRF at the specified evaluation points based on Appendix 5. In nonventilated subjects in whom blood gasses are not drawn, a PaO_2/FiO_2 score of 0 may be assigned.

7.4.1.7 Chest Radiographs

A chest radiograph (posterior/anterior or portable [when the subject's condition does not permit transport to the radiology department]) will be performed at the specified evaluation points: Screening, EOT, TOC, at Day 14 if dosing is to be extended to 21 days, and when clinically indicated. If appropriate, additional radiography (eg, CT scan) could be performed to better delineate lung pathology according to local practice. The results will be entered in the eCRF, preferably by a certified radiologist.

7.4.2 Efficacy Criteria for Clinical Outcomes for Early Assessment, End of Treatment, and Test of Cure

The clinical outcomes will be assessed by the investigator according to the following criteria at EA, 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 eCRF.

- **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 additional antibacterial therapy is required for the treatment of the current infection at the EA and EOT visits, and no antibacterial therapy is required for the treatment of the current infection at 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.

7.4.3 Clinical Outcomes for Follow-up

The clinical outcomes will be assessed by the investigator according to the following criteria. The clinical outcomes will be entered in the eCRF.

- **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.
- **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.

7.4.4 Microbiological Outcomes for Early Assessment, End of Treatment, and Test of Cure

The microbiological outcomes by baseline pathogen will be determined by the sponsor according to the following criteria at EA, EOT, and TOC. In case treatment duration is extended beyond 14 days, an additional microbiological outcome will be assessed on Day 14. An overall per-subject microbiological outcome will also be determined based on the individual microbiological outcomes for each baseline pathogen. Emergent (ie, nonbaseline) pathogens will be considered separately and will not affect the per-subject microbiological outcome.

- **Eradication:** Absence of the baseline Gram-negative pathogen from an appropriate clinical specimen. If it is not possible to obtain a sample for 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 EOT or TOC will be carried forward.
- **Indeterminate:** No culture obtained from an appropriate clinical specimen or additional antibacterial therapy for the treatment of the current infection.

7.4.5 Microbiological Outcomes for Follow-up

Microbiological outcomes by baseline pathogen will be determined by the sponsor according to the following criteria at FU.

- **Sustained Eradication:** Absence of the baseline Gram-negative pathogen from an appropriate clinical specimen after TOC. If it is not possible to obtain a sample for 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 test of cure culture was negative.
- **Indeterminate:** No culture obtained from an appropriate clinical specimen or subject received additional antibacterial therapy for the treatment of the current infection.

7.5 Pharmacokinetic Assessments

All subjects will have blood drawn for sparse pharmacokinetic sampling of plasma concentrations of S-649266. Pharmacokinetic blood sampling will preferably be performed on Day 3 or 4. Every effort should be made to collect all 4 blood samples after administration of the same dose of study drug or at least the same day of administration, in order to reduce variability. The following is the schedule for the sampling time points (see Table 7-2 for acceptable time windows):

(1) Just prior to the start of the 3-hour infusion
(2) 1 hour after the start of infusion
(3) Before the end of infusion
(4) 1 hour after the end of infusion

The actual sampling date and time will be recorded. If the subject is on a ventilation device, the FiO_2 should be recorded.

The pharmacokinetic blood sampling will be repeated in the event that the drug dosage was changed due to changes in renal function determined at EA; this should occur 24 to 72 hours after the change in dosing regimen.

If possible, a single blood sampling should be performed as soon as possible (within 24 hours) in the case of premature EOT, which is defined as receiving < 7 days of intravenous treatment with either S-649266 or meropenem.

Plasma samples will be shipped to a designated bioanalytical laboratory for drug concentration analysis. Detailed procedures for sample collection, handling, labeling, storage, and shipping will be specified in the laboratory manual. Shipping labels, instructions for shipping, and courier service will be provided by the sponsor or CRO.

Only blood samples from S-649266 subjects will be assayed. To maintain the blind, results of the assays will not be reported to the sponsor until after the database is locked.

A substudy may be developed to determine drug concentrations in epithelial lining fluid (ELF) in subjects with VABP receiving S-649266. The plasma sampling for drug concentrations will be the same as that for the pharmacokinetic portion of the study. Ventilator-associated bacterial pneumonia subjects participating in the ELF study will only provide blood samples during the ELF pharmacokinetic study. Any substudy designed to determine the concentrations of S-649266 in ELF would require a separate written informed consent by the subject or representative.

7.6 Safety Assessments

7.6.1 Physical Examinations

A complete physical examination will be performed at Screening. A limited physical examination relevant to the subject's current condition will be performed at the specified evaluation time points (see Section 8 and/or Appendix 1). Body weight in kilograms and height in centimeters will be obtained at Screening. The physical examination should be performed according to the normal practice of the clinical study site by the investigator or subinvestigator. Clinically significant findings on physical examination will be recorded as AEs. Weight and height will be entered in the eCRF.

7.6.1.1 Glasgow Coma Scale

The Glasgow Coma Scale (GCS) will be estimated based on eye (4), verbal (5), and motor (6) criteria. The investigator or qualified designee will calculate the GCS according to Appendix 2, record it in the source document, and use it to complete the APACHE II and SOFA scores in the eCRF at the specified evaluation points. In ventilated and sedated subjects, the GCS cannot be properly assessed, and a normal score of 15 could be used to complete the APACHE II and SOFA scores. If a reliable presedation score is available, it can be used.

7.6.1.2 APACHE II Score

The component values, observations, and calculation of the APACHE II score will be collected and used as a method to establish the severity of disease for a given subject. The APACHE II score will be collected and entered in the eCRF at Screening by the investigator or qualified designee based on Appendix 3. If a core temperature measurement is not available (ie, tympanic, rectal, esophageal), oral and axillary temperatures could be adjusted by adding 0.5°C and 1°C, respectively.

7.6.2 Vital Sign Measurements

Vital sign measurements are described in Section 7.4.1.5.

7.6.3 Electrocardiography

A standard 12-lead ECG will be performed during Screening. The ECG will be performed at a paper speed of 25 mm/second after the subject has been in a supine or

semirecumbent position for several minutes. Electrocardiograms obtained by the site within the 48 hours prior to signing the ICF could be acceptable as screening data for this study. If that ECG is not a standard 12-lead ECG, a 12-lead ECG will have to be completed during Screening.

The following ECG parameters will be recorded: heart rate, PR interval, RR interval, QRS duration, QT interval, and diagnostic statements. The QTc data will be calculated using Fridericia's correction by the electronic data capture system once the basic ECG data are entered therein.

The investigator or subinvestigator will assess whether the ECG is normal or abnormal, if abnormal, was it associated with any AE or Medical History. The results of this ECG evaluation and its interpretation will be entered in the eCRF.

Additional ECGs conducted per local clinical practice should also be assessed for any clinically significant abnormalities, which should then be reported as AEs and assessed as to whether they meet the criteria for being serious (see Section 7.6.5).

7.6.4 Clinical Laboratory Tests

7.6.4.1 Laboratory Parameters

Blood and urine samples will be collected for clinical laboratory tests at specified times as specified in Appendix 1. Safety laboratory tests obtained within 24 hours prior to randomization as a standard of care are allowed to be used for screening tests.

The samples other than some specialized tests, as outlined in Table 7-1, will be measured at a local laboratory, and the results will be entered in the eCRF. If required for specialized testing, detailed procedures for sample collection, handling, labeling, storage, and shipping will be provided in the separate study laboratory manual. Shipping labels, instructions for shipping, and courier service will be provided from the sponsor or CRO.

The investigator or subinvestigator will assess whether any abnormal changes from baseline are clinically significant (see also Section 7.6.5.5).

7.6.4.2 Microbiologic Cultures

Appropriate clinical specimens are to be obtained from all subjects within 48 hours prior to the start of infusion of the first dose of study treatment. Lower respiratory tract specimens (eg, sputum, endotracheal aspiration [ETA], endobronchial culture specimens collected by bronchoalveolar lavage [BAL], or protected specimen brush [PSB], lung biopsy tissue, pleural effusions, etc) and blood for microbiologic cultures are to be sent to the local laboratory for identification of all pathogens causing the infection. Lower respiratory tract specimens should be grown semiquantitatively or quantitatively with appropriate method-specific dilutions. Two blood samples from separate venipunctures are to be obtained from all subjects and sent to the local laboratory. After initiation of study treatment, appropriate clinical specimens, including blood samples, are to be obtained at the specified evaluation points. Subsequent blood cultures are to be completed only if the immediate previous culture is positive. Culture results obtained prior to

informed consent, but directly related to the current infection, should be recorded and may form the basis for subject inclusion in the study.

For patients who failed empiric treatment (as defined in inclusion criterion 9), clinical specimens obtained within 72 hours of randomization in this study could be used as screening/baseline cultures. A culture should be done again before first dose of study drug is administered, and the pathogen isolated sent to central laboratory.

Local culture results should be recorded in the eCRF and identified isolates sent to the central laboratory.

All baseline respiratory specimens should also have a Gram stain of infected material (not from a swab) performed. The low-power microscopic view of the Gram stain can be used to ascertain the quality of the respiratory specimen, which helps to ensure that the respiratory specimen sent for culture does not represent oropharyngeal contamination (ie, fewer than 10 squamous epithelial cells and > 25 neutrophils is an example of an adequate expectorated sputum specimen) and should only be performed for ETA and expectorated sputum (microscopic check is not required for BAL, mini-BAL, or PSB). The high power microscopic view of the Gram stain can be used to characterize the general type of bacteria causing the pneumonia (eg, a Gram-positive or a Gram-negative bacterial pathogen). A report of both inflammatory cells and bacteria is necessary. A Gram stain result showing the presence of Gram-negative bacteria is a primary indication of the infection that will be most appropriate for this study.

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

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

Carbapenem resistance is defined by the in vitro susceptibility phenotype (MIC, E-test, disc diffusion) and subject to the approved breakpoints for carbapenems in the respective countries. For this study, intermediate breakpoints to imipenem/cilastatin, doripenem, or meropenem are classified as carbapenem-susceptible. Imipenem/cilastatin, doripenem, or meropenem have been chosen for the carbapenem-resistant criteria for this study because of their coverage against Gram-negative species. Carbapenem resistance for isolated pathogens will be recorded in the eCRF.

Bacteria in the airway may persist as a colonizer following treatment of pneumonia, without causing signs or symptoms of infection. When the bacteria considered to be a causative pathogen at Screening (baseline) are identified later to be a colonizer, the isolate of the colonizer, regardless of whether it is Gram-negative or Gram-positive, should be sent to the central laboratory. The rationale for performing identification and antimicrobial susceptibility by the central laboratory is to provide information of

antibiotic susceptibility over time, which is important in understanding the pathogenicity of the bacteria and development of resistance to study drugs.

7.6.4.3 Routine Laboratory Tests

Clinical laboratory tests are shown in Table 7-1.

Table 7-1 Routine Laboratory Tests

Category	Evaluation Items
Hematology Tests	Hematocrit, hemoglobin, platelet count, RBC, WBC with differential and morphology indices, INR, and PTT
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[a]	Glucose, blood, protein, ketones, bilirubin, urobilinogen, leukocyte esterase, and microscopic[b] (WBC, RBC, crystals, and casts)
Specialized Tests	Iron, TIBC, transferrin iron saturation, and hepcidin at Screening, and TOC
Others	Serum or urine pregnancy test at Screening CrCl and eGFR: from serum at screening and at EA (see Section 7.6.4.4) CrCl determined from a timed urine collection at Screening and EA[c] (see Section 7.6.4.4)

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; MDRD-eGFR = estimated glomerular filtration rate calculated with the modification of diet in renal disease (MDRD) equation; PTT = partial thromboplastin time; RBC = red blood cell; TBL = total bilirubin level; TIBC = total iron-binding capacity; TOC = Test of Cure; WBC = white blood cell

a Urinalysis for anuric patients is not mandatory

b If sediment is present.

c For subject with MDRD-eGFR $\geq$ 90 mL/min/1.73 m^2 and CrCl $\geq$ 120 mL/min by Cockcroft-Gault equation at Screening or at EA.

False positive urinalysis tests for protein or ketones (by dipstick) were found in the previous Phase 1 study (Study R2111). In the case that a positive dipstick test is found, the result will be confirmed by a secondary laboratory method.

7.6.4.3.1 Pregnancy Tests

A serum or urine pregnancy test for females who are not postmenopausal or surgically sterile will be performed at Screening.

7.6.4.4 Creatinine Clearance

Renal function should be monitored per local clinical practice and dosage adjustments made accordingly and captured in the eCRF.

7.6.4.4.1 Creatinine Clearance from Serum Creatinine

In addition, a CrCl (the Cockcroft-Gault equation) and eGFR (the MDRD equation) will be calculated from the serum creatinine for all subjects at Screening and at EA. If renal function has changed at EA from Screening, dosage adjustment will be required as per Table 5-1. Examples of the MDRD equation and the Cockcroft-Gault equation are as follows [32-34]:

MDRD equation

- Japanese
  - ✧ eGFR (mL/min/1.73 m^2) = 194 × (age in years)$^{-0.287}$ × sCr$^{-1.094}$ × (0.739 if female)
- Non-Japanese
  - ✧ eGFR (mL/min/1.73 m^2) = 175 × (age in years)$^{-0.203}$ × sCr$^{-1.154}$ × (0.742 if female) × (1.212 if African descent)

Cockcroft-Gault equation

- CrCl (mL/min) = weight × (140 − age in years)/(72 × sCr) × (0.85 if female)
  where sCr is the serum creatinine concentration (mg/dL)

7.6.4.4.2 Urine Measured Creatinine Clearance

For subjects with eGFR calculated with the MDRD equation (MDRD-eGFR) ≥ 90 mL/min/1.73 m^2 and CrCl ≥ 120 mL/min by the Cockcroft-Gault equation at baseline, urine samples will be collected for a time interval as short as 2 hours or up to 8 hours at Screening or at EA. The total volume of urine, hours, and urinary creatinine concentration will be measured and recorded in the eCRF.

The CrCl calculated using timed urine collections, which is given by the following equation, will be performed for the subjects suspected to have ARC (ie, MDRD-eGFR ≥ 90 mL/min/1.73 m^2 and CrCl ≥ 120 mL/min by Cockcroft-Gault equation) to confirm the presence of ARC.

CrCl (mL/min) = uCr × volume/sCr/(time × 60)

where uCr is urinary creatinine concentration (mg/dL), volume is urine volume (mL), sCr is serum creatinine concentration (mg/dL), and time is collection time (hours).

7.6.5 Adverse Event Assessments

7.6.5.1 Performing Adverse Event Assessments

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 found by the subject's spontaneous complaint, subject comment cards, or as a result of nonleading questions, physical examinations, vital signs, or laboratory tests. Adverse events include any occurrences that are new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. Medical histories not related to the infection that are reported at baseline and worsen will be considered AEs.

Lack of efficacy, aggravation, or relapse of HABP/VABP/HCABP infection or related symptoms and signs will not be considered AEs in the study and, therefore, also not SAEs (unless fatal). This statement applies until TOC. Any aggravation or relapse of HABP/VABP/HCABP after TOC should be considered an AE.

New onset infection involving a site other than lung such as blood stream infection is considered an AE.

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

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

7.6.5.2 Timing

Adverse events will be collected from the time of having signed informed consent through approximately 28 days after the last dose of the study treatment (ie, EOS) for randomized subjects. If a subject withdraws early from the study, the investigator or subinvestigator will make an effort to collect AEs until EOS. Major nonfatal events (eg, acute respiratory distress syndrome, respiratory failure, septic shock, empyema, bacteremia, endocarditis, and meningitis) if present, should also be evaluated on Days 14 and 28 at the same time as the evaluation of survival. Major nonfatal events will be reported and followed through EOS.

All SAEs, regardless of causality will be followed until resolution, stabilization, the condition becomes chronic, or the subject is lost to follow-up.

7.6.5.3 Severity

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

- **Mild:** A finding or symptom is minor and does not interfere with usual daily activities.

- **Moderate:** The event causes discomfort and interferes with usual daily activity or affects clinical status.
- **Severe:** The event causes an interruption of the subject's usual daily activities or has a clinically significant effect.

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

7.6.5.4 Relationship

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

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

7.6.5.5 Expectedness

A treatment-related AE is considered expected if it is listed in Expected Adverse Reactions in Section "Undesirable Effects" of "SUMMARY OF DATA AND GUIDANCE FOR INVESTIGATORS" in the current Investigator's Brochure for S-649266. The expected adverse reactions of meropenem will be those found in the EMA SmPC. The expected adverse reactions of linezolid will be those found in the EMA SmPC. Expectedness will be assessed by the sponsor.

7.6.6 Clinical Laboratory Adverse Events

For any abnormal laboratory test results (hematology, blood chemistry, or urinalysis) or other safety assessments (eg, physical examinations, vital signs) that are worsening from baseline or occur thereafter in the course of the study, the investigator or subinvestigator will consider whether these results are clinically significant. Abnormal laboratory test results are defined as values outside the reference range. Any test results that are considered to be clinically significant at the discretion of the investigator or subinvestigator are to be recorded as AEs. If an abnormal laboratory finding is associated with disease or organ toxicity, the investigator should report only the disease or organ toxicity as AEs. These AEs should also be assessed as to whether they meet the definition of seriousness and reported accordingly.

The investigator or subinvestigator will consider test results to be clinically significant in the following circumstances:

- Test result leads to any of the outcomes included in the definition of an SAE
- Test result leads to discontinuation from the study
- Test result leads to a concomitant medication treatment or other therapy
- Test result requires additional diagnostic testing or other medical intervention
- Test result meets the management criteria for liver function abnormalities identified in the Appendix 6

7.6.6.1 Liver Abnormalities

Management and Discontinuation Criteria for Abnormal Liver Function tests have been designed to ensure subject safety and evaluate liver event etiology. The investigator or subinvestigator must review study subject laboratory results as they become available to identify if any values meet the criteria in Appendix 6. When any test result meets the management criteria for liver function abnormalities, the results of further assessments and required follow-up should be recorded in the Liver Event Form.

7.6.7 Serious Adverse Events

7.6.7.1 Definition

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

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

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at-home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse. Test results that meet the criteria of Hy's law are considered SAEs (Appendix 6). The investigator or subinvestigator will determine the seriousness of AEs.

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

7.6.7.2 Reporting Serious Adverse Events

All SAEs must be reported to CRO or the sponsor in detail within 24 hours from the point in time when the investigator first becomes aware of the SAE. All SAEs must be reported regardless of causal relationship to the study treatment. An SAE should be reported using the appropriate page in the eCRF. If technical difficulties are encountered or the eCRF page for SAE reporting is unavailable, a paper SAE Form should be used instead. A sample of the SAE Form and further instructions can be found in the site regulatory binder. Follow-up information on the SAE may be requested by the sponsor.

When reporting SAEs, the investigator should record the diagnosis whenever possible. If no diagnosis is available at the time of reporting, individual signs and symptoms can be reported.

In the event of any SAE reported or observed during the study, whether or not attributable to the study treatment, site personnel must report within 24 hours. SAEs can be reported by electronic data capture system eCRF or by phone or fax, if eCRF is not available.

[redacted]:

[redacted]

[redacted]

OR

[redacted]

United States: [redacted]		Canada: [redacted]
Belgium: [redacted]		France: [redacted]
Ukraine: [redacted]		Germany: [redacted]
Russia: [redacted]		Spain: [redacted]
Georgia: [redacted]		Hungary: [redacted]
Czech Republic: [redacted]		Serbia: [redacted]
Israel: 1[redacted]		Estonia: 8[redacted]
Japan: [redacted]		Philippines: 1[redacted]
Latvia: [redacted]		Brazil: [redacted]
Taiwan: [redacted]		United Kingdom: [redacted]

If the sponsor requires a follow-up assessment, the investigator should provide new information as it becomes available and then report to the CRO or the sponsor. Discharge summaries, consultant reports, autopsy reports, or other relevant documents must be

evaluated by the investigator, and all relevant information must be reported. Copies of these reports may also be requested by the sponsor.

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

Any SAEs occurring after the AE assessment period specified in this section that are considered by the investigator to be related to drug treatment must be reported to the CRO or the sponsor.

The investigator will be responsible for reporting all SAEs to the IRB or IEC and the CRO or the sponsor. The sponsor or CRO will be responsible for reporting SAEs to the regulatory authorities as required by the applicable regulatory requirements.

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

Abuse, misuse, overdose, or medication errors (as defined below) in subjects treated with S-649266 or meropenem must be reported by the investigator to the CRO or the sponsor via fax using a Special Situations Report Form within 24 hours of becoming aware (refer to Section 7.6.7.2 for reporting destination). Special Situations information for Linezolid is not required to be reported. Adverse Events or SAEs associated with the administration of any medication will be reported by the investigator.

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

7.6.7.4 Pregnancy

Women of childbearing potential will be screened for pregnancy at the time of study enrollment. A positive test is reason for exclusion. Female subjects will be instructed to avoid conception until 28 days following treatment or according to country specific requirements, whichever is longer.

If a female subject becomes pregnant during the study, investigator or subinvestigator will immediately discontinue study drug treatment and appropriate antibiotic therapy should be provided. All pregnancies that occur after the first dose of the study treatment through the EOS must be reported by the investigator to the CRO or sponsor within 24 hours of becoming aware of the pregnancy using the Pregnancy Form (refer to

Section 7.6.7.2 for reporting destination). Pregnancy complications and elective terminations for medical reasons must be reported as AEs or SAEs as appropriate. Spontaneous abortion must be reported as an SAE. The outcome of the pregnancy (ie, birth, miscarriage, abortion) should be followed by the study site and must be reported using the Pregnancy Form.

7.6.7.5 Treatment-emergent Adverse Events

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

7.7 Subject Withdrawal or Discontinuation from the Study Treatment

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

Withdrawal

A subject may withdraw consent to participate in the study for any reason at any time. The investigator will advise the sponsor about the withdrawal of any subject from the study by using the eCRF. Date of completion/ discontinuation of the study treatment, period of discontinuation, and reason for discontinuation will be entered in the CRF. For subjects who withdraw consent at any time after the start of treatment, all EOS study visit assessments should be completed, if possible.

Discontinuation

The investigator or subinvestigator may discontinue a subject from the study treatment for any of the following reasons. Please note that unless the subject withdraws consent to participate in the study, all randomized subjects should be followed for the entire duration of the study even if study drug treatment was discontinued prematurely due to AE or treatment failure:

- A serious or intolerable AE occurs and the investigator considers that the subject should be withdrawn because of the AE
- The target disease worsens because of poor response to the study treatment and the investigator considers that the subject should be withdrawn
- The subject is lost to follow-up
- The investigator determines that the subject should be removed from the study because of other reasons

For subjects who are discontinued by the investigator or subinvestigator at any time after the start of treatment, they will be still considered to be in the study, and they should still be followed through to the completion of all study activities (ie, EOT, TOC, FU, and EOS, if possible). All subjects discontinued due to AEs will be followed until resolution of any AEs, until the unresolved AEs are judged by the investigator to have stabilized or the subject is lost to FU.

All withdrawn or discontinued subjects will remain in the study for safety and clinical outcome purposes. Subjects withdrawn or discontinued from study treatment should receive additional standard of care antibiotic therapy if, in the judgment of the investigator, such treatment is clinically indicated (see Section 6.2.4).

7.8 Other Study Procedures

Not applicable

7.9 Appropriateness of Measurements

The primary measure of efficacy selected in the study, all-cause mortality, has been discussed with regulatory agencies. The individual efficacy measurements for clinical or microbiological outcome selected for the study are commonly used in clinical trials of subjects with pneumonia. Therefore, these measurements are considered appropriate.

The safety evaluations selected for the study are typical of those for this subject population and type of investigation and utilize widely accepted measures that are appropriate.

7.10 Acceptable Time Windows

Measurements for efficacy or safety endpoints will be performed according to the schedule of assessments shown in Appendix 1. The following time window, shown in Table 7-2, is acceptable.

Table 7-2 Acceptable Time Windows

Study Activity		Acceptable Time Window
Screening	---	−48 hours
Randomization	Day 1	---
Day 3 pharmacokinetic blood sampling	At approximately the same time as the 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	+ 1 day
EOT	Last day of study treatment, clinical evaluations	As soon as possible after last dose (same calendar day or within 24 hours)
Unexpected EOT (an EOT with < 7 days of treatment)	Last day of study treatment clinical evaluations, and a blood sample should be obtained if possible	Same calendar day or within 24 hours
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; TOC = Test of Cure

8. STUDY ACTIVITIES

The overall schedule of events for the study is presented in Appendix 1. The general philosophy about obtaining measurements, samples, or evaluations for this study is that any particular item that is obtained because of the standard of care for the ICU would not have to be repeated and the information can go directly into the eCRF. In the event that Screening and Randomization take place on the same day, only 1 set of laboratory evaluations, including microbiological cultures and clinical laboratory tests, needs to be drawn/recorded before initiation of treatment. Laboratory results, ECGs, and microbiological cultures obtained prior to informed consent for this study may be added to the screening eCRF as needed to complete the subject evaluation.

8.1 Screening (Day –2 to Randomization)

- Informed consent
- Inclusion and exclusion criteria assessments
- Baseline subject characteristics (demographics)
- Medical history, including previous significant medical conditions
- Pregnancy test
- Physical examination, including height and body weight
- Vital signs, including blood pressure, body temperature, pulse rate, and respiratory rate
- Clinical laboratory tests, including hematology, blood chemistry, urinalysis, specialized tests, and others; see Table 7-1
- 12-lead ECG
- GCS
- Calculate APACHE II score
- Calculate SOFA score
- Provide parameters for CPIS score
- Clinical assessment of signs and/or symptoms
- Oxygenation status
- Chest radiograph
- Lower respiratory tract specimens and blood for microbiological culture
- AE assessment (begins with the signing of the informed consent form)
- Prior and concomitant therapies
- CrCl by Cockcroft-Gault equation and eGFR by MDRD equation (see Section 7.6.4.4)
- Screen subject via IRT
- Hospitalization

8.2 Treatment Period (Days 1 to 14)

8.2.1 Randomization and Treatment Initiation (Day 1)

- Randomize subject via IRT
- Initiate treatment based on eGFR by MDRD equation and CrCl by Cockcroft-Gault equation

8.2.2 All Treatment Days

- Continue randomized treatment
- Vital signs, including blood pressure, body temperature, pulse rate, and respiratory rate
- Oxygenation status

- Concomitant therapy
- AE assessment
- Hospitalization
- Dosage adjustment considered necessary on review of renal function conducted per local clinical practice; however, the second or later dose adjustment needs to be done at least 24 hours after the previous dose adjustment
- Survival

8.2.3 Treatment Day 3 or Day 4

- Activities for all treatment days (see Section 8.2.2)
- Clinical assessment of signs and/or symptoms
- Plasma drug concentration for all subjects (see Section 7.5)

8.2.4 Early Assessment (Occurs Once at the Investigator's Discretion During Day 3 or 4)

- Activities for all treatment days (see Section 8.2.2)
- Limited physical examination relevant to the subject's current condition
- Clinical laboratory tests, including hematology, blood chemistry, urinalysis; see Table 7-1
- CrCl by Cockcroft-Gault equation and eGFR by MDRD equation
- CrCl from urinary creatinine with a 2- to 8-hour urine collection, if needed
- GCS
- Calculate SOFA score
- Provide parameters for CPIS score
- Clinical assessment of signs and/or symptoms
- Chest radiograph, if clinically indicated
- Lower respiratory tract specimens and, if necessary, blood for microbiological culture
- Assess clinical outcome
- Assess microbiological outcome
- Survival

8.2.5 Treatment Day 14 (If Not End of Treatment)

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

- Activities for all treatment days (see Section 8.2.2)
- Limited physical examination relevant to the subject's current condition
- Clinical laboratory tests, including hematology, blood chemistry, and urinalysis;

see Table 7-1
- GCS
- Calculate SOFA score
- Provide parameters for CPIS score
- Clinical assessment of signs and/or symptoms
- Chest radiograph, if clinically indicated
- Lower respiratory tract specimens and, if necessary, blood for microbiological culture
- Assess clinical outcome
- Assess microbiological outcome
- Survival
- Record extension of treatment up to 21 days via IRT and reason for extension via eCRF as per Section 5.2

8.2.6 End of Treatment (Last Day of Study Treatment)

- Activities for all treatment days (see Section 8.2.2)
- If premature EOT, defined as < 7 days of treatment, a single blood draw for pharmacokinetics (within 24 hours of last dose) should be performed
- Limited physical examination relevant to the subject's current condition
- Clinical laboratory tests, including hematology, blood chemistry, and urinalysis; see Table 7-1
- GCS
- Calculate SOFA score
- Provide parameters for CPIS score
- Clinical assessment of signs and/or symptoms
- Chest radiograph
- Lower respiratory tract specimens and, if necessary, blood for microbiological culture
- Assess clinical outcome
- Assess microbiological outcome
- Record subject as EOT via IRT

8.3 Study Day 14 (14 Days After Initiation of Treatment)

- Survival
- Major nonfatal events, if present, should be evaluated

8.4 Test of Cure (End of Treatment + 7 Days)

- Limited physical examination relevant to the subject's current condition

- Vital signs, including blood pressure, body temperature, pulse rate, and respiratory rate
- Clinical laboratory tests, including hematology, blood chemistry, urinalysis, and specialized tests; see Table 7-1
- Clinical assessment of signs and/or symptoms
- Oxygenation status
- Chest radiograph
- Lower respiratory tract specimens and, if necessary, blood for microbiological culture
- GCS
- Calculate SOFA score
- Provide parameters for CPIS score subjects
- AE assessment
- Concomitant therapy
- Assess clinical outcome
- Assess microbiological outcome
- Hospitalization
- Survival

8.5 Follow-up (End of Treatment + 14 Days)

- Limited physical examination relevant to the subject's current condition
- Vital signs, including blood pressure, body temperature, pulse rate, and respiratory rate
- Clinical laboratory tests, including hematology, blood chemistry, and urinalysis; see Table 7-1
- Clinical assessment of signs and/or symptoms
- Oxygenation status
- Chest radiograph, if clinically indicated
- Lower respiratory tract specimens and, if necessary, blood for microbiological culture
- GCS
- Calculate SOFA score
- Provide parameters for CPIS score
- AE assessment
- Concomitant therapy
- Assess clinical outcome
- Assess microbiological outcome
- Hospitalization

- Survival

8.6 Study Day 28 (28 Days After Initiation of Treatment)

- Survival
- Major nonfatal events, if present, should be evaluated

8.7 End of Study (End of Treatment + 28 Days)

- Limited physical examination relevant to the subject's current condition
- Vital signs, including blood pressure, body temperature, pulse rate, and respiratory rate
- Clinical laboratory tests, including hematology, blood chemistry, and urinalysis; see Table 7-1, if required to follow abnormal safety test results
- AE assessment
- Concomitant therapy
- Hospitalization
- Survival

The EOS assessment may be performed by phone to document current subject status, in which case, the physical examination, vital signs, and laboratory tests will not be performed.

9. PLANNED STATISTICAL METHODS

9.1 General Considerations

The statistical analyses and pharmacokinetic analyses will be performed by the sponsor or designee. The detailed statistical analyses methods will be specified in a SAP. Deviations from analyses outlined in the protocol will be detailed and justified in the SAP. The SAP will be finalized before the scheduled database lock. The separate detailed population pharmacokinetic analysis and PK/PD analysis plans also will be prepared.

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

All subject study data, including data not appearing in tables, will be presented in data listings by subject. In general, all tables and associated graphics will be presented by treatment group. Individual subject data, pharmacokinetic data, and any derived data will be presented by treatment and subject. All analyses and tabulations will be performed by using SAS® Version 9.2 or higher, Phoenix® WinNonlin® Version 6.2.1 or higher, and NONMEM® Version 7.3 or higher.

All statistical testing is performed with a significance level of 2-sided 0.05 unless

otherwise noted.

The following individual evaluations have been planned at these prespecified milestones during the course of the study:

- When approximately 50 and 150 subjects have completed treatment and FU, an evaluation of safety and efficacy data will be performed by the Data Safety Monitoring Board (DSMB).
- The nonevaluable 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.
- A blinded evaluation of all-cause mortality will be done after approximately 150 subjects are enrolled and blinded re-estimation of sample size may be performed if deemed necessary.
- If the mortality rate is deemed too low (≤ 8%) compared with the assumption of 10% based on a blinded mortality rate when 50 subjects have completed the study, the lower limit of the acceptable APACHE II score will be set to ≥ 8.

9.2 Determination of Sample Size

The study design and the primary objective are based on the hypothesis that S-649266 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 S-649266 is more than 12.5% inferior to meropenem for the endpoint of all-cause mortality at Day 14. The 12.5% noninferiority margin was discussed with and agreed to by the US FDA.

A sample size of 244 evaluable subjects (122 evaluable subjects in the S-649266 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 nonevaluable, and therefore excluded from the primary population, because they have not received any doses of 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 nonevaluable 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 may perform a blinded re-estimation of sample size if deemed necessary.

9.3 Analysis Populations

The following analysis populations will be examined in this study:

- Intent-to-treat (ITT) population: all randomized subjects who received at least 1 dose of a study drug treatment

- Modified ITT (mITT) population: 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 microbiologic diagnosis

  Note: Subjects with bacterial pneumonia caused by Gram-positive aerobic or anaerobic (Gram-positive or Gram-negative) bacteria only will be excluded from the mITT population.
- Micro-evaluable Per-protocol (ME-PP) population: all subjects in the mITT population who do not have major protocol violations and have a culture confirmed diagnosis of a Gram-negative bacterium
- Safety population: all randomized subjects who receive at least 1 dose of the study treatment (ITT population); this population will be analyzed according to the treatment that the subjects actually received, rather than the treatment to which the subjects were randomized
- The pharmacokinetic concentration population: all subjects who undergo plasma sampling and have at least 1 evaluable pharmacokinetic assay result for S-649266; this population will be used for the concentration listing, plotting of the concentration-time data, population pharmacokinetic analyses, PK/PD analyses, and the concentration summary

9.4 Handling of Missing Data

Missing data will not be replaced.

9.5 Subject Disposition

Among the randomized subjects in the Safety population, the ITT population, the mITT population, and the ME-PP population, the number and percentage of subjects who complete the study and those subjects who prematurely discontinue before completing at least 7 days of treatment from the study will be summarized. In addition, reasons leading to study discontinuation will be summarized for each treatment group. The number and percentage of subjects randomized to each study treatment in each analysis population also will be presented.

9.6 Demographic and Baseline Characteristics

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

9.7 Prior Therapies

Prior therapies for drugs will be coded using the World Health Organization Drug Dictionary (WHO-DD). Subjects who received prior therapy will be listed and summarized for the Safety population and the mITT population.

9.8 Concomitant Therapies

Concomitant therapies for drugs will be coded using the WHO-DD. Subjects who received concomitant therapy will be listed and summarized for the Safety population and the mITT population.

9.9 Efficacy Analyses

The mITT population will be the primary population for efficacy. The ITT population and the ME-PP population will be used for sensitivity analyses.

9.9.1 Primary Efficacy Endpoint

All-cause mortality at Day 14 for S-649266 or the active comparator, meropenem, in adult subjects with either HABP, VABP, or HCABP.

The adjusted estimates of the difference in the all-cause mortality at Day 14 between S-649266 and meropenem will be presented along with 95% CIs based on a stratified analysis using Cochran-Mantel-Haenszel (CMH) weights. The CI will be 2-sided. The CMH weights will be calculated with stratification factor APACHE II score (≤ 15 and ≥ 16). 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 (S-649266 and meropenem) is smaller than a noninferiority margin of 12.5%.

9.9.2 Key Secondary Endpoints

The key secondary endpoints will be compared between treatment groups.

- The clinical outcome of treatment with S-649266 or meropenem per subject at TOC
- The microbiologic outcome of treatment with S-649266 or meropenem per subject at TOC
- Day 14 all-cause mortality rates of S-649266 with meropenem for superiority of S-649266

In the analysis of key secondary endpoints, a fixed-sequence testing approach will be applied for multiplicity adjustment with the primary efficacy analysis in order of (1) the microbiologic outcome at TOC, (2) the clinical outcome at TOC, and (3) Day 14 all-cause mortality rates of S-649266 with meropenem for superiority of S-649266

A per-subject microbiological outcome is determined based on individual microbiological outcomes for each baseline Gram-negative pathogen. For the subject to have a favorable microbiological outcome (ie, eradication), the outcome for each baseline Gram-negative pathogen has to be favorable (ie, all baseline pathogens are eradicated at the specified time point). If the microbiological outcome for any Gram-negative pathogen is unfavorable, the subject is considered to have an unfavorable overall (per-subject) microbiological outcome.

Superiority of S-649266 over meropenem can be concluded if the 2-sided 95% CI for the difference in mortality at Day 14 between the 2 treatment groups (S-649266 and meropenem) lies completely below zero.

9.9.3 Other Secondary Efficacy Endpoints

The other secondary endpoints will be compared between treatment groups.

- The clinical outcome of treatment with S-649266 or meropenem per subject at EA, EOT, and FU
- The microbiologic outcome of treatment with S-649266 or meropenem per subject at EA, EOT, and FU
- The all-cause mortality at Day 28
- The all-cause mortality during treatment and the follow-up period (until EOS)
- The resource utilization required for the treatment of the study-qualifying infection. This end point will not be included in the CSR, but it will be analyzed based upon a separate analytical plan after the conclusion of the study.

9.10 Safety Analyses

Safety assessments consist of AEs, clinical laboratory tests (hematology, blood chemistry, and urinalysis), specialized chemistry tests, and vital signs. Safety analyses will be performed for the Safety population.

9.10.1 Adverse Events

Adverse events will be classified by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA). Of AEs reported in the eCRF, TEAEs will be used for the safety analyses. The definition of TEAE is described in Section 7.6.7.5.

The number and the percentage of subjects who experienced TEAEs will be summarized by treatment group. TEAEs will be tabulated in a similar fashion. The number of AEs, which are counted by cases reported, will also be presented in the same AE category in the overall summary.

For the summary of TEAEs by System Organ Class and Preferred Term, the number of subjects who experienced AEs will be presented for each treatment group with the percentage of subjects. The summary by severity and the summary by relationship to study treatment will be presented by System Organ Class and Preferred Term.

All AEs including AEs that have occurred before or after the first dose of the study treatment will be listed.

9.10.2 Vital Signs

Summary statistics for vital signs will be presented for EOT, TOC, and for the change from baseline to each time point. Baseline will be the last value obtained before randomization.

9.10.3 Clinical Laboratory Analysis

Summary statistics for laboratory test data will be presented for each scheduled time point and for the change from baseline to each time point. Baseline will be the last value obtained before randomization.

9.11 Pharmacokinetics

Individual plasma concentrations of S-649266 will be listed and summarized by nominal sampling time window, and if possible, dosing group based on renal function. The time course of individual and mean plasma concentrations will be presented by appropriate graphics. Population pharmacokinetic analyses will be performed and reported separately by Clinical Pharmacology & Pharmacokinetics of Shionogi & Co., Ltd.

9.12 Pharmacokinetic/Pharmacodynamic Analyses

The PK/PD analyses will be performed and reported separately by the Clinical Pharmacology & Pharmacokinetics of Shionogi & Co., Ltd. For each subject randomized to S-649266 with an identified Gram-negative pathogen, the $\%fT_{>MIC}$ will be calculated and the relationship between $\%fT_{>MIC}$, and clinical and microbiologic outcome will be described.

9.13 Pharmacoeconomics Associated with Treatment

The pharmacoeconomics of treatment collected during the study will focus primarily on the resource utilization required for the treatment of the study-qualifying infection. Facility utilization will be assessed by determination of the time in 24-hour days associated with the treatment of the infection:

- Length of hospital stay attributable to the infection
- Days in ICU
- Hours on assisted mechanical ventilation including ventilation method and parameters
- Days in isolation for infection control (ICU or ward)
- Discharge status, eg, to home, hospice, or other healthcare facility (nursing home or long-term acute hospital)

Analyses of the above data will not be included in the CSR, but it will be analyzed based upon a separate analytical plan after the conclusion of the study.

9.14 Data Safety Monitoring Board Safety and Efficacy Evaluation

When approximately 50 and 150 randomized and treated subjects have completed treatment and FU, an evaluation of safety and efficacy data will be performed by the DSMB according to the DSMB charter. A safety review, including AEs and clinical laboratory tests (hematology, blood chemistry, urinalysis, vital signs, and physical examinations), will be summarized by treatment group. An efficacy review, including clinical evaluations, central laboratory findings, and central microbiological laboratory findings, will be summarized by treatment group. The description of the DSMB is described in Section 10.8.1. After the review, the DSMB will communicate their recommendations to the sponsor. The recommendations may include, but are not limited to, continuing, stopping, or modifying the study; they will also provide the reason for each recommendation.

9.15 Interim Analysis

The results of interim analyses performed by the DSMB are blinded to sponsor's personnel and not shared with the sponsor. An alpha spend of 0.0001 based on Haybittle-Peto will be used to control alpha for each interim analysis.

10. ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

Sponsor for North America and South America:	Shionogi Inc. 300 Campus Drive, Florham Park, NJ 07932 USA
Sponsor for Europe/Middle East:	Shionogi B.V. Kingsfordweg 151, 1043 GR Amsterdam, Netherlands
Sponsor for Asia-Pacific:	Shionogi & Co., Ltd. (Head Office) 1-8 Doshomachi, 3 Chrome, Chuo-ku, Osaka 541-0045, Japan (Development Office) 12F, Hankyu Terminal Bldg., 1-4, Shibata 1-chome, Kita-ku, Osaka 530-0012, Japan
Sponsor Contact:	[redacted] Shionogi Inc. 300 Campus Drive Florham Park, NJ 07932, USA [redacted] [redacted] Shionogi B.V. Kingsfordweg 151, 1043 GR Amsterdam, Netherlands [redacted] E-mail: [redacted]

[redacted]
Clinical Research Department, Shionogi & Co., Ltd.
1-1-4, Shibata, Kita-ku, Osaka 530-0012, Japan
Tel: [redacted]

[redacted]

[redacted]

Medical Monitor in Shionogi:

[redacted] Clinical Development
Shionogi Inc.
300 Campus Drive
Florham Park, NJ 07932, USA

Medical Monitor in CRO:

[redacted]

Investigator and Study Center: Multicenter

Study Monitoring:

[redacted]

Bioanalytical Laboratory:

[redacted]

Microbiological Laboratory:

[redacted]

10.2 Institutional Review Board or Institutional Ethics Committee Approval

Relevant IRBs/IECs will safeguard the rights, safety, and well-being of the subjects by reviewing the following study documents: the protocol, informed consent form, written information on subject recruitment procedures (if applicable), other written information

given to the subjects, Investigator's Brochure, safety updates, annual progress reports (if applicable), and any significant revisions to these documents. The investigator or the sponsor will provide these study documents to the IRB/IEC. The IRB/IEC will be appropriately constituted in accordance with ICH good clinical practice (GCP), and local requirements, as applicable. The study will be undertaken only after the IRB/IEC has given full approval and the sponsor has received a document being approved.

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

10.3 Ethical Conduct of the Study

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

10.4 Subject Information and Consent

The sponsor will provide the investigators with a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements. The sponsor must agree to any changes to the proposed consent form suggested by the investigator prior to submission to the IRB/IEC, and the IRB/IEC approved version must be provided to the site monitor after IRB/IEC approval.

The investigator will generate an informed consent form for the study. The consent form will include all the elements required by the ICH GCP and any additional elements required by local regulations and will be reviewed and approved by the appropriate IRB/IEC before use. The investigator or subinvestigator will explain the nature, purpose, methods, reasonable anticipated benefits, and potential hazards of the study to the subject or, if incapacitated, to his/her legally qualified representative in simple terms by using the consent form before the subject is entered into the study. The method of obtaining and documenting informed consent will comply with ICH GCP and all applicable regulatory requirements.

10.5 Subject Confidentiality

Procedures for protecting subject privacy must adhere to applicable data privacy laws and regulations. In order to maintain subject privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the subject by the subject number. The investigator will grant site monitors and auditors of the sponsor or designee and regulatory authorities access to all source documents for verification of data collected on the eCRFs and for verification of the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations. The investigator and the sponsor are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, Health Insurance Portability and Accountability Act [HIPAA]).

Appropriate consent and authorization for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

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

10.6 Study Monitoring

The sponsor or designee will monitor the study to ensure that the study is conducted in accordance with ICH GCP requirements and protocol. The study monitoring will be performed by a representative of the sponsor (site monitor) through on-site monitoring visits as frequently as necessary and by frequent communications (e-mail, letter, telephone, and fax). The site monitor will review data recorded in the eCRFs, verify the eCRF entries with direct access to source documents, collect any safety/efficacy information on subjects, verify that amounts of unused study drugs are accurate, and check retention of source documents and essential documents.

10.7 Case Report Forms and Source Documents

10.7.1 Case Report Forms

The eCRFs for each subject who signed informed consent will be made accessible to the investigator, and historical information and study data, which are specified by the protocol, will be recorded in the eCRFs by the investigator. All subject data from the study evaluations must be collected on source documents and promptly entered in the eCRFs in accordance with the specific instructions. The eCRF entries will be performed by an investigator, subinvestigator, and study coordinator who are authorized in documentation.

When queries are generated by the sponsor or designee to the participating medical institutions for resolution, eCRF data may be changed or a response will be recorded in accordance with the specific instructions. Appropriate documentation of any changes to the eCRF will be maintained in the study record. The investigator must ensure that data reported on the eCRF are accurate, complete, legible, and timely and sign the eCRFs to verify the integrity of the data recorded.

A list of the reference ranges for all laboratory tests to be undertaken will be a part of the documentation to be collated prior to the initiation of study. The list of reference ranges for all laboratory tests should be updated if changes occur during the study. If a central laboratory has been selected to perform any or all tests, it is essential that all the reference ranges for the laboratory tests should also be collected.

10.7.2 Source Documents

Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures,

AEs, and subject status. However, the following data can be recorded directly in the eCRF as source data:

- Reason for use of prior therapy or concomitant therapy
- Severity, seriousness, and causal relationship to the study treatment of AE
- Any comments inserted into eCRF

Data automatically calculated by the eCRF system do not have to be captured in source documents, eg, QTc.

The investigator must maintain source documents, such as laboratory reports and complete medical history and physical examination reports. All the source documents must be accessible for verification by the site monitor, auditor, IRB/IEC, and inspectors from regulatory authorities. Direct access to these documents must be guaranteed by the investigator, subinvestigator, or study coordinator, who must provide support at all times for these activities. For all sources of original data required to complete the eCRF, the nature and location of the source documents will be identified by the sponsor and the site staff. If electronic records are maintained at the medical institution, the method of verification must be specified in a document within the medical institution.

10.7.3 External Data

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

- Microbiological results from central laboratory
- Clinical laboratory results from central laboratories
- Concentration of S-649266 in plasma, ELF, or other biological fluids/tissues determined by the bioanalytical laboratory, according to procedures specified in a separate document
- Population pharmacokinetics and PK/PD analyses results

10.8 Committees

10.8.1 Independent Data Safety Monitoring Board

An independent DSMB will be established for this study. Details of the DSMB composition, roles, and responsibilities, and processes will be documented in a separate DSMB charter.

10.9 Termination or Suspension of the Study

10.9.1 Termination or Suspension of the Entire Study

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

- Ensuring subject safety becomes difficult due to safety concerns (eg, the occurrence of many treatment-related SAEs)

- Achieving the purpose of the study is considered impossible (eg, data suggest lack of efficacy/safety, inadequate recruitment of subjects)

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

For withdrawal criteria for individual subjects, see Section 7.7.

10.9.2 Termination or Suspension of the Study by Medical Institution

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

The sponsor may request the investigator to prematurely terminate or suspend the study in the medical institution at any time due to major violations/deviations from the protocol, other procedures, or ICH GCP guidelines.

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

10.10 Protocol Deviations and Modifications

The investigator will conduct the study in compliance with the protocol provided by the sponsor and the approval/favorable opinion given by the IRB/IEC and the regulatory authorities. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard to subjects.

The investigator or subinvestigator should document any deviation from the protocol and the reason. If the investigator deviates from the protocol or a change of the protocol to eliminate an immediate hazard to subjects, the record should be immediately submitted to the sponsor, the medical institution, and the IRB/IEC by the investigator, and the IRB/IEC will provide expedited review and approval/favorable opinion. After the investigator obtained approval/favorable opinion of the IRB/IEC, the investigator should obtain written agreement of the sponsor.

When a deviation from the protocol is required to eliminate immediate hazards to subjects, the investigator will contact the sponsor, if circumstances permit, to discuss the planned course of action. Any deviations from the protocol must be fully documented on source documentation.

10.11 Data Management

The sponsor or designee will be responsible for data management and data analysis. These procedures are specified in a separate document.

10.12 Retention of Data

The study documents must be maintained as specified in the ICH GCP guidelines and as required by the applicable regulatory requirements. The investigator and study site should take measures to prevent accidental or premature destruction of these documents.

If the sponsor is granted manufacturing and marketing approval for the drug, the sponsor will promptly notify the investigator or the head of the study center in writing.

Records will be retained for any of the following periods:

- At least 2 years after the last marketing application approval
- 2 years after formal discontinuation of the clinical development of the investigational product
- Another period according to applicable country regulatory requirements, whichever is later

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

10.13 Quality Control and Assurance

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

This study will be conducted in accordance with the provisions of the Declaration of Helsinki and all revisions thereof, in accordance with ICH GCP, and as required by the applicable regulatory requirements.

Necessary training for the study will be provided at the investigator's meeting and for study center personnel prior to the initiation of the study.

10.14 Publication and Disclosure Policy

All information regarding S-649266 supplied by the sponsor to the investigator is privileged and confidential. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the sponsor. It is

understood that there is an obligation to provide the sponsor with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of S-649266 and may be disclosed to regulatory authorities, other investigators, corporate partners, or consultants as required.

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

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

10.15 Financial Disclosure

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

11. REFERENCE LIST

1. Diene SM, Rolain JM. Carbapenemase genes and genetic platforms in gram-negative bacilli: Enterobacteriaceae, *Pseudomonas* and *Acinetobacter* species. Clin Microbiol Infect 2014;20(9):831-8.
2. Livermore DM. Current epidemiology and growing resistance of gram-negative pathogens. Korean J Intern Med 2012;27:128-42.
3. Li XZ, Plésiat P, Nikaido H. The challenge of efflux-mediated antibiotic resistance in Gram-negative bacteria. Clin Microbiol Rev 2015;28(2):337-418.
4. Nordmann P, Naas T, Poirel L. Global spread of carbapenemase-producing Enterobacteriacea. Emerg Infect Dis 2011;17(10):1791-8.
5. Falagas ME, Tansarli GS, Karageorgopoulos DE, Vardakas KZ. Deaths attributable to carbapenem-resistant Enterobacteriaceae infections. Emerg Infect Dis 2014;20(7):1170-5.
6. Bullen JJ. The significance of iron in infection. Rev Infect Dis 1981;3:1127-38.
7. Buchanan SK. Bacterial metal detectors. Mol Microbiol 2005;58(5):1205-9.
8. Curtis NA, Eisenstadt RL, East SJ, Cornford RJ, Walker LA, White AJ. Iron-regulated outer membrane proteins of *Escherichia coli* K-12 and mechanism and action of catechol-substituted cephalosporins. Antimicrob Agents Chemother 1988;32(12):1879-86.
9. Krewulak KD, Vogel HJ. Structural biology of bacterial iron uptake. Biochim Biophys Acta. 2008;1778(9):1781-804.
10. Morrissey I, Hackel M, Badal R, et al. A review of ten years of the Study for Monitoring Antimicrobial Resistance Trends (SMART) from 2002 to 2011. Pharmaceuticals (Basel) 2013;6:1335-46.
11. Colpan A, Johnston B, Porter S, et al. *Escherichia coli* sequence type 131 (ST131) subclone H30 as an emergent multidrug-resistant pathogen among US veterans. Clin Infect Dis 2013;57(9):1256-65.
12. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. Clin Infect Dis 2011;53(1):60-7.
13. Munoz-Price LS, Poirel L, Bonomo RA, et al. Clinical epidemiology and global expansion of *Klebsiella pneumoniae* carbapenemases. Lancet Infect Dis 2013;13(9):785-96.
14. Cantón R, Akóva M, Carmeli Y, et al. Rapid evolution and spread of carbapenemases among Enterobacteriaceae in Europe. Clin Microbiol Infect 2012;18(5):413-31.
15. Marchaim D, Chopra T, Pogue JM, et al. Outbreak of colistin-resistant, carbapenem-resistant *Klebsiella pneumoniae* in metropolitan Detroit, Michigan. Antimicrob Agents Chemother 2011;55(2):593-9.

16. Magiorakos AP, Srivivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18(3);268-281.

17. American Thoracic Society. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388-416.

18. MHRA SPC for Meropenem Trihydrate http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1466143257366.pdf Accessed 09 December 2016.

19. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26(1):1-10.

20. Drusano GL. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug.' Nat Rev Microbiol 2004;2(4):289-300.

21. Hatano K, Wakai Y, Watanabe Y, et al. Simulation of human plasma levels of beta-lactams in mice by multiple dosing and the relationship between the therapeutic efficacy and pharmacodynamic parameters. Chemotherapy 1994;40(1):1-7.

22. Turnidge JD. The pharmacodynamics of beta-lactams. Clin Infect Dis 1998;27(1):10-22.

23. Lodise TP, Lomaestro BM, Drusano GL. Application of antimicrobial pharmacodynamic concepts into clinical practice: focus on beta-lactam antibiotics: insights from the Society of Infectious Diseases Pharmacists. Pharmacotherapy 2006;26(9):1320-32.

24. Micek S, Kollef M, Torres A, et al. *Pseudomonas aeruginosa* nosocomial pneumonia: impact of pneumonia. Infect Control Hosp Epidemiol 2015;36(10):1190-7.

25. Torres A, Ferrer M, Badia RJ. Treatment guidelines and outcomes of hospital-acquired and ventilator-associated pneumonia. Clin Infect Dis 2010;51(Suppl1):S48-S53.

26. Talbot G, Powers J, Hoffmann S. Biomarkers Consortium of the Foundation for the National Institutes of Health CABP-ABSSSI and HABP-VABP Project Teams. Developing Outcomes Assessments as Endpoints for Registrational Clinical Trials of Antibacterial Drugs: 2015 Update From the Biomarkers Consortium of the Foundation for the National Institutes of Health. Clin Infect Dis 2016;62(5):603-7.

27. Guidance for Industry. Antibacterial Therapies for Patients with Unmet Medical Need for the Treatment of Serious Bacterial Diseases. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2013, July.

28. Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. European Medicine Agency, Committee for Human Medicinal Products (CHMP) 24 October 2013 EMA/CHMP/351889/2013.

29. Guidance for Industry. Drug Interaction Studies. — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2012 February.

30. Guideline on the investigation of drug interactions. European Medicine Agency, Committee for Human Medicinal Products (CHMP) 21 June 2012 EMA/CPMP/EWP/560/95/Rev. 1 Corr. 2.

31. Concept Paper on revision of the points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products (CHMP/EWP/2655/99) and conversion to a CHMP guideline. European Medicine Agency, Committee for Human Medicinal Products (CHMP) 2014, February.

32. Levey AS, Greene T, Kusek J, Beck G. A simplified equation to predict glomerular filtration rate from serum creatinine [abstract]. J Am Soc Nephrol 2000;11:155A.

33. Irie F, Iso H, Sairenchi T, et al. The relationships of proteinuria, serum creatinine, glomerular filtration rate with cardiovascular disease mortality in Japanese general population. Kidney Int 2005;69:1264-71.

34. Cockcroft DW, Gault MD. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

35. Merrem I.V. [Package Insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2016. http://www.azpicentral.com/merrem/merremiv.pdf Accessed 09 December 2016.

Appendix 1 Time and Events Schedule

Evaluation	Screening/ Baseline	Randomization	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		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			

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)
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]
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)	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.

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 immediate previous 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 endpoints

Appendix 2 Glasgow Coma Scale

Eye Opening	Spontaneous	4
	To speech	3
	To pain	2
	None	1
Best Verbal Response	Orientated	5
	Confused	4
	Words	3
	Sounds	2
	None	1
Best Motor Response	Obey commands	6
	Localizing	5
	Normal flexion	4
	Flexing	3
	Extension	2
	None	1

In ventilated and sedated subjects, the Glasgow Coma Scale cannot be properly assessed, and a normal score of 15 could be used to complete the APACHE II and SOFA scores. If a reliable presedation score is available, it can be used.

Reference:

Teasdale G, Maas A, Lecky F, Manley G, Stocchetti N, Murray G. The Glasgow Coma Scale at 40 years: standing the test of time. Lancet Neurol 2014;13:844-54.

Appendix 3 APACHE II Score

The APACHE II Severity of Disease Classification System

Physiologic Variable	High Abnormal Range					Low Abnormal Range			
	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature – Rectal* (°C)	≥41	39 to 40.9		38.5 to 38.9	36 to 38.4	34 to 35.9	32 to 33.9	30 to 31.9	≤29.9
Mean Arterial Pressure - mm Hg	≥160	130 to 159	110 to 129		70 to 109		50 to 69		≤49
Heart Rate (ventricular response)	≥180	140 to 179	110 to 139		70 to 109		55 to 69	40 to 54	≤39
Respiratory Rate (non-ventilated or ventilated)	≥50	35 to 49		25 to 34	12 to 24	10 to 11	6 to 9		≤5
Oxygenation: A-aDO_2 **or** PaO_2 (mm Hg) a. FIO_2 ≥0.5 record A-aDO_2 b. FIO_2 <0.5 record PaO_2	≥500	350 to 499	200 to 349		<200 >70	61 to 70		55 to 60	<55
Arterial pH (preferred) **or** Serum HCO_3 (venous mEq/L) (not preferred, but may use if no ABGs)	≥7.7 ≥52	7.6 to 7.69 41 to 51.9		7.5 to 7.59 32 to 40.9	7.33 to 7.49 22 to 31.9		7.25 to 7.32 18 to 21.9	7.15 to 7.24 15 to 17.9	<7.15 <15
Serum Sodium (mEq/L)	≥180	160 to 179	155 to 159	150 to 154	130 to 149		120 to 129	111 to 119	≤110
Serum Potassium (mEq/L)	≥7	6 to 6.9		5.5 to 5.9	3.5 to 5.4	3 to 3.4	2.5 to 2.9		<2.5
Serum Creatinine (mg/dL) Double point score for acute renal failure	≥3.5	2 to 3.4	1.5 to 1.9		0.6 to 1.4		<0.6		
Hematocrit (%)	≥60		50 to 59.9	46 to 49.9	30 to 45.9		20 to 29.9		<20
White Blood Cell Count (total/mm^3) (in 1000s)	≥40		20 to 39.9	15 to 19.9	3 to 14.9		1 to 2.9		<1
Glasgow Coma Score (GCS)	Score = 15 minus actual GCS								
A. Total Acute Physiology Score (sum of 12 above points)									
B. Age points (years) ≤44=0; 45 to 54=2; 55 to 64=3; 65 to 74=5; ≥75=6									
C. Chronic Health Points (see below)									
Total APACHE II Score (add together the points from A+B+C)									

A-aDO_2 = alveolar-arterial pressure difference for oxygen; ABG = arterial blood gas; APACHE II = Acute Physiology and Chronic Health Evaluation II; FiO_2 = fraction of inspired oxygen; GCS = Glasgow Comma Score; PaO_2 = partial pressure of oxygen

* If core temperature measurement is not available (ie, tympanic, rectal, esophageal), oral and axillary temperatures could be adjusted by adding 0.5°C and 1°C, respectively.

Chronic Health Points: If the subject has a history of severe organ system insufficiency or is immunocompromised as defined below, assign points as follows: 5 points for

nonoperative or emergency postoperative subjects and 2 points for elective postoperative subjects.

Definitions: organ insufficiency or immunocompromised state must have been evident prior to this hospital admission and conform to the following criteria:

- **Liver** – biopsy proven cirrhosis and documented portal hypertension; episodes of past upper gastrointestinal bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma
- **Cardiovascular** – New York Heart Association Class IV
- **Respiratory** – chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction (eg, unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension [> 40 mm Hg], or respirator dependency)
- **Renal** – receiving chronic dialysis
- **Immunocompromised** – the subject has received therapy that suppresses resistance to infection (eg, immunosuppression, chemotherapy, radiation, long-term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection [eg, leukemia, lymphoma, AIDS])

Reference:

Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818-29.

Appendix 4 Sequential Organ Failure Assessment Score

The Sequential Organ Failure Assessment (SOFA) Score[a]					
	SOFA Score				
Variables	**0**	**1**	**2**	**3**	**4**
Respiration PaO_2/FiO_2, mm Hg	> 400	≤ 400	≤ 300	≤ 200[b]	≤ 100[b]
Coagulation Platelets $\times 10^3/\mu L$	> 150	≤ 150	≤ 100	≤ 50	≤ 20
Liver Bilirubin, mg/dL[c]	< 1.2	1.2 – 1.9	2.0 – 5.9	6.0 – 11.9	> 12.0
Cardiovascular Hypotension	No hypotension	Mean arterial pressure < 70 mm Hg	Dop ≤ 5 or dob (any dose)[d]	Dop > 5, epi ≤ 0.1, or norepi ≤ 0.1[d]	Dop > 15, epi > 0.1, or norepi > 0.1[d]
Central Nervous System Glasgow Coma Score Scale	15	13 - 14	10 - 12	6 -9	< 6
Renal Creatinine, mg/dL or Urine Output, mL/d[e]	< 1.2	1.2 – 1.9	2.0 – 3.4	3.5 – 4.9 or < 500	> 5.0 or < 200

FiO_2 = fraction of inspired oxygen; PaO_2 = partial pressure of oxygen, norepi = norepinephrine; dob = dobutamine; Dop = dopamine; epi = epinephrine; and FiO2 =, fraction of inspired oxygen.

a In nonventilated subjects, a respiration score of 0 may be assigned.

b Values are with respiratory support.

c To convert bilirubin from mg/dL to µmol/L, multiply by 17.1.

d Adrenergic agents administered for at least 1 hour (doses given are in µg/kg/minute).

e To convert creatinine from mg/dL to µmol/L, multiply by 88.4.

Reference:

Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA. 2001;286(14):1754-8.

Appendix 5 Clinical Pulmonary Infection Score Parameters

CPIS Points	0	1	2
Tracheal Secretions[a]	Few	Moderate	Large
Chest radiograph Infiltrates[b]	None	Patchy or diffuse	Localized
Temperature (°C)	≥ 36.1 and ≤ 38.4	≥ 38.5 and ≤ 38.9	≥ 39.0 or ≤ 36.0
Leukocytes (/mm^3)	≥ 4,000 and ≤ 11,000	< 4,000 or > 11,000	
PaO_2/FiO_2 (mm Hg)[b]	> 240 or evidence of Acute Respiratory Distress Syndrome (ARDS)		≤ 240 and no evidence of ARDS

ARDS = Acute Respiratory Distress Syndrome; CPIS = Clinical Pulmonary Infection Score Parameters; FiO_2 = fraction of inspired oxygen; PaO_2 = partial pressure of oxygen

In nonventilated subjects in whom blood gasses are not drawn, a PaO_2/FiO_2 score of 0 may be assigned.

a If purulent: +1.

b When multiple blood gas measured in 1 day, use first blood gas measure in the morning.

Reference:

Luna CM, Blanzaco D, Niederman MS, et al. Resolution of ventilator-associated pneumonia: prospective evaluation of the Clinical Pulmonary Infection Score as an early clinical predictor of outcome. Crit Care Med. 2003;31:676-82.

Appendix 6 Management and Discontinuation Criteria for Abnormal Liver Function Tests

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

Abnormal Liver Chemistry Criteria:

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

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

Action to Be Taken by Investigator:

If any 1 of the abnormal liver chemistry criteria is met, the investigator or subinvestigator must do the following:

- Instruct the subject to discontinue study drug immediately if the abnormal laboratory values cannot be explained by an alternate reason (eg, PT-INR values increase due to administration of warfarin). Investigators are advised to use medical judgment in such cases and consult with the sponsor if in doubt. If an alternate reason is not available, the investigator or subinvestigator should not rechallenge the subject with the investigational product without consulting the sponsor.
- Following the initial observed elevation, every effort should be made to have the subject reassessed within 48 to 72 hours to repeat liver function chemistries and for further hepatic evaluation.
- Every effort should be made to monitor the subject 2 to 3 times per week until liver function chemistries (ALT, AST, alkaline phosphatase, TBL) resolve, stabilize, or return to within the normal range or to baseline levels.
- Report the event to the sponsor as soon as possible, but not later than 72 hours after learning of its occurrence on the Liver Event Form.
- Consider consultation with a specialist, such as a hepatologist.
- Consider liver imaging (ie, ultrasound, magnetic resonance imaging, computerized tomography).

For Criterion b, the case must be reported as a serious adverse event.

Follow-up Examination:

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

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

Appendix 7 Empiric Therapy Case: Eligibility Flow Chart

Appendix 8 Sponsor Signature

Form 510-01

Study Protocol 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

Study Protocol Number: 1615R2132

Version Number: 4

Issue Date: 22 Feb 2019

Sponsor signatory:

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

See electronic signature page

[redacted]

See electronic signature page

Date: day-month-year

Appendix 9 Investigator's Signature

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
Study Number:	1615R2132
Date of Original: (Version 1)	2 Aug 2016
Date of Latest Amendment (Version 4)	22 Feb 2019

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

Signed:_____ Date:_____

Printed Name: _____

Title: _____

Affiliation: _____