Shionogi Study Title:	A Multicenter, Randomized, Open-label Clinical Study of S-649266 or Best Available Therapy for the Treatment of Severe Infections Caused by Carbapenem-resistant Gram-negative Pathogens
Shionogi Study Number:	1424R2131
ClinicalTrials.gov Registration No.	NCT02714595
Study Document	Protocol Version 4 (Amendment 3) 16 November 2017

History of Protocol Amendments

Version 1 (Original)	11 November 2015
This version of the protocol was not used to enroll participants	
Version 2	18 January 2016
This version of the protocol was not used to enroll participants	
Version 3	09 November 2016
• Better defined the inclusion criteria for patients that had fail previous empiric antibiotic therapy • Improved the descriptions of acceptable birth control methods and patients who were eligible without birth control • Better described vasopressor therapy use as far a inclusion criteria were concerned • Clarified the WBC type which is used to define neutropenia and the minimum allowed cell count thereof • Clarified the time limits for previous use of potentially effective antibiotic therapy • Added exclusion criteria for patients on peritoneal dialysis • Removes the post-ventilation time criterion as a definition of HAP • Provides guidance on other means of measuring temperature which would qualify a patient as having fever or hypothermia • Clarifies that de-escalation of Gram-negative antibiotics in BAT subjects should also be considered at EA visit • The number of sites was increased to reduce the overall time to complete the study • Clarified that resistance to a carbapenem, which might be different in different countries, is defined as any carbapenem • A section was added to introduce the use of diagnostic tests for carbapenem-resistant, Gram-negative bacteria that could help physicians identify drug resistant pathogens earlier in the treatment process • Description of the results of the thorough QTc study were included • The requirement that the planned standard of care regimen needs to be recorded prior to randomization of the patient • Clarified the timing of the use of an adjunctive Gram-negative antibiotic and	

explicitly does not permit adding systemic antibiotics until the TOC • Described the possible use of investigation diagnostics to establish treatment plans and the requirement that an informed consent form be signed if that was the case • Described the means of obtaining data needed to complete various Scoring systems or vital signs if the typical means were prevented by the nature of the infection or treatment • Established a time frame for acceptable cultures from patients that had failed previous therapy • Changed the procedure for retaining study records at a site that is unable to store the records	
Version 4	16 November 2017
• Clarified and better defined the acceptability of bronchiectasis patients • Removed methotrexate, procainamide, and probenecid from the list of unacceptable concomitant medications • Additional new information from ongoing or completed studies was added to drug information background • Required that the history of the patient for systemic antibiotics go back in time to 45 days instead of just 2 weeks. • Added an independent Data Safety Monitoring Board to the study in place of an ad hoc Medical Review Committee	

CLINICAL STUDY PROTOCOL: 1424R2131

Study Title:	A Multicenter, Randomized, Open-label Clinical Study of S-649266 or Best Available Therapy for the Treatment of Severe Infections Caused by Carbapenem-resistant Gram-negative Pathogens
Study Number:	1424R2131
EudraCT Number:	2015-004703-23
Study Phase:	3
IND Number:	116,787
Product Name:	S-649266 (INN generic name: Cefiderocol)
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Issue Date:	
Version 1:	11 November 2015
Version 2:	18 January 2016
Version 3:	09 November 2016
Version 4	16 November 2017

* The study sponsor may be one 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, Open-label Clinical Study of S-649266 or Best Available Therapy for the Treatment of Severe Infections Caused by Carbapenem-resistant Gram-negative Pathogens

Study Number: 1424R2131

Study Phase: 3

Primary Objectives:

- To assess, at test of cure (TOC)[1], the clinical outcome of treatment with S-649266 or best available therapy (BAT) in adult patients with either hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP)/healthcare-associated pneumonia (HCAP) or bloodstream infections/sepsis (BSI/sepsis)[2] caused by carbapenem-resistant Gram-negative pathogens
- To assess, at TOC, the microbiologic outcome of treatment with S-649266 or BAT in adult patients with complicated urinary tract infection (cUTI) caused by carbapenem-resistant Gram-negative pathogens

Secondary Objectives:

- To assess the safety of S-649266

The other secondary objectives of this study are established as follows:

- To assess the clinical outcome of treatment with S-649266 or BAT in patients with either HAP/VAP/HCAP or BSI/sepsis at End of Treatment (EOT)[3] and Follow-up (FUP)
- To assess the clinical outcome of treatment with S-649266 or BAT in patients with cUTI at EOT, TOC, and FUP
- To assess the microbiologic outcome of treatment with S-649266 or BAT in patients with either HAP/VAP/HCAP or BSI/sepsis at EOT, TOC, and FUP[4]
- To assess the microbiologic outcome of treatment with S-649266 or BAT in patients with cUTI at EOT and FUP
- To assess the microbiologic outcome of treatment with S-649266 or BAT in patients with bacteremia (regardless of the primary infection diagnosis) at EOT, TOC, and FUP
- To assess the composite clinical and microbiologic outcome of treatment with S-649266 or BAT in patients with cUTI at EOT, TOC, and FUP

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1 TOC is defined as end of treatment (EOT) + 7 days (± 2 day).

2 BSI/sepsis is a group of patients with documented carbapenem-resistant Gram-negative infections in the blood stream (BSI) or in a body site other than the urinary tract (cUTI) or lung (HAP/VAP/HCAP) and in case of sepsis, evidence of systemic inflammatory response syndrome (SIRS).

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

4 FUP = follow-up is defined as EOT + 14 days (± 3 days).

- To assess the all-cause mortality at Day 14 and Day 28 in patients with HAP/VAP/HCAP and BSI/sepsis
- To assess the relationship between the pharmacodynamic parameter $\%fT_{>MIC}$ based on plasma drug concentrations at steady state and the clinical and microbiologic outcomes of treatment with S-649266 in patients with HAP/VAP/HCAP, cUTI, or BSI/sepsis
- To assess the resource utilization required for the treatment of the study-qualifying infection
- To compare S-649266 with BAT in patients with HAP/VAP/HCAP, cUTI, or BSI/sepsis based on the composite endpoint of survival and no change in antibiotic treatment due to either lack of therapeutic benefit or drug-related toxicity at TOC

Study Design:

This is a Phase 3, multicenter (multinational), open-label, parallel group, randomized, active-controlled study in approximately 150 patients with documented carbapenem-resistant Gram-negative bacterial infections. Patients meeting eligibility criteria and assessed by the investigator to require 7 to 14 days of intravenous treatment in hospital will be randomized (2:1) to either S-649266 2 g administered intravenously over 3 hours, every 8 hours (q8h) or BAT.

Study Population:

Patients with the following infections caused by a carbapenem-resistant Gram-negative pathogen will be enrolled:

- HAP/VAP/HCAP or
- cUTI or
- BSI/sepsis

General Inclusion Criteria:

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

1. Hospitalized male and female patients, 18 years or older at the time of signing informed consent
2. Patients who have provided written informed consent or their informed consent was provided by legal guardian. (Note: Country specific rules and local Ethics Committee approval for legal guardian informed consent will determine whether or not and how a patient unable to comprehend or sign the informed consent is allowed to be enrolled in the study)
3. Patients with clinically documented infection (HAP/VAP/HCAP, cUTI, or BSI/sepsis) caused by a Gram-negative pathogen with evidence of carbapenem resistance
4. Patients who have been treated previously with an empiric antibiotic regimen and failed treatment, both clinically and microbiologically, are eligible for the study, if they have an identified carbapenem-resistant, Gram-negative pathogen which has either been shown to be nonsusceptible in vitro to each of the antibiotic(s) of the

empiric antibiotic regimen or been grown from a culture performed after at least 2 days of the empiric antibiotic regimen

5. Patient is male (no contraception required) or female and meets one of the following criteria:
   - Surgically sterile by hysterectomy and/or bilateral oophorectomy or bilateral salpingectomy or tubal ligation for the purpose of contraception for at least 6 weeks with appropriate documentation of such surgery
   - Postmenopausal (defined as older than 45 years of age with cessation of regular menstrual periods for 6 months and confirmed by a follicle-stimulating hormone level of > 40 mIU/mL, or amenorrhea for at least 12 months)
   - Of childbearing potential and using combined (estrogen and progestogen) or progestogen-only hormonal contraception associated with inhibition of ovulation (including oral, intravaginal, injectable, implantable, and transdermal contraceptives), or an intrauterine device (IUD), or intrauterine hormone-releasing system (IUS) for the entire duration of the study
   - Of childbearing potential and practice abstinence as a preferred and usual lifestyle, and agrees to continue practicing abstinence from Screening and for the entire duration of the study
   - Of childbearing potential, whose sole heterosexual partner has been successfully vasectomized and agrees to not have other heterosexual partners for the entire duration of the study
6. Patients meeting specific inclusion criteria for each infection site (See Diagnosis-Specific Inclusion Criteria)

General Exclusion Criteria:

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

1. Patients who have a history of any moderate or severe hypersensitivity or allergic reaction to any β-lactam (Note: for β-lactams, a history of a mild rash followed by uneventful re-exposure is not a contraindication to enrollment)
2. Patients who need more than 3 systemic antibiotics as part of BAT for the treatment of the Gram-negative infection (patients with mixed Gram-positive or anaerobic infections may receive appropriate concomitant narrow-spectrum antibiotics [eg, vancomycin, linezolid, metronidazole, clindamycin])
3. Patients with coinfection caused by invasive aspergillosis, mucormycosis or other highly lethal mold
4. Patients who have a central nervous system infection (eg, meningitis, brain abscess, shunt infection)
5. Patients with infection requiring > 3 weeks of antibiotic treatment (eg, bone and joint infection, endocarditis)
6. Patients with cystic fibrosis or moderate to severe bronchiectasis

7. Patients in refractory septic shock defined as persistent hypotension despite adequate fluid resuscitation or despite vasopressive therapy at the time of Randomization
8. Patients with severe neutropenia, ie, polymorphonuclear neutrophils (PMNs) < 100 cells/μL
9. Female patients who have a positive pregnancy test at Screening or who are lactating
10. Patients with Acute Physiology and Chronic Health Evaluation II (APACHE II) score > 30
11. Patients who have received a potentially effective antibiotic regimen for the carbapenem-resistant, Gram-negative infection for a continuous duration of more than 24 hours in cUTI, or 36 hours in HAP/VAP/HCAP or BSI/sepsis during the 72 hours leading to Randomization
12. Patients with any condition or circumstance that, in the opinion of the investigator, would compromise the safety of the patient or the quality of the study data
13. Patients who have received another investigational drug or device within 30 days prior to study entry
14. Patients who have previously been randomized in this study or received S-649266
15. Patients receiving peritoneal dialysis
16. Patients meeting specific exclusion criteria for each infection site (See Diagnosis-Specific Exclusion Criteria)

Diagnosis-Specific Inclusion and Exclusion Criteria

HAP/VAP/HCAP Definitions:

The diagnosis of HAP, VAP, or HCAP will be specified and recorded in the eCRF.

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

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

HCAP is defined as below when at least one of the criteria is met:

- an acute bacterial pneumonia in a patient who was hospitalized in an acute care hospital for 2 or more days within 90 days of the infection;
- resided in a nursing home or long-term care facility;
- received intravenous antibiotic therapy, chemotherapy, or wound care; or attended a hemodialysis clinic within the past 30 days of the current infection.

HAP/VAP/HCAP Specific Inclusion Criteria

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

1. All patients must have at least one of the following clinical features:
   a. New onset or worsening of pulmonary symptoms or signs, such as cough, dyspnea, tachypnea (eg, respiratory rate greater than 25 breaths/minute), expectorated sputum production, or requirement for mechanical ventilation
   b. Hypoxemia (eg, a partial pressure of oxygen less than 60 mmHg while the patient is breathing room air, as determined by arterial blood gas [ABG] or worsening of the ratio of the partial pressure of oxygen 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
2. All patients must have at least one of the following signs:
   a. Documented fever (eg, core body temperature [tympanic, rectal, esophageal] greater than or equal to 38°C [100.4°F], oral temperature greater than or equal to 37.5°C or axillary temperature greater than or equal to 37°C)
   b. Hypothermia (eg, core body temperature [tympanic, rectal, esophageal] less than or equal to 35°C [95°F], oral temperature less than or equal to 35.5°C or axillary temperature less than or equal to 36°C)
   c. Leukocytosis with a total peripheral white blood cell (WBC) count greater than or equal to 10,000 cells/mm^3
   d. Leukopenia with total peripheral WBC count less than or equal to 4,500 cells/mm^3
   e. Greater than 15% immature neutrophils (bands) noted on peripheral blood smear
3. All patients must have a chest radiograph or lung computed tomography (CT) scan within 48 hours prior to randomization showing the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia.

HAP/VAP/HCAP Specific Exclusion Criteria

The diagnosis of HAP, VAP or HCAP will be specified and recorded in the eCRF. Patients who meet any of the following criteria at Screening will be excluded from the study:

1. Patients who have known or suspected community-acquired bacterial pneumonia, atypical pneumonia, viral pneumonia or chemical pneumonia (including aspiration of gastric contents, inhalation injury)
2. Patients receiving concomitant aerosolized antibiotics with Gram-negative activity

cUTI Definition

cUTI is defined as a clinical syndrome characterized by pyuria and a documented microbial pathogen on urine culture, accompanied by local and systemic signs and symptoms including fever, chills, malaise, flank pain, back pain, and/or costovertebral angle pain or tenderness that occur in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterization and who require hospitalization for the parenteral (intravenous) treatment of cUTI will be enrolled in the study.

cUTI Specific Inclusion Criteria

Patients who have a clinical diagnosis of either cUTI with pyelonephritis or cUTI without pyelonephritis and fulfill the following criteria at Screening will be included in the study:

1. All patients must have a cUTI with a history of at least one of the following:
   a. Indwelling urinary catheter or recent instrumentation of the urinary tract (within 14 days prior to Screening)
   b. Urinary retention caused by benign prostatic hypertrophy
   c. Urinary retention of at least 100 mL or more of residual urine after voiding (neurogenic bladder)
   d. Obstructive uropathy (nephrolithiasis, fibrosis, etc)
   e. Azotemia caused by intrinsic renal disease (BUN and creatinine values greater than normal clinical laboratory values)
2. All patients must have at least 2 of the following signs or symptoms:
   a. Chills, rigors, or warmth associated with fever (body temperature greater than or equal to 38°C [100.4°F])
   b. Flank pain (pyelonephritis) or suprapubic/pelvic pain (cUTI)
   c. Nausea or vomiting
   d. Dysuria, urinary frequency, or urinary urgency
   e. Costovertebral angle tenderness on physical examination
3. All patients must have evidence of pyuria on urinalysis demonstrated by either:
   a. Dipstick analysis positive for leukocyte esterase

   OR

   b. ≥ 10 WBCs /μL in unspun urine, or ≥ 10 WBCs /high power field in spun urine
4. Patients who had a positive urine culture within 48 hours prior to Randomization containing ≥ 10^5 colony forming unit (CFU)/mL of a carbapenem-resistant Gram-negative uropathogen are eligible for this study (Note: patients may be randomized prior to the results of the urine culture if they have evidence of a carbapenem-resistant pathogen)
5. Patients receiving antibiotic prophylaxis for cUTI who present with signs and symptoms consistent with an active new cUTI may be enrolled provided all other eligibility criteria are met including obtaining a pretreatment qualifying urine culture

cUTI-specific Exclusion Criteria

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

1. Patient's urine culture at study entry isolates more than 2 uropathogens, regardless of colony count, or patient has a confirmed fungal cUTI
2. Patients with asymptomatic bacteriuria, the presence of $> 10^5$ CFU/mL of a uropathogen and pyuria but without local or systemic symptoms
3. Patients with an ileal loop for urine outflow (for patients with BSI/sepsis and an ileal loop are eligible)
4. Patients with acute uncomplicated pyelonephritis, ie, absence of anatomic urinary tract abnormality
5. Patients with vesico-ureteric reflux

BSI/Sepsis Definitions

The BSI/sepsis category includes bacteremia or sepsis caused by infections other than HAP/VAP/HCAP or cUTI. The diagnosis of BSI or sepsis and the causal infection will be specified and recorded in the eCRF. Patients will be enrolled in the BSI/sepsis group with either:

a. Documented BSI caused by a carbapenem-resistant Gram-negative pathogen

OR

b. Systemic response to infection, meeting the clinical criteria of SIRS and an identified infection source (eg, severe skin infection, intra-abdominal infection) caused by a carbapenem-resistant Gram-negative pathogen

Note: The inclusion/exclusion criteria for BSI and sepsis are not the same. It is possible to meet the criteria for one without the other.

Bloodstream Infection-specific Inclusion Criteria

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

1. Patients who have one or more positive blood cultures identifying a carbapenem-resistant Gram-negative pathogen that is consistent with the patient's clinical condition
2. Patients who have signs or symptoms associated with bacteremia

Bloodstream Infection Specific Exclusion Criteria

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

1. Patients who have a positive blood culture only obtained from an intravenous catheter. If both peripheral venipuncture blood culture and intravenous catheter blood culture show the same organism, the patient is eligible
2. Patients with BSI considered to be due to an endovascular source, eg, endocarditis, infected vascular graft, a permanent intravascular device that cannot be removed during the course of treatment

Sepsis Specific Inclusion Criteria:

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

1. Patients defined for SIRS, indicated by having 2 or more of the following responses:
   a. Oral or tympanic body temperature greater than 38°C (100.4°F) or less than 36°C (96.8°F)
   b. Tachycardia, heart rate greater than 90 beats/minute
   c. Tachypnea, manifested by a respiratory rate greater than 20 breaths/minute or hyperventilation, as indicated by an arterial partial pressure of carbon dioxide ($PaCO_2$) of less than 32 mmHg
   d. WBC greater than 12,000 cells/mm³, less than 4000 cells/mm³, or > 10% immature (band) forms
2. Patients with an identified infection site from which a carbapenem-resistant Gram-negative pathogen has been isolated using an appropriate clinical specimen

Sepsis-Specific Exclusion Criteria:

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

1. Patient does not have an identified source of a bacterial infection and an identified carbapenem-resistant Gram-negative pathogen
2. Patient has an alternative explanation for the physiologic parameters of SIRS, eg, cardiogenic shock, cardiac arrhythmia, or hyperthyroid storm
3. Patients with infections where isolation of a Gram-negative pathogen is unlikely to be causing the infection such as that in the upper respiratory system, head and neck, pelvic or genital organ, etc.

Test Drug, Dose, and Mode of Administration:

S-649266 2 g administered intravenously q8h as a 3-hour infusion with/without adjunctive Gram-negative antibiotic therapy in patients with normal renal function. Dose adjustment is shown in the following table. The solution volume for infusion must be at least 100 mL. Under no circumstances is S-649266 to be administered in a saline solution of less than 100 mL.

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

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)[a]	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/1.73m^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
Patient 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; ESRD = end-stage renal disease; HD = hemodialysis; MDRD-eGFR = modification of diet in renal disease-estimated glomerular filtration rate calculated with the MDRD equation; q6h = every 6 hours; q8h = every 8 hours; q12h = every 12 hours.

a A CrCl will be calculated by Cockcroft-Gault equation at Screening. A urine measured CrCl will be calculated by using timed urine collections of 2-8 hours at early assessment (EA).

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 an excessive exposure and complexity of clinical operation.

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

Adjunctive Antibiotic Therapy:

Patients with cUTI should receive S-649266 monotherapy, ie, without combining with any additional Gram-negative antibiotics.

Patients with HAP/VAP/HCAP or BSI/sepsis randomized to treatment with S-649266 may receive a second (but not a third) Gram-negative antibiotic other than a polymyxin (colistin or polymyxin B) or a cephalosporin/carbapenem including combination with beta-lactamase inhibitor (eg, ceftazidime/avibactam, or ceftolozane/tazobactam) at the initiation of study drug. This decision should be based on the investigators consideration of the patient's condition, the causative pathogen, and current best practices.

If a second Gram-negative antibiotic is administered with S-649266 at the time of Randomization, the investigator must reassess the need for the second Gram-negative antibiotic upon availability of susceptibility testing to S-649266 no later than Early Assessment (EA) visit. The adjunctive antibiotic therapy should be discontinued (de-escalated) accordingly.

Control Treatment Regimen:

The control population will be treated with BAT, locally sourced by study sites, within the local standard of care determined by the investigator for each infection diagnosis. This will usually involve 1 or 2 or possibly 3 antibiotic agents specifically for the carbapenem-resistant Gram-negative pathogen.

If the investigator chooses to use a polymyxin (either polymyxin B or colistin [polymyxin E]), the investigator is encouraged to follow European Medicines Agency's (EMA's) dosing recommendations.

De-escalation in the BAT arm should also be considered in line with best local standard of care.

Duration of Treatment:

The treatment duration for S-649266 or BAT is anticipated to be 7 to 14 days which are consistent with published treatment guidelines for serious infections. Based on the investigator's clinical assessment of the patient, treatment may be extended up to 21 days. The reason for the extension should be clearly documented. All study treatments will be performed in the hospital.

Prohibited Concomitant Therapy:

For patients randomized to S-649266

- Systemic antibiotics with Gram-negative activity, other than a single Gram-negative adjunctive antibiotic therapy for HAP/VAP/HCAP or BSI/sepsis patients, are not permitted until TOC
- Aerosolized antibiotics are not permitted until TOC
- Refer to the label of any adjunctive antibiotic therapy being used in combination with S-649266 for information about contraindicated therapies to those adjunctive antibiotic therapies

For patients randomized to BAT

- More than 3 systemic antibiotics with Gram-negative activity are not permitted until TOC
- Aerosolized antibiotics are not permitted until TOC
- Refer to label of BAT drugs for contraindicated therapies

Efficacy Assessment:

Both clinical and microbiological outcomes will be assessed by the investigator at EA, EOT, TOC, and FUP. In case treatment duration is extended beyond 14 days, an additional clinical outcome will be assessed on Day 14.

Safety Assessments:

Patient safety will be assessed daily from the time of informed consent, while the patient is hospitalized, and through to EOS by the identification of adverse events (AEs). Adverse events defined as new or worsening symptoms since the time of Randomization will be used to determine the safety of the study treatment. In case treatment duration is extended beyond 14 days, additional safety assessments will be conducted on Day 14. Safety surveillance will extend to up to 28 days after the last dose of the study drug. Clinical laboratory tests of blood chemistry, hematology, and urinalysis will be performed at Screening, EA, EOT, TOC, and FUP. In addition, an electrocardiograph (ECG) will be performed at Screening/baseline. Vital signs including body temperature and AEs will be recorded daily.

Pharmacokinetic Assessments:

All patients treated with S-649266 will have blood drawn for sparse pharmacokinetic (PK) sampling of plasma concentrations of study drug. The actual sampling date and time will be recorded. PK blood sampling will occur on Day 3 (after at least 6 doses of drug) at 4 timepoints: (1) just prior to the start of infusion, (2) 1 hour after start of infusion, (3) at the end of infusion, and (4) 1 hour after the end of the infusion. Patients with non-stable renal function resulting in a dosage adjustment (dose or interval) at EA will undergo another blood PK sampling (4 samples at the above specified

timepoints) within 24 to 72 hours after their dosing adjustment. The timing for PK blood draws is same as above timing on Day 3. If possible, a single blood sampling should be performed as soon as possible at EOT in case of premature EOT.

Statistical Methods:

For the primary endpoint, that is clinical response at TOC with patients of HAP/VAP/HCAP or BSI/sepsis and microbiological response at TOC with patients of cUTI, each response rate will be provided with the 95% confidence interval (CI) by treatment group. For the secondary efficacy endpoints of clinical response and microbiological response, each response rate will be also provided with 95% CI by treatment group. For the other secondary endpoints, similar statistics will be provided. Descriptive statistics for all efficacy parameters will be provided.

Sample Size:

Approximately 150 patients

Given the challenges involved in recruiting patients meeting the criteria for inclusion in this study, and, after discussions with the EMA, it was agreed that approximately 150 patients would be enrolled and randomized 2:1 to S-649266 and BAT, respectively.

Stratification at Randomization:

Randomization will be performed by the stochastic minimization method using their infection site (HAP/VAP/HCAP, cUTI, and BSI/sepsis), APACHE II score (≤ 15 and ≥ 16), and region (N. America, S. America, Europe, and Asia-Pacific) as allocation factors.

Number of Study Sites/Countries:

It is estimated that approximately 100 study sites from US, Asia-Pacific including Japan, EU, Israel, Turkey, and Latin America will participate in this clinical study.

Study Duration:

Study duration for individual patients: approximately 5 to 7 weeks

Planned duration of the study is approximately 37 months (35 months for enrollment and 5 to 7 weeks to complete the study).

Date of Original (Version 1): 11 November 2015

Date of Latest Version 4: 16 November 2017

TABLE OF CONTENTS

TABLE OF CONTENTS....14
LIST OF IN-TEXT TABLES....18
LIST OF IN-TEXT FIGURES....18
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS....20
GLOSSARY....23
1. INTRODUCTION....24
1.1 Background and Rationale....24
1.2 Biological Features of S-649266 for Injection....25
1.2.1 Use of Rapid Diagnostic Tests....27
1.3 Nonclinical Experience....27
1.3.1 Pharmacokinetics/Pharmacodynamics....29
1.4 Clinical Experience....33
1.4.1 Phase 1....33
1.5 Phase 2 and Phase 3....34
1.5.1 Phase 2 Complicated Urinary Tract Infections....34
2. STUDY OBJECTIVES....36
2.1 Primary Objectives....36
2.2 Secondary Objectives....36
3. INVESTIGATIONAL PLAN....38
3.1 Overall Study Design and Plan....38
3.2 Rationale for Study Design and Control Group....39
3.2.1 Rationale for Patient Population....39
3.2.2 S-649266 Dose Regimen....40
3.2.3 BAT Regimens....42
3.2.4 Duration of Study Treatment....42
3.3 Study Duration....43
3.3.1 Study Duration in Individual Patients....43
4. STUDY POPULATION SELECTION....43
4.1 Study Population....43
4.2 General Inclusion Criteria....45
4.3 General Exclusion Criteria....45
4.4 Diagnosis Specific Inclusion and Exclusion Criteria....46
4.4.1 HAP/VAP/HCAP Patients....46
4.4.2 cUTI Patients....48
4.4.3 Bloodstream Infections/Sepsis Patients....49
5. STUDY TREATMENT(S)....52

5.1 Description of Treatment(s) 52
5.1.1 Test Drug 52
5.1.2 Control Treatment Regimen 52
5.2 Treatments To Be Administered 52
5.2.1 S-649266 Group 53
5.2.2 BAT Group 54
5.3 Selection and Timing of Dose for Each Patient 54
5.4 Randomization to Treatment Groups 56
5.5 Blinding 56
5.6 Packaging and Labeling, Storage and Accountability 57
5.6.1 S-649266 57
5.6.2 BAT 57
5.7 Investigational Product Retention at Study Site 58
5.8 Treatment Compliance 58
5.8.1 Changes in Treatment Regimen 58
6. RESTRICTIONS 59
6.1 Prior Therapy 59
6.2 Concomitant Therapy during the Study 59
6.2.1 Antibiotic Therapies 59
6.2.2 Nonantibiotic Therapies and Procedures 60
6.2.3 Prohibited Therapy 60
6.2.4 Rescue Therapy 60
7. STUDY PROCEDURES AND METHODS OF ASSESSMENTS 62
7.1 Informed Consent 62
7.2 Baseline Patient Characteristics and Medical History 62
7.3 Hospitalization 63
7.4 Physical Examination 63
7.4.1 Glasgow Coma Scale 63
7.4.2 APACHE II 64
7.5 Vital Signs 64
7.6 Electrocardiography 64
7.7 Clinical Laboratory Tests 65
7.7.1 Microbiologic Cultures 65
7.7.2 Clinical Laboratory Parameters 68
7.8 Efficacy, and Safety Evaluations 70
7.8.1 General Evaluations 70
7.8.2 HAP/VAP/HCAP Specific Evaluations 71
7.8.3 Complicated Urinary Tract Infection Specific Evaluation 71

7.8.4 Blood Stream Infection/Sepsis Specific Evaluations....72
7.9 Pharmacokinetic Sample Collection, Storage, and Shipping....72
7.9.1 Pharmacokinetic Blood Sampling....72
7.9.2 Other Tissue or Body Fluid Sampling for Pharmacokinetics....72
7.10 Enrollment in the Study and Dispensing Study Drug....72
7.11 Efficacy Assessments....73
7.11.1 Efficacy Criteria for Infection Site Specific Clinical Outcomes for EA, EOT, and TOC....73
7.11.2 Clinical Outcomes for FUP....74
7.11.3 Microbiological Outcomes for EA, EOT, and TOC....75
7.11.4 Microbiological Outcomes for FUP....76
7.11.5 New Pathogens....77
7.12 Adverse Events Assessments....77
7.12.1 Performing Adverse Events Assessments....77
7.12.2 Timing....78
7.12.3 Severity....78
7.12.4 Relationship....78
7.12.5 Expectedness....78
7.12.6 Clinical Laboratory Adverse Events....79
7.12.7 Serious Adverse Events....79
7.12.8 Special Situations-Abuse, Misuse, Overdose, and Medication Error....81
7.12.9 Pregnancy....82
7.12.10 Treatment-Emergent Adverse Events....82
7.13 Withdrawal or Discontinuation of Patients from the Study or Study Treatment....82
7.14 Appropriateness of Measurements....83
7.15 Acceptable Time Windows....83
8. STUDY ACTIVITIES....85
8.1 Screening (Day –2 to Randomization)....85
8.2 Treatment Period (Day 1 to up through Day 14)....86
8.2.1 Randomization and Treatment Initiation Day 1....86
8.2.2 All Treatment Days....86
8.2.3 Treatment Day 3....86
8.2.4 Early Assessment (EA) (Occurs once at investigator's discretion during Days 3 to 4)....86
8.2.5 Treatment Day 14....87
8.2.6 Last Day of Study Treatment (EOT)....87
8.3 Test of Cure (TOC [EOT + 7 days])....88

8.4 Follow-up (FUP [EOT + 14 days]) 88
8.5 End of Study (EOS [EOT + 28 days]) 89
9. PLANNED STATISTICAL METHODS 90
9.1 General Considerations 90
9.2 Determination of Sample Size 90
9.3 Analysis Populations 90
9.4 Handling of Missing Data 91
9.5 Patient Disposition 91
9.6 Demographics and Baseline Characteristics 91
9.7 Prior Therapies 91
9.9 Efficacy Analyses 92
9.9.1 Primary Efficacy Endpoint 92
9.9.2 Secondary Efficacy Endpoints 92
9.9.3 Primary Efficacy Analyses 93
9.9.4 Secondary Efficacy Analyses 93
9.10 Safety Analyses 93
9.10.1 Adverse Events 94
9.10.2 Vital Signs 94
9.10.3 Clinical Laboratory Analysis 94
9.11 Pharmacokinetic Analysis 94
9.12 Pharmacokinetic/Pharmacodynamic Analysis 94
9.13 Pharmacoeconomics Associated with Treatment 95
9.14 Interim Analysis 95
10. ADMINISTRATIVE CONSIDERATIONS 96
10.1 Investigators and Study Administrative Structure 96
10.2 Institutional Review Board or Institutional Ethics Committee Approval 98
10.3 Ethical Conduct of the Study 98
10.4 Patient Information and Consent 98
10.5 Patient Confidentiality 98
10.6 Study Monitoring 99
10.7 Case Report Forms and Source Documents 99
10.7.1 Case Report Forms 99
10.7.2 Source Documents 100
10.7.3 External Data 100
10.8 Committees 100
10.8.1 Independent Data Safety Monitoring Board 100
10.9 Termination or Suspension of the Study 101
10.9.1 Termination or Suspension of the Entire Study 101

10.9.2 Termination or Suspension of the Study by Medical Institution 101
10.10 Protocol Deviations and Modifications 101
10.11 Data Management 102
10.12 Retention of Data 102
10.13 Quality Control and Assurance 102
10.14 Publication and Disclosure Policy 103
10.15 Financial Disclosure 103
11. REFERENCE LIST 104
Appendix 1 Time and Events Schedule 107
Appendix 2 SIRS Criteria 110
Appendix 3 European Medicines Agency Completes Review of Polymyxin-based Medicines 111
Appendix 4 Microbiology Tests 113
Appendix 5 Glasgow Coma Scale 116
Appendix 6 APACHE II Score 117
Appendix 7 SOFA Score 119
Appendix 8 Clinical Pulmonary Infection Score (CPIS) Parameters 120
Appendix 9 Management Criteria for Abnormal Liver Function Tests 121
Appendix 10 Sponsor Signature 123
Appendix 11 Investigator's Signature 124

LIST OF IN-TEXT TABLES

Table 1-1 %$fT_{>MIC}$ Required for Static Effect and 1-$\log_{10}$ Reduction in Murine Thigh Infection Model 31
Table 1-2 %$fT_{>MIC}$ Required for Static Effect and 1-$\log_{10}$ Reduction in Murine Lung Infection Model 32
Table 3-1 Probability of Target Attainment for Patients with Augmented Renal Clearance 42
Table 5-1 Study Treatment Administration 53
Table 5-2 S-649266 Dosing Adjustments for Various Degrees of Renal Function and Augmented Renal Clearance 55
Table 7-1 Clinical Laboratory Tests 68
Table 7-2 Acceptable Time Windows 84

LIST OF IN-TEXT FIGURES

Figure 1-1 Depiction of Cefiderocol Cell Entry and Mechanism of Action 26

Figure 1-2 Efficacy of S-649266 (Human 3 hr 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....30
Figure 3-1 Study Schematic....39
Figure 3-2 Probability of Target Attainment for 50% or 75% $fT_{>MIC}$....41
Figure 4-1 Study Schematic Showing Possible Pathways for Study Entry...44
Figure 7-1 Schematic of Clinical Specimen Handling....67

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
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARC	augmented renal clearance
ABG	arterial blood gas
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BAL	bronchoalveolar lavage
BAT	best available therapy (see glossary for definition)
BSI	bloodstream infection (bacteremia)
BUN	blood urea nitrogen
CFU	colony forming unit
CI	confidence interval
CR	carbapenem-resistant
CR-ME	carbapenem-resistant microbiologically evaluable population
CR Micro-ITT	carbapenem-resistant microbiological intent to treat population
CrCl	creatinine clearance
CRO	contract research organization
cUTI	complicated urinary tract infection
DMPK	drug metabolism and pharmacokinetics
DSMB	data safety monitoring board
EA	Early Assessment
ECG	electrocardiograph
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELF	epithelial lining fluid
EMA	European Medicines Agency
EOT	End of Treatment
EOS	End of Study
ESBL	extended-spectrum beta-lactamase
FDA	Food and Drug Administration
FUP	Follow-up

GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
HAP	hospital-acquired pneumonia
HCAP	healthcare-associated pneumonia
HIPAA	Health Information Portability and Accountability Act
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	Institutional Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-treat population
IWRS/IVRS	interactive web or voice response system
LDH	lactate dehydrogenase
MDR	multidrug resistant
MDRAB	multidrug resistant *Acinetobacter baumannii*
MDRD	modification of diet in renal disease
MDRP	multidrug resistant *Pseudomonas aeruginosa*
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
Micro-ITT	Microbiological Intent-to-treat population
NOAEL	no observed adverse-effect level
OAT1 (3)	organic anion transporter with associated identifier, eg, 1 (3)
OCT2	organic cation transporter with associated identifier, eg, 2
PBP	penicillin-binding protein
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PTA	probability of target attainment
RBC	red blood cell (count)
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SIRS	systemic inflammatory response syndrome
SOC	system organ class
SOFA	Sequential Organ Failure Assessment
SmPC	Summary of Product Characteristics
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TOC	test of cure

ULN	upper limit of normal
VAP	ventilator-associated pneumonia
WBC	white blood cell (count)
WHO-DD	World Health Organization Drug Dictionary
XDR	extensively drug-resistant

GLOSSARY

Adjunctive Antibiotic Therapy	An antibiotic combined with S-649266 specifically to treat the target carbapenem-resistant Gram-negative bacterial infections except in cUTI, where S-649266 is to be used as monotherapy
ARC	Augmented renal clearance (ARC) 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 (eGFR)($\geq$ 90 mL/min/1.73 m^2) and a creatinine clearance (CrCl $\geq$ 120 mL/min).
BAT	Best available therapy (BAT) is the standard of care treatment as determined by the investigator based on his/her assessment of the patient's clinical condition, the site of infection and the causative organism (including available susceptibility data). BAT consists of 1 to 3 antibiotics prescribed for the carbapenem-resistant Gram-negative pathogen. BAT is considered a treatment regimen, but is not considered study drug.
Carbapenem Resistance	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 the purpose of this study, resistance is defined as 'non-susceptible," ie, resistance would include intermediate breakpoints to any carbapenem.
Concomitant Antibiotic	A concomitant antibiotic is an antibiotic added to the primary Gram-negative antibiotic treatment regimen to treat Gram-positive and/or anaerobic bacterial infections. Antibiotics used for prophylaxis, ie, to prevent, not to treat an infection, would also be considered a concomitant antibiotic.
Effective Antibiotic	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
Study Drug	Study drug refers only to S-649266
Study Treatment	Refers to either S-649266 with/without adjunctive antibiotic therapy or BAT antibiotics used to treat the protocol specific Gram-negative infection. It does not include concomitant antibiotics

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 bacilli, including Enterobacteriaceae and the non-fermenters *Pseudomonas aeruginosa* 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 a metallo-β-lactamase, IMP-1, in *P. aeruginosa*, a serine carbapenemase, OXA-23, in *A. baumannii*, and a serine carbapenemase, KPC-1, in *Klebsiella pneumonia,* carbapenemase-encoding genes have spread worldwide, and are now distributed throughout different species of Gram-negative MDR bacteria, which are now responsible for a large and increasing numbers of nosocomial infections. These carbapenemases inhibit almost all β-lactam antibiotics, including carbapenems, and are now 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) which are particularly prevalent among extensively drug-resistant *P. aeruginosa* [2, 3]. Not infrequently, several 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 [4]. 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, to likely be caused mainly by nosocomial carbapenemase producing *K. pneumoniae* of all types.

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 [5]. A pooled analysis of 9 studies showed that the death rate was higher among those patients infected with carbapenem-resistant Enterobacteriaceae than those infected with carbapenem-susceptible Enterobacteriaceae (Relative Risk [RR] 2.05, 95% confidence interval [CI] 1.56 -2.69) [5].

S-649266 now has an approved international nonproprietary name (INN) generic name: Cefiderocol. For purposes of this protocol, S-649266 will be the name of the study drug.

S-649266 is being developed to address the unmet medical need to treat CR infections caused by Gram-negative bacteria, including Enterobacteriaceae, *Pseudomonas*, and *Acinetobacter* species independent of the underlying mechanism of CR. Although S-649266 has bacterial killing ability for CR species of Gram-negative bacteria, it also has improved bacterial killing ability for common community acquired Gram-negative bacterial infections as demonstrated by reduced minimum inhibitory concentration (MIC) values (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.

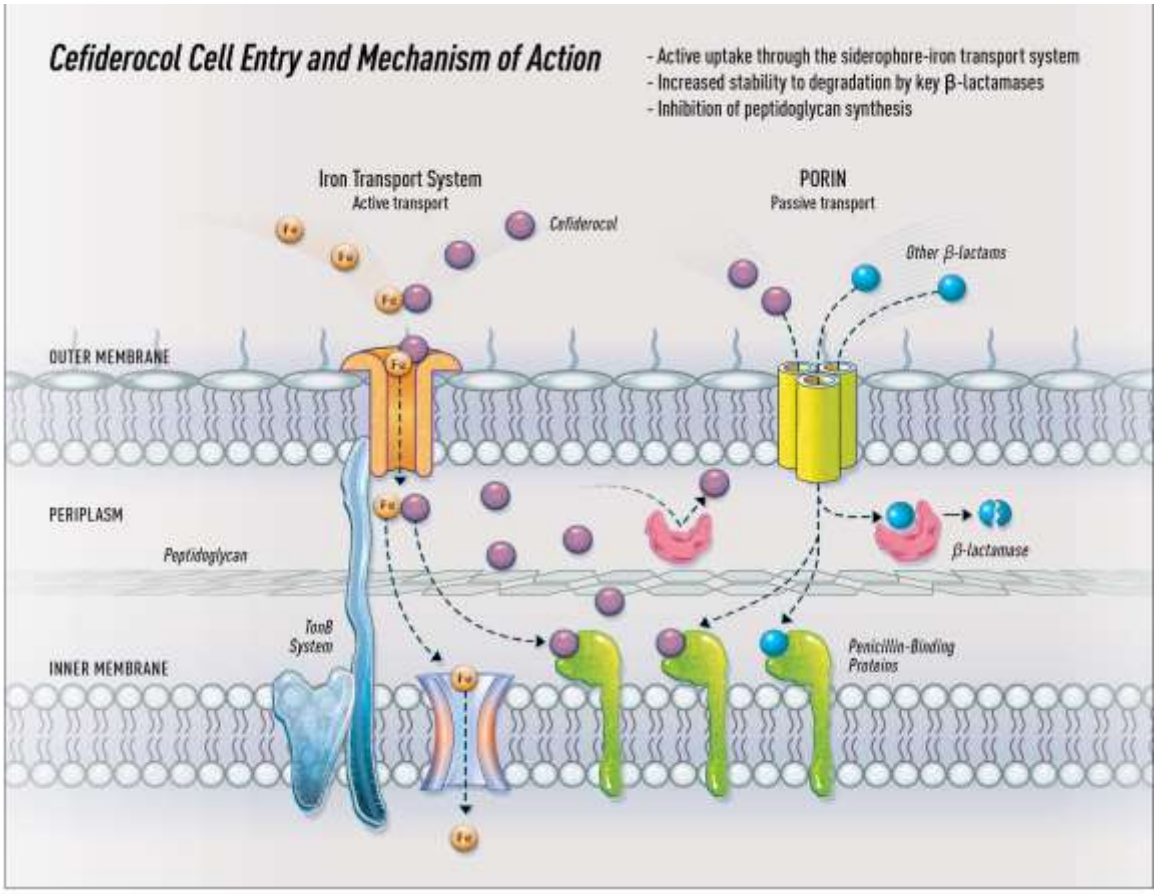
The chemical structure of S-649266 is similar to cefepime which is a fourth-generation cephalosporin with an extended spectrum of activity against Gram-positive and Gram-negative bacteria with greater activity against both types of organisms than third-generation agents. The major difference in the chemical structure of S-649266 compared to cefepime is the addition of a catechol group on the side chain at position 3. Furthermore, S-649266 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:

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 β-lactamase enzymes including carbapenemases of the serine or metallo-β-lactamase classes.
3. Enhanced activity against aerobic Gram-negative bacteria especially, Enterobacteriaceae particularly *K. pneumoniae* and *E. coli*, and the non-fermenters *P. aeruginosa* 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 which scavenge for available free iron [7]. S-649266 is a siderophore compound which 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]. Figure 1-1below provides a pictorial description of the process. 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 β-lactamases. 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



The greatest unmet medical need in the treatment of bacterial infections is focused on multidrug resistant (MDR) aerobic Gram-negative bacilli, including broadly the Enterobacteriaceae and the non-fermenters *P. aeruginosa* and *A. baumannii*. MDR bacteria, defined as > 3 class antibiotic resistance, include most Enterobacteriaceae producing AmpC or extended-spectrum beta-lactamase (ESBL) serine β-lactamases (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 *Klebsiella pneumoniae* carbapenemases (KPCs), oxacillinases (OXAs), and metallo-beta-lactamases , eg, verona integron-encoded metallo-beta-lactamase (VIM), imipenemase (IMP), and New Delhi metallo-beta-lactamase-1 (NDM) 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* and *A. baumannii* have also acquired carbapenemases and are also considered XDR bacteria. Rarely, these XDR pathogens

may also be resistant to polymyxins, and, therefore, can be considered pandrug-resistant (PDR) or PDR organisms, defined as resistance to all classes [15].

The principal objective for S-649266 clinical development is to demonstrate efficacy for the treatment of carbapenem-resistant Enterobacteriaceae, carbapenem-resistant *P. aeruginosa* and carbapenem-resistant *A. baumannii* with appropriate benefit-risk for serious illness as outlined in the Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidances for bacterial infections, and currently considered as a highly important unmet medical need [16-18]. Consequently, the objective of the clinical development is to provide sufficient evidence of efficacy in the treatment of serious, potentially life-threatening Gram-negative infections from a variety of infection sites and an appropriate safety profile for these indications where there is a clear unmet medical need.

1.2.1 Use of Rapid Diagnostic Tests

Although patients who fail empiric therapy microbiologically and clinically can be enrolled, it is in the patients' best interest that diagnosis of resistance is made early and the most appropriate targeted antibacterial therapy initiated as soon as possible [19]. The use of rapid diagnostic procedures has the potential of identifying resistant organisms earlier than typical microbiological laboratory procedures, which would help in the selection of antibiotic regimens [20]. Successful incorporation of new diagnostic technologies has the potential benefit of improving not only patient treatment but also infection control and antimicrobial stewardship. Rapid diagnostics based on gene content may provide results within hours of obtaining an appropriate clinical specimen. Methods requiring culturing for either enhancing a sample for additional testing or using selective culture media for both identification of the species and the possibility of resistance potentially could give useable results after the initial culture. Since the current rapid diagnostics are relatively early in development for Gram-negative bacteria, the usual and typical microbiological laboratory procedures will be required for confirmation of the rapid results and also to identify drug sensitivities.

1.3 Nonclinical Experience

In vitro, S-649266 showed potent antibacterial activity against carbapenem-resistant Enterobacteriaceae including metallo-β-lactamase producing isolates, MDR *A. baumannii* (MDRAB), and MDR *P. aeruginosa* (MDRP). 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 MDRP, carbapenem-resistant *A. baumannii*, or enteric bacteria such as extended-spectrum β-lactamase-producing *E. coli* and *K. pneumoniae*.

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

and 3-month intravenous toxicity study, the safety pharmacology studies, and the antigenicity study.

In the rat 3-month intravenous toxicity study (dose 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 in female and male rats, respectively) was approximately 17-fold of the maximum plasma concentration (C_{max}) value in humans (89.7 μg/mL from the thorough QT [TQT] study [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 QTc interval 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 NOAEL and provides a minimum of a 9- to 10-fold margin relative to the expected C_{max} of S-649266 in the current study (eg, C_0 of 770 and 876 μg/mL 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 [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.

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 [21] and EMA guideline [22] of drug interaction, and therefore, a clinical DDI study was performed (Study 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 area under the concentration time curve (AUC) for rosuvastatin by 21%, but because it is unlikely that oral medications such as rosuvastatin, other statins, or medications that are OATP1B3 substrates will occur during a treatment course requiring intravenous antibiotics, the potential for a clinically meaningful outcome in the clinical setting is considered to be low.

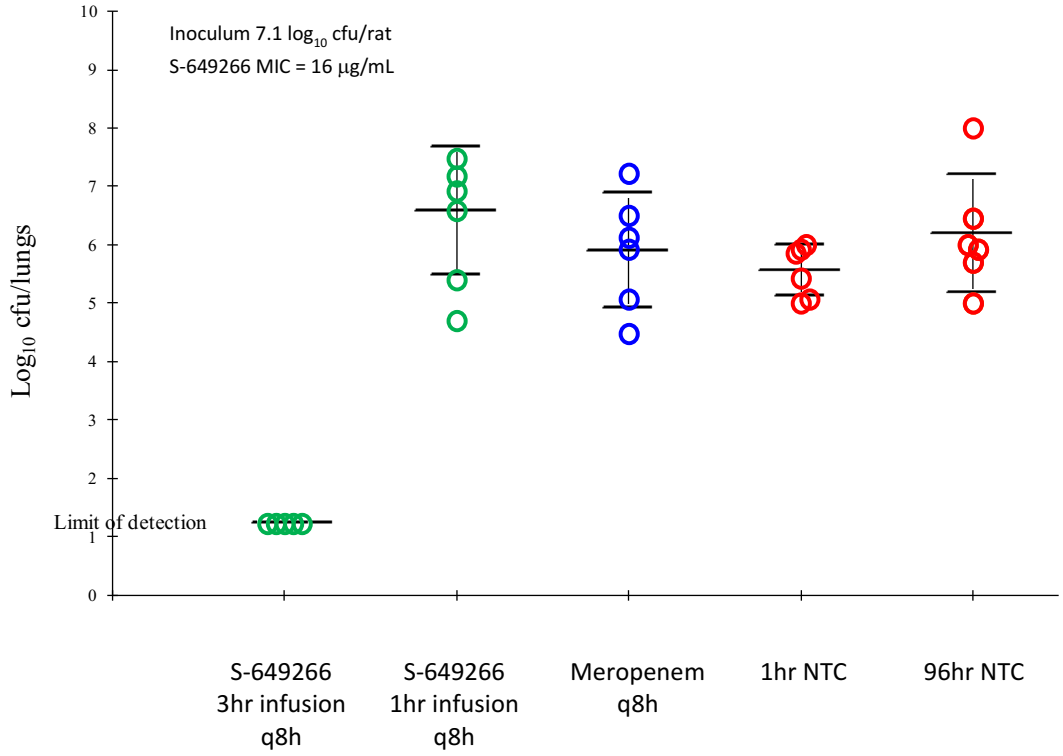
1.3.1 Pharmacokinetics/Pharmacodynamics

1.3.1.1 Animal Models of Efficacy

As with all β-lactams that target penicillin-binding proteins (PBPs), the controlling pharmacodynamic (PD) parameter for S-649266 is the percentage of the dosing interval required for free-drug plasma concentration to be above the minimum inhibitory concentration (%$fT_{>MIC}$), and while the plasma pharmacokinetic (PK) measurement 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 utilized 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 hr 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



IV = intravenous; NTC = non-treatment 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 (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-log10 reduction were approximately 60% to 70% and 70% to 80%, respectively. The $\%fT_{>MIC}$ values required for efficacy were similar among bacterial species (Table 1-1, and for additional information, refer to the current Investigator's Brochure).

Table 1-1 %$fT_{>MIC}$ Required for Static Effect and 1-log_{10} Reduction in Murine Thigh Infection Model

Species	Strain Number	Characteristic	S-649266 MIC (μg/mL)	%$fT_{>MIC}$	
				Static Effect	1-log_{10} Reduction
Pseudomonas aeruginosa	ATCC27853	Cephalosporin susceptible	0.5	74.8	84.9
	SR27001	MDRP, IMP-1 producer	8	41.7	54.2
Klebsiella pneumoniae	ATCC43816	Cephalosporin susceptible strain	≤0.016	≥38.3	≥58.7
	ATCC13883		0.125	60.2	74.1
	1478266		0.5	17.7	27.6
	1478677	CTX-M-3 producer	0.125	67.4	81.5
	NCTC13443	NDM-1 producer	16	72.6	80.0
	6560-MAR		1	94.2	>100
	KI2		8	80.9	88.8
	VA375	KPC producer	0.25	82.7	91.6
	VA357		2	41.4	65.8
	VA391		8	65.5	69.9
	VA361		16	66.2	72.1
	VA384		16	71.0	78.4
	VA360		16	76.3	84.2
Escherichia coli	ATCC25922	Cephalosporin susceptible strain	0.125	32.5	49.7

CTX-M = cefotaximase Munich, IMP-1 = imipenemase, KPC = *Klebsiella pneumoniae* beta-lactamase, MDRP = multidrug resistant Pseudomonas aeruginosa, MIC = Minimum inhibitory concentration by broth micro dilution method in Chelex-treated ISB, NDM-1 = New Delhi metallo-beta-lactamase

Animal: Jcl:ICR, male, N=5.

Neutropenic by intraperitoneal injection of cyclophosphamide with 150 and 100 mg/kg at 4 and 1 days before infection, respectively.

Infection: intramuscularly injection.

Treatment protocols: Administration was initiated at 2 hours post infection and repeated at regular intervals of every 3 hours ie, a total of 8 doses.

Evaluation item: Viable cells in thigh at 24 hours after initiation of treatment.

The magnitude of the PK/PD parameter required for efficacy was also determined in a murine lung model of infection caused by 21 strains of Gram-negative bacilli with widely divergent MICs. The %$fT_{>MIC}$ values of S-649266 required for a static effect and 1-log_{10} reduction were approximately 50% to 70% and 70% to 90%, respectively. The %$fT_{>MIC}$ values required for efficacy were similar among bacterial species (Table 1-2), and refer to the current Investigator's Brochure).

Table 1-2 %$fT_{>MIC}$ Required for Static Effect and 1-log_{10} Reduction in Murine Lung Infection Model

Species	Strain Number	Characteristic	S-649266 MIC (μg/mL)	%$fT_{>MIC}$	
				Static Effect	1-log_{10} Reduction
Pseudomonas aeruginosa	ATCC27853	Cephalosporin susceptible	0.5	48.7	74.2
	SR27001	MDRP, IMP-1 producer	8	31.4	51.9
	NTU	MDRP, VIM-2 producer	0.5	38.3	62.8
	NCTC13437	MDRP, VIM-10 producer	2	63.6	75.4
Acinetobacter baumannii	ATCC19606	Cephalosporin susceptible	0.125	66.1	74.0
	1515988	Carbapenem susceptible	0.25	40.3	60.8
	1485176	MDRAB	0.25	69.7	77.4
	1485247		2	77.6	85.8
	NCTC13301	MDRAB, OXA-23 producer	2	67.4	75.0
	BEN ST BRI	MDRAB, OXA-24 producer	0.5	90.4	92.9
Klebsiella pneumoniae	6560-MAR	NDM-1 producer	1	68.4	> 100
	KI2		8	50	75.4
	NCTC13443		16	59.1	88.3
	VA375	KPC producer	0.25	34.4	58.1
	VA357		2	37.4	56.8
	VA391		8	93	> 100
	VA361		16	83.3	94.8
	VA384		16	77.9	77.9
	PLE	OXA-48 producer	0.063	41.2	64.3
Escherichia coli	AB	NDM-4 producer	4	96.5	> 100
	IR-5	NDM-1 producer	4	54.3	83.9

KPC = Klebsiella pneumoniae beta-lactamase, MDRP = multidrug resistant Pseudomonas aeruginosa, MIC = Minimum inhibitory concentration by broth micro dilution method in Chelex-treated ISB, NDM-1 = New Delhi metallo-beta-lactamase, OXA = oxacillinases, VIM = verona integron-encoded metallo-beta-lactamase.

Animal: Jcl:ICR, male, N = 5.

Neutropenic by intraperitoneal injection of cyclophosphamide with 150 and 100 mg/kg at 4 and 1 days before infection, respectively.

Infection: intranasal injection.

Treatment protocols: Administration was initiated at 2 hours post infection and repeated at regular intervals of every 3 hours (q3h), ie, a total of 8 doses.

Evaluation item: Viable cells in lung at 24 hours after initiation of treatment.

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 DDI 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, electrocardiograph (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 [Study R2111]) and single 2- to 4-g doses, infused over 3 hours (thorough QT/QTc [TQTc] study [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 dosed every 8 hours (q8h) infused over 1 hour (once daily doses on Days 1 and 10 and q8h doses from Days 2 to 9), only a slight accumulation (1.05- to 1.16-fold) for the C_{max} and AUC of 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 [14C]-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 small amounts (2.8%) excreted in feces (Study R2114).

A Phase 1 study was conducted to examine the intrapulmonary PK of S-649266 following a single 2-g dose over 1-hour infusion of S-649266 in healthy adult male subjects (Study R2112). Twenty subjects were enrolled and completed the study. Samples of bronchial secretions were obtained by bronchoalveolar lavage (BAL) at prespecified times post infusion. Corresponding timed plasma samples were also obtained. S-649266 levels in epithelial lining fluid (ELF) peaked at 14 µg/mL at the end of the infusion and decreased to 1.4 µg/mL by 6 hours. The ELF levels appeared to

parallel the concentration time profile of plasma. There were no deaths, SAEs, or AEs leading to withdrawal.

A Phase 1 study of the PK of S-649266 in subjects with varying degrees of renal function (mild, moderate, severe, and end-stage renal disease on dialysis) was conducted (Study R2113). A total of 38 subjects received a 1-g dose over 1-hour infusion of S-649266. The results of a PK analysis established dose adjustments that would be needed for patients with decreased renal function or for patients on hemodialysis. The results for the mild impairment group were not significantly different from those of the healthy group. The moderate and severe impairment groups demonstrated significant differences that require a dosage adjustment for each group in order to maintain the plasma level of drug at the same level as patients with normal renal function. One subject experienced a nonserious AE of urticaria resulting in premature discontinuation of study drug.

A Phase 1 study to assess the repolarization effects of S-649266 on the human heart was conducted as a thorough QT/QTc (TQTc) study in accordance with the ICH E14 Guidance and subsequent Q&A (Study R2116). The first part of the study consisted of a sequential-group safety and tolerability study in which 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 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-g 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 timepoints. For the moxifloxacin treatment, a prolongation of the QTcF interval was observed for all timepoints 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 the 1-sided 95% CI of LS means in the ΔΔQTcF > 5 msec). The results indicate that single 2-g 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.

1.5 Phase 2 and Phase 3

1.5.1 Phase 2 Complicated Urinary Tract Infections

The primary objective of Study 1409R2121 was to compare the response rate for the composite of both clinical cure and microbiologic eradication of S-649266 at the Test of Cure (TOC) with those of imipenem/cilastatin (IPM/CS) in a patient population at risk for multidrug resistant (MDR) Gram-negative pathogens originating from a cUTI with or without pyelonephritis or acute uncomplicated pyelonephritis. The primary efficacy assessment was performed at the TOC (approximately 7 days following the End of Treatment [EOT]).

Randomization was 2:1 to receive intravenous S-649266 (2 g) or IPM/CS (1/1 g) over 1 hour, every 8 hours for 7 to 14 days and no intravenous to oral antibiotic step down was permitted. The primary efficacy population was the Microbiological Intent-to-treat (Micro-ITT) Population, defined as subjects having received at least 1 dose of the study drug and with a Gram-negative uropathogen at baseline causing the cUTI.

Four hundred and fifty-two subjects were randomized, and 448 subjects were treated. Of the 448 treated subjects, 371 subjects met the definition of the Micro-ITT Population.

A higher percentage of S-649266-treated subjects were men (47.2% [119/252] compared with 40.3% [48/119] of IPM/CS-treated subjects) and had cUTIs (74.2% [187/252] compared with 70.6% [84/119] of IPM/CS-treated subjects). For the primary endpoint of composite of both clinical cure and microbiological eradication at the TOC, the response rate was 72.6% (183/252 subjects) for S-649266 and 54.6% (65/119 subjects) for IPM/CS. The adjusted treatment difference of 18.58% (95% CI: 8.23%, 28.92%) in favor of S-649266 met the criteria to demonstrate noninferiority with a prespecified 20% margin, since the lower limit of the 95% CI exceeded -20%. The lower limit of the 95% CI also exceeded −15%, and noninferiority with another prespecified 15% margin was demonstrated. This result showed superiority of S-649266 to IPM/CS (the lower limit of 95% CI was above 0).

Forty point seven percent (122/300) of subjects treated with S-649266 experienced at least 1 AE, compared with 51.4% (76/148) of subjects treated with IPM/CS. The most frequently observed adverse event was diarrhoea, which was experienced by 4.3% (13/300) and 6.1% (9/148) of S-649266- and IPM/CS-treated subjects, respectively. Fourteen (4.7%) of the 300 subjects treated with S-649266 experienced at least 1 SAE, compared with 12 (8.1%) of the 148 subjects treated with IPM/CS. There was one death of cardiac failure in the S-649266 group which the investigator considered not related to study drug. One (0.3%) of the 300 subjects treated with S-649266 experienced a treatment-related SAE, and 1 (0.7%) of the 148 subjects treated with IPM/CS experienced a treatment-related SAE, both events were *Clostridium difficile* colitis, which resolved with treatment. The results from this study indicated no unexpected safety concerns with S-649266.

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

1.5.1.1 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 nosocomial pneumonia caused by Gram-negative pathogens has been started (Study R2132). This randomized study (NCT03032380) is enrolling subjects with hospital-acquired pneumonia, ventilator-associated pneumonia and health-care associated pneumonia caused by Gram-negative pathogens compared with meropenem.

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

2. STUDY OBJECTIVES

2.1 Primary Objectives

- To assess, at test of cure (TOC[1], the clinical outcome of treatment with S-649266 or best available therapy (BAT) in adult patients with either hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP)/healthcare-associated pneumonia (HCAP) or bloodstream infections/sepsis (BSI/sepsis)[2] caused by carbapenem-resistant Gram-negative pathogens
- To assess, at TOC, the microbiologic outcome of treatment with S-649266 or BAT in adult patients with cUTI caused by carbapenem-resistant Gram-negative pathogens

2.2 Secondary Objectives

- To assess the safety of S-649266

The other secondary objectives of this study are established as follows:

- To assess the clinical outcome of treatment with S-649266 or BAT in patients with either HAP/VAP/HCAP or BSI/sepsis at End of Treatment (EOT)[3] and Follow-up (FUP) [4]
- To assess the clinical outcome of treatment with S-649266 or BAT in patients with cUTI at EOT, TOC, and FUP
- To assess the microbiologic outcome of treatment with S-649266 or BAT in patients with either HAP/VAP/HCAP or BSI/sepsis at EOT, TOC, and FUP
- To assess the microbiologic outcome of treatment with S-649266 or BAT in patients with cUTI at EOT and FUP
- To assess the microbiologic outcome of treatment with S-649266 or BAT in patients with bacteremia (regardless of the primary infection diagnosis) at EOT, TOC, and FUP
- To assess the composite clinical and microbiologic outcome of treatment with S-649266 or BAT in patients with cUTI at EOT, TOC, and FUP
- To assess the all-cause mortality at Day 14 and Day 28 in patients with HAP/VAP/HCAP and BSI/sepsis
- To assess the relationship between the PD parameter $\%fT_{>MIC}$ based on plasma drug concentrations at steady state and the clinical and microbiologic outcomes of treatment with S-649266 in patients with HAP/VAP/HCAP, cUTI, or BSI/sepsis

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1 TOC is defined as end of treatment (EOT) + 7 days (± 2 days).

2 BSI/sepsis is a group of patients with documented carbapenem-resistant Gram-negative infections in the blood stream (BSI) or in a body site other than the urinary tract (cUTI) or lung (HAP/VAP/HCAP) and in case of sepsis, evidence of systemic inflammatory response syndrome (SIRS) is required.

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

4 FUP = follow-up is defined as EOT + 14 days (± 3 days).

- To assess the resource utilization required for the treatment of the study-qualifying infection
- To compare S-649266 with BAT in patients with HAP/VAP/HCAP, cUTI, or BSI/sepsis based on the composite endpoint of survival and no change in antibiotic treatment due to either lack of therapeutic benefit or drug-related toxicity at TOC

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 3, multicenter (multinational), open-label, parallel group, randomized, active-controlled study in approximately 150 patients with documented carbapenem-resistant Gram-negative bacterial infections. Patients meeting eligibility criteria and assessed by the investigator to require 7 to 14 days of intravenous treatment in a hospital will be randomized (2:1) to either S-649266 2 g administered intravenously over 3 hours, q8h or BAT.

Patient eligibility is focused on the identification of carbapenem-resistant Gram-negative pathogens from a protocol-defined infection prior to Randomization. The eligible pathogens include, but are not limited to, carbapenem-resistant Enterobacteriaceae, carbapenem-resistant *P. aeruginosa*, or carbapenem-resistant *A. baumannii*. Identification of pathogen and/or carbapenem resistance identification may be made with the use of approved and investigational rapid diagnostic tests. After Randomization, pathogen identification will be confirmed through standard microbiological methods.

Patients will be randomized to S-649266 or BAT in a 2:1 ratio. Their infection site (HAP/VAP/HCAP, cUTI, and BSI/sepsis), baseline Acute Physiology and Chronic Health Evaluation II (APACHIE II) score (≤ 15 and ≥ 16) and region (N. America, S. America, Europe, and Asia-Pacific) will be balanced using the stochastic minimization method [21].

BAT will be chosen by the investigator and may include up to 3 antibacterial agents. BAT will be categorized as either a polymyxin-based (polymyxin B or colistin) regimen or a nonpolymyxin based regimen.

Since S-649266 is mainly eliminated unchanged in urine, patients with reduced renal function (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2) determined by modification of diet in renal disease (MDRD) equation, will have their dose reduced based on the degree of renal impairment (Table 5-2). Patients on various forms of hemodialysis, except peritoneal dialysis, are also eligible for the study and dosage will be adjusted as described in Section 5.2. Patients with augmented renal clearance (ARC) determined by eGFR ≥ 90 mL/min/1.73 m^2 and creatinine clearance (CrCl) ≥ 120 mL/min calculated by the Cockcroft-Gault equation will have their dosing interval shortened (Table 5-2). Dose adjustment should be done both after study required renal function tests as well as those conducted per the best local clinical practice.

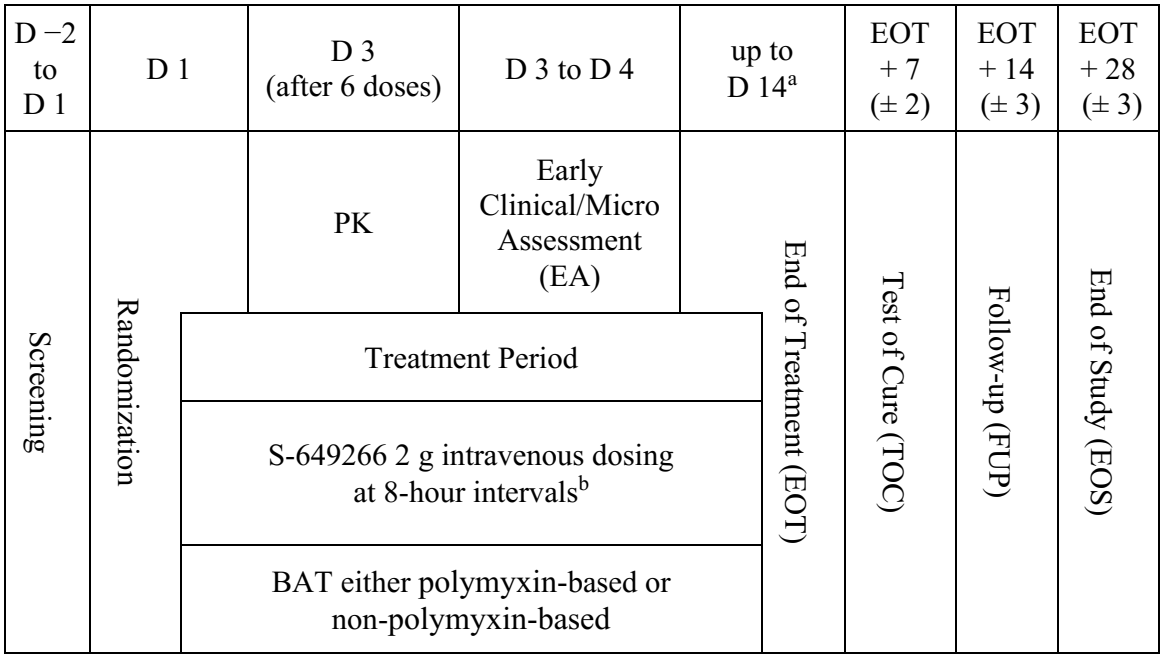
Dose adjustment for patients randomized to BAT with reduced renal function will be made according to each drug's country specific label based on the degree of renal impairment.

Sequential oral antibiotic (step-down) therapy is not permitted by this protocol. De-escalation (withdrawal of unneeded antibiotics after consideration of the bacterial culture and susceptibility results) will be assessed no later than Early Assessment (EA).

A patient'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). End of trial for this study is defined as the last visit of the last patient and is 28 days (± 3 days) after the end of treatment for that patient.

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



BAT = best available therapy; D = day; EA = early assessment; EOT = end of treatment (last day of study treatment); PK = pharmacokinetics

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

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

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

3.2 Rationale for Study Design and Control Group

3.2.1 Rationale for Patient Population

This study is designed to provide evidence of efficacy of S-649266 in the treatment of serious infections caused by a variety of carbapenem-resistant Gram-negative pathogens for a range of infection sites, ie, HAP/VAP/HCAP, cUTI, and BSI/sepsis. The target pathogens include, but are not limited to, carbapenem-resistant Enterobacteriaceae, carbapenem-resistant *P. aeruginosa*, or carbapenem-resistant *A. baumannii*. The target pathogens do not include Gram-positive or anaerobic bacteria. In cases of mixed infections with target and nontarget bacteria, additional antibiotic therapy may be used specifically to treat nontarget bacteria.

Although the urinary tract is a common source of carbapenem-resistant Enterobacteriaceae, carbapenem-resistant bacteremia, septicemia, and lung infections are the more difficult to treat infections. Therefore, the proportion of cUTI patients will be limited to no more than 30% of the total study population. Additionally, the proportion of patients with lung infections (HAP/VAP/HCAP) will be approximately 50% with VAP accounting for a little more than half (approximately 30% of the total patient population) of those patients, and BSI or sepsis as the primary diagnosis will be the remaining 20% of the patient population for the study.

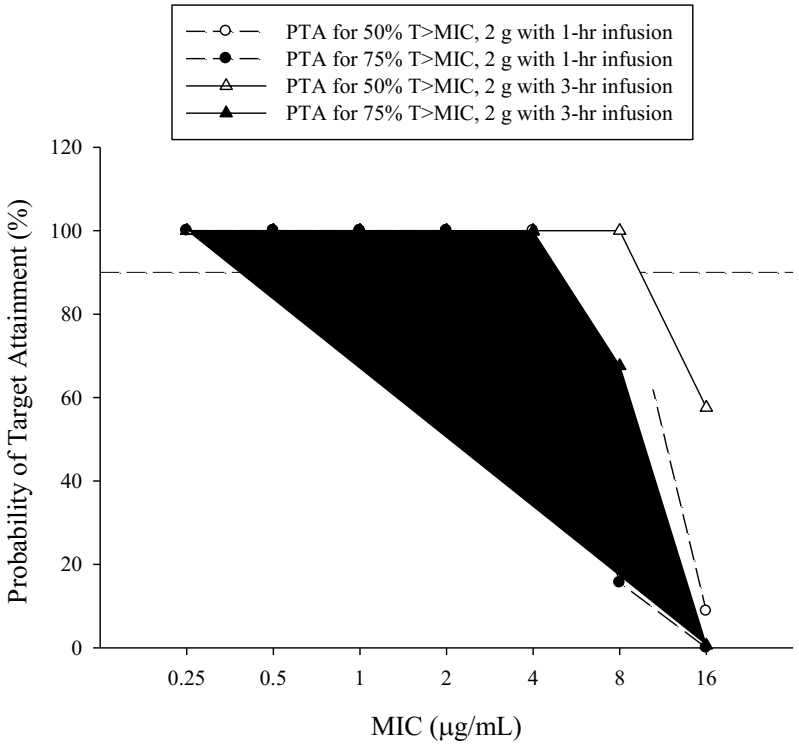
BSI is defined as a documented bacteremia in a patient with a documented infection other than HAP/VAP/HCAP or cUTI. Sepsis is defined as an infection other than HAP/VAP/HCAP or cUTI associated with systemic inflammatory response syndrome (SIRS).

3.2.2 S-649266 Dose Regimen

The dose and dose regimen for this study were developed from extensive PK/PD analyses of treatment of infections in appropriate animal models and PK modeling based on human PK. The controlling PD parameter for S-649266 is $\%fT_{>MIC}$. Although the plasma PK measurement 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 infections caused by carbapenem-resistant Gram-negative bacteria including carbapenem-resistant Enterobacteriaceae and carbapenem-resistant strains of *P. aeruginosa and A. baumannii* (Section 1.3.1).

Monte Carlo simulations using a population PK model, which was developed with data from the ascending dose Phase 1 study (Study R2111), were performed to assess the dose regimens which 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 (PTA) with administration of 2 g q8h with 1- or 3-hour infusion is shown in Figure 3-2.

Figure 3-2 Probability of Target Attainment for 50% or 75% *f*T > MIC



MIC = minimum inhibitory concentration; PTA = Probability of target attainment

The results indicated that with administration of 2 g q8h with 1- or 3-hour infusion, more than 90% of patients with normal renal function would achieve 50% $T_{f>MIC}$ at MIC of 8 μg/mL and 75% $T_{f>MIC}$ at MIC of 4 μg/mL. A 2 g q8h dosage regimen with 3-hour infusion could be considered a potential treatment for > 90% of the target pathogens, ie, carbapenem-resistant Enterobacteriaceae, MDRP and MDRAB based on susceptibility testing (each of MIC90: ≤ 4 μg/mL, 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 proposed S-649266 dose regimen for the treatment of serious, life-threatening infections with carbapenem-resistant Gram-negative pathogen for diagnoses such as HAP/VAP/HCAP, cUTI, or BSI/sepsis is 2 g q8h over a 3-hour infusion.

Adjustments for either impaired renal function or ARC are provided in this study to allow for enrollment of patients with significant comorbidities while maintaining the target drug exposure.

The dosages of S-649266 for patients with various degrees of renal function were calculated based on the result of Study R2113. Mild impairment did not result in a need to alter the dosage of drug. Moderate and severe impairment required a decrease in the amount of drug administered during an 8-hour infusion cycle (Table 5-2). Treatment

regimens for patients on various forms of hemodialysis, except peritoneal dialysis, are proposed in Table 5-2.

While it is usual to decrease drug dosage of cephalosporins in patients with impaired renal function, some patients, particularly trauma patients and those in intensive care unit (ICU) on ventilators, have increased renal clearance resulting in suboptimal drug exposure. Therefore, dosing adjustment was evaluated for patients with ARC (CrCl ≥ 120 mL/min) based on the population PK model that was developed by using the data from the healthy volunteer study (Study R2111) and the renal impairment study (Study R2113). The PK structural model is a 3-compartment model and the model includes CrCl as a covariate for a renal function index ($CL = 4.83 \times [1 + 0.00404 \times [CrCl - 100]$). A 2 g every 6 hours (q6h) dosage regimen with a 3-hour infusion is proposed for patients with ARC, in which > 90% PTA would be expected against pathogens requiring an MIC of 4 μg/mL as shown in the Table 3-1.

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

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

Inter-individual variability of 40% was assumed.
CrCl = creatinine clearance calculated by Cockcroft-Gault equation; q8h = every 8 hours.

3.2.3 BAT Regimens

Because of the life-threatening nature of the protocol specified infections, a placebo-controlled study is not appropriate. A standardized comparator is not feasible because the most appropriate treatment for patients with carbapenem-resistant Gram-negative bacterial infection is often a highly variable combination of several antibiotics and is usually tailored to the patient's specific infection, determined by both (a) the site of infection, microbiologic identification, and antibiotic susceptibility of the patient's causative bacteria, and (b) the availability of approved antibiotics within a country [22-26]. Therefore, the comparator will be BAT which will be determined by the Investigator using clinical judgment and local standard of care and will include only products approved in their respective country. Because BAT cannot be precisely defined in the protocol, blinding of this study is not possible.

3.2.4 Duration of Study Treatment

The treatment duration for S-649266 or BAT is anticipated to be 7-14 days which are consistent with published treatment guidelines for serious infections [27-29]. Based on the investigator's clinical assessment of the patient, treatment may be extended up to 21 days. The reason for the extension should be clearly documented. All study treatments will be performed in the hospital.

3.3 Study Duration

3.3.1 Study Duration in Individual Patients

All patients will be followed for safety for approximately 28 days following EOT. The total study participation from treatment initiation to EOS will be approximately 5 to 7 weeks for each patient.

4. STUDY POPULATION SELECTION

4.1 Study Population

Male or female patients 18 years of age or older who have a documented infection caused by a carbapenem-resistant Gram-negative pathogen and who require hospitalization for the parenteral (intravenous) treatment of the infection may be enrolled in the study.

Patients with the following infections will be enrolled:

- HAP/VAP/HCAP or
- cUTI or
- BSI/sepsis
  Note: Patients with BSI/sepsis secondary to HAP/VAP/HCAP or cUTI will be categorized based on the primary infection diagnosis, ie, HAP/VAP/HCAP or cUTI.[1]

The proportion of patients with the various infection diagnoses will be controlled at the time of Randomization through a central Randomization system.

- Approximately 50% of randomized patients will have HAP/VAP/HCAP
- No more than 30% of randomized patients will have cUTI
- The remainder of randomized patients will have BSI/sepsis

The initial evidence of carbapenem-resistant Gram-negative bacterial pathogen may be derived from various scenarios as follows:

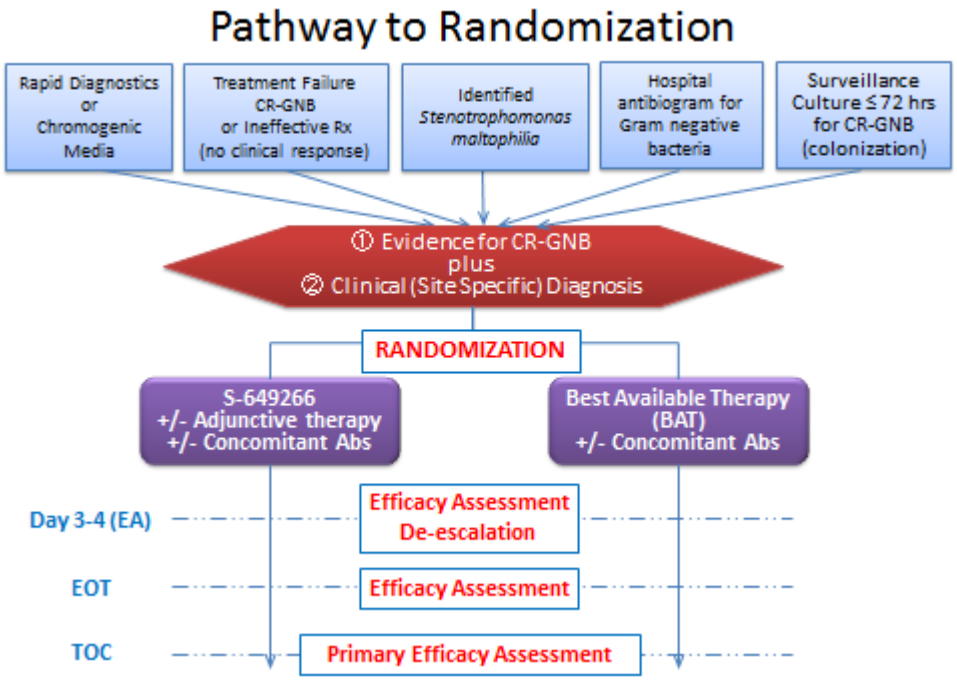
- Rapid diagnostic tests identifying the presence of carbapenemase or selective chromogenic media may be used to identify carbapenem-resistant Gram-negative bacterial infections prior to the availability of MIC results for the specific infection
- Empiric treatment has failed and the target pathogen has been identified as a carbapenem-resistant Gram-negative pathogen
- An identified infection with *Stenotrophomonas maltophilia* is eligible because it is inherently carbapenem resistant.

[1] BSI/sepsis is a separate treatment group of patients with documented carbapenem-resistant Gram-negative infections defined as either a blood stream infection (BSI) or an infection site other than cUTI or HAP/VAP/HCAP and in case of evidence of systemic inflammatory response syndrome (SIRS)

- Current hospital antibiogram for Gram negative bacteria showing a CR rate of > 90% is taken as evidence of CR for the isolated Gram-negative pathogens from the patient. Supporting documentation, submitted to Shionogi for approval prior to implementation, may take the form of a copy of local hospital epidemiological data from within the past year, an official (annual) report containing aggregate data with sensitivities would be preferable, or a Note to File indicating sensitivity data prepared by the microbiologist or principle investigator may be acceptable.
- Patient is known to be colonized (as evidenced by prior cultures from the same site as the infection) with a carbapenem-resistant Gram-negative pathogen prior to developing acute infection, ie, prior culture within the previous 72 hours

The possible pathways for enrollment in the study are presented in Figure 4-1.

Figure 4-1 Study Schematic Showing Possible Pathways for Study Entry



CR-GNB = Carbapenem-resistant Gram-negative bacilli, EA = early assessment; EOT = end of treatment; TOC = Test of Dure; hrs = hours

Patients who were initially randomized based on one of the above scenarios, but failed to demonstrate a study required carbapenem-resistant Gram-negative infection on central laboratory testing will remain in the study and continue to receive their study treatment regimen, if the treatment regimen is assessed by the investigator as adequate.

4.2 General Inclusion Criteria

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

1. Hospitalized male and female patients, 18 years or older at the time of signing informed consent
2. Patients who have provided written informed consent or their informed consent was provided by legal guardian (Note: Country specific rules and local Ethics Committee approval for legal guardian informed consent will determine whether or not and how a patient unable to comprehend or sign the informed consent is allowed to be enrolled in the study)
3. Patients with clinically documented infection (HAP/VAP/HCAP, cUTI, or BSI/sepsis) caused by a Gram-negative pathogen with evidence of carbapenem resistance (see Section 4.1).
4. Patients who have been treated previously with an empiric antibiotic regimen and failed treatment, both clinically and microbiologically, are eligible for the study, if they have an identified carbapenem-resistant, Gram-negative pathogen which has either been shown to be nonsusceptible in vitro to each of the antibiotic(s) of the empiric antibiotic regimen or been grown from a culture performed after at least 2 days of the empiric antibiotic regimen
5. Patient is male (no contraception required) or female and meets one of the following criteria:
   - Surgically sterile (has had a hysterectomy and/or bilateral oophorectomy, or bilateral salpingectomy or tubal ligation for the purpose of contraception for at least 6 weeks with appropriate documentation of such surgery)
   - Postmenopausal (defined as older than 45 years of age with cessation of regular menstrual periods for 6 months and a follicle-stimulating hormone level of > 40 mIU/mL, or amenorrhea for at least 12 months)
   - Of childbearing potential and using combined (estrogen and progestogen) or progestogen-only hormonal contraception associated with inhibition of ovulation (including oral, intravaginal, injectable, implantable, and transdermal contraceptives), or an intrauterine device (IUD), or intrauterine hormone-releasing system (IUS) for the entire duration of the study
   - Of childbearing potential and practices abstinence as a preferred and usual lifestyle, and agrees to continue practicing abstinence from Screening and for the entire duration of the study
   - Of childbearing potential, whose sole heterosexual partner has been successfully vasectomized and agrees to not have other heterosexual partners for the entire duration of the study
6. Patients meeting specific criteria for each infection site (See Section 4.4)

4.3 General Exclusion Criteria

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

1. Patients who have a history of any moderate or severe hypersensitivity or allergic reaction to any β-lactam (Note: for β-lactams, a history of a mild rash followed by uneventful re-exposure is not a contraindication to enrollment)
2. Patients who need more than 3 systemic antibiotics as part of BAT for the treatment of the Gram-negative infection (Patients with mixed Gram-positive or anaerobic infections may receive appropriate concomitant narrow-spectrum antibiotics [eg, vancomycin, linezolid, metronidazole, clindamycin])
3. Patients with coinfection caused by invasive aspergillosis, mucormycosis or other highly lethal mold
4. Patients who have central nervous system infection (eg, meningitis, brain abscess, shunt infection)
5. Patients with infection requiring > 3 weeks of antibiotic treatment (eg, bone and joint infection, endocarditis)
6. Patients with cystic fibrosis or moderate to severe bronchiectasis
7. Patients in refractory septic shock defined as persistent hypotension despite adequate fluid resuscitation or despite vasopressive therapy at the time of randomization
8. Patients with severe neutropenia, ie, polymorphonuclear neutrophils (PMNs) < 100 cells/μL
9. Female patients who have a positive pregnancy test at Screening or who are lactating
10. Patients with Acute Physiology and Chronic Health Evaluation II (APACHE II) score > 30
11. Patients who have received a potentially effective antibiotic regimen for the carbapenem-resistant, Gram-negative infection for a continuous duration of more than 24 hours in cUTI, or 36 hours in HAP/VAP/HCAP or BSI/sepsis during the 72 hours leading to Randomization
12. Patients with any condition or circumstance that, in the opinion of the investigator, would compromise the safety of the patient or the quality of the study data
13. Patients who have received another investigational drug or device within 30 days prior to study entry
14. Patients who have previously been randomized in this study or received S-649266
15. Patients receiving peritoneal dialysis
16. Patients meeting specific exclusion criteria for each infection site (See Diagnosis-Specific Exclusion Criteria)

4.4 Diagnosis Specific Inclusion and Exclusion Criteria

4.4.1 HAP/VAP/HCAP Patients

4.4.1.1 HAP/VAP/HCAP Definitions

The diagnosis of HAP, VAP, or HCAP will be specified and recorded in the eCRF. HAP is defined as an acute bacterial pneumonia in a patient hospitalized for more than

48 hours or developing within 7 days after discharge from a hospital. Patients may experience acute respiratory failure and require mechanical ventilation for HAP (ventilated-HAP).

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

HCAP is defined as below when at least one of the criteria is met:

- an acute bacterial pneumonia in a patient who was hospitalized in an acute care hospital for 2 or more days within 90 days of the infection;
- resided in a nursing home or long-term care facility;
- received intravenous antibiotic therapy, chemotherapy, or wound care; or attended a hemodialysis clinic within the past 30 days of the current infection.

4.4.1.2 HAP/VAP/HCAP Specific Inclusion Criteria

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

1. All patients must have at least one of the following clinical features:
   a. New onset or worsening of pulmonary symptoms or signs, such as cough, dyspnea, tachypnea (eg, respiratory rate greater than 25 breaths/minute), expectorated sputum production, or requirement for mechanical ventilation
   b. Hypoxemia (eg, a partial pressure of oxygen less than 60 mmHg while the patient is breathing room air, as determined by arterial blood gas [ABG] or worsening of the ratio of the partial pressure of oxygen 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
2. All patients must have at least one of the following signs:
   a. Documented fever (eg, core body temperature [tympanic, rectal, esophageal] greater than or equal to 38°C [100.4°F], oral temperature greater than or equal to 37.5°C or axillary temperature greater than or equal to 37°C)
   b. Hypothermia (eg, core body temperature [tympanic, rectal, esophageal] less than or equal to 35°C [95°F], oral temperature less than or equal to 35.5°C or axillary temperature less than or equal to 36°C)
   c. Leukocytosis with a total peripheral WBC count greater than or equal to 10,000 cells/mm^3
   d. Leukopenia with total peripheral WBC count less than or equal to 4,500 cells/mm^3

e. Greater than 15% immature neutrophils (bands) noted on peripheral blood smear

3. All patients must have a chest radiograph or lung computed tomography (CT) scan within 48 hours of randomization showing the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia.

4.4.1.3 HAP/VAP/HCAP Specific Exclusion Criteria

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

1. Patients who have known or suspected community-acquired bacterial pneumonia, atypical pneumonia, viral pneumonia or chemical pneumonia (including aspiration of gastric contents, inhalation injury)
2. Patients receiving concomitant aerosolized antibiotics with Gram-negative activity

4.4.2 cUTI Patients

4.4.2.1 cUTI Definition

cUTI is defined as a clinical syndrome characterized by pyuria and a documented microbial pathogen on urine culture, accompanied by local and systemic signs and symptoms including fever, chills, malaise, flank pain, back pain, and/or costovertebral angle pain or tenderness that occur in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterization and who require hospitalization for the parenteral (intravenous) treatment of cUTI will be enrolled in the study.

4.4.2.2 cUTI Specific Inclusion Criteria

Patients who have a clinical diagnosis of either cUTI with pyelonephritis or cUTI without pyelonephritis and fulfill the following criteria at Screening will be included in the study:

1. All patients must have a cUTI with a history of at least one of the following:
   a. Indwelling urinary catheter or recent instrumentation of the urinary tract (within 14 days prior to Screening)
   b. Urinary retention caused by benign prostatic hypertrophy
   c. Urinary retention of at least 100 mL or more of residual urine after voiding (neurogenic bladder)
   d. Obstructive uropathy (nephrolithiasis, fibrosis, etc)
   e. Azotemia caused by intrinsic renal disease (BUN and creatinine values greater than normal clinical laboratory values)
2. All patients must have at least 2 of the following signs or symptoms:
   a. Chills, rigors, or warmth associated with fever (body temperature greater than or equal to 38°C [100.4°F])
   b. Flank pain (pyelonephritis) or suprapubic/pelvic pain (cUTI)

c. Nausea or vomiting
d. Dysuria, urinary frequency, or urinary urgency
e. Costovertebral angle tenderness on physical examination

3. All patients must have evidence of pyuria on urinalysis demonstrated by either:
   a. Either dipstick analysis positive for leukocyte esterase

   OR

   b. ≥ 10 WBCs /μL in unspun urine, or ≥ 10 WBCs /high power field in spun urine
4. Patients who had a positive urine culture within 48 hours prior to Randomization containing ≥ 10^5 colony forming unit (CFU)/mL of a carbapenem-resistant Gram-negative uropathogen are eligible for this study (Note: patients may be randomized prior to the results of the urine culture if they have evidence of a carbapenem-resistant pathogen)
5. Patients receiving antibiotic prophylaxis for cUTI who present with signs and symptoms consistent with an active new cUTI may be enrolled provided all other eligibility criteria are met including obtaining a pretreatment qualifying urine culture

4.4.2.3 cUTI Specific Exclusion Criteria

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

1. Patient's urine culture at study entry isolates more than 2 uropathogens, regardless of colony count, or patient has a confirmed fungal cUTI
2. Patients with asymptomatic bacteriuria, the presence of >10^5 CFU/mL of a uropathogen and pyuria but without local or systemic symptoms [30]
3. Patients with an ileal loop for urine outflow (for patients with BSI/sepsis and an ileal loop are eligible)
4. Patients with acute uncomplicated pyelonephritis, ie, absence of anatomic urinary tract abnormality
5. Patients with vesico-ureteric reflux

4.4.3 Bloodstream Infections/Sepsis Patients

4.4.3.1 BSI/Sepsis Definitions

The BSI/sepsis category includes bacteremia or sepsis caused by infections other than HAP/VAP/HCAP or cUTI. The diagnosis of BSI or sepsis and the causal infection will be specified and recorded in the eCRF. Patients will be enrolled in the BSI/sepsis group with either:

a. Documented BSI caused by a carbapenem-resistant Gram-negative pathogen

   OR

b. Systemic response to infection, meeting the clinical criteria of SIRS [29] and an

identified infection source (eg, severe skin infection, intra-abdominal infection) caused by a carbapenem-resistant Gram-negative pathogen

Note: The inclusion/exclusion criteria for BSI and sepsis are not the same. It is possible to meet the criteria for one without the other.

4.4.3.2 Bloodstream Infection-specific Inclusion Criteria

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

1. Patients who have one or more positive blood cultures identifying a carbapenem-resistant Gram-negative pathogen that is consistent with the patient's clinical condition
2. Patients who have signs or symptoms associated with bacteremia

4.4.3.3 Bloodstream Infection-specific Exclusion Criteria

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

1. Patients who have a positive blood culture only obtained from an intravenous catheter. If both peripheral venipuncture blood culture and intravenous catheter blood culture show the same organism, the patient is eligible
2. Patients with BSI considered to be due to an endovascular source, eg, endocarditis, infected vascular graft, a permanent intravascular device that cannot be removed during the course of treatment

4.4.3.4 Sepsis-specific Inclusion Criteria

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

1. Patients defined for SIRS (Appendix 2), indicated by having 2 or more of the following responses:
   a. Oral or tympanic body temperature greater than 38°C (100.4°F) or less than 36°C (96.8°F)
   b. Tachycardia, heart rate greater than 90 beats/minute
   c. Tachypnea, manifested by a respiratory rate greater than 20 breaths/minute or hyperventilation, as indicated by an arterial partial pressure of carbon dioxide ($PaCO_2$) of less than 32 mm Hg
   d. WBC greater than 12,000 cells/mm^3, less than 4000 cells/mm^3, or > 10% immature (band) forms
2. Patients with an identified infection site from which a carbapenem-resistant Gram-negative pathogen has been isolated using an appropriate clinical specimen

4.4.3.5 Sepsis Specific Exclusion Criteria

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

1. Patient does not have an identified source of a bacterial infection and an identified carbapenem-resistant Gram-negative pathogen
2. Patient has an alternative explanation for the physiologic parameters of SIRS, eg, cardiogenic shock, cardiac arrhythmia, or hyperthyroid storm
3. Patients with infections where isolation of a Gram-negative pathogen is unlikely to be causing the infection such as that in the upper respiratory systems, head and neck, pelvic or genital organ, etc.

5. STUDY TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 Test Drug

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

5.1.2 Control Treatment Regimen

The control population will be treated with BAT, locally sourced by study sites, within the local standard of care determined by the investigator for each infection diagnosis. This will usually involve 1 or 2 or possibly 3 antibiotic agents specifically for the carbapenem-resistant Gram-negative pathogen.

One or 2 or possibly 3 antibiotic agents: Published clinical studies, usually retrospective or non-randomized observational studies, have not shown conclusively that combinations of antibiotics are superior to monotherapy. Results of these studies are highly variable and often dependent on the type of infection or the specific causative pathogen [22-26].

5.2 Treatments To Be Administered

Each patient who is qualified for entry in the study will be randomized into 1 of 2 treatment groups according to the method of treatment assignment as specified in Section 5.4. The treatment groups are shown in Table 5-1.

S-649266 will be administered intravenously over 3 hours q8h. The adjunctive antibiotic to S-649266 and BAT will be administered according to the country specific package label and the discretion of the investigator.

The treatment duration for S-649266 or BAT is anticipated to be 7 to 14 days which are consistent with published treatment guidelines for serious infections [27-29]. Only in cUTI is a minimum of 5 days permissible if in the opinion of the investigator, the patient’s infection has been cured and it is in the patient's best interest. It is recommended that dosing does not exceed 14 calendar days or 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 patient. The reason for the extension should be clearly documented. All study treatments will be performed in the hospital.

If a patient needs to be treated for longer than 21 days, an EOT visit should be performed as soon as possible after last dose (same calendar day) and the patient should be discontinued from the study treatment: 1) in the case of S-649266 (and the adjunctive antibiotic), treatment should then follow local clinical practice; 2) in the case of BAT, it should be continued or changed per local clinical practice. These patients are still considered to be in the study and should be followed through to the completion of all study activities, ie, TOC, FUP, and EOS.

Table 5-1 Study Treatment Administration

Treatment Groups	Study Treatment
S-649266	S-649266 2 g* administered intravenously every 8** hours as a 3-hour infusion with/without another single adjunctive Gram-negative antibiotic other than a polymyxin or a cephalosporin/carbapenem including combination with beta-lactamase inhibitor (eg, ceftazidime/avibactam or ceftolozane/tazobactam)
BAT	Standard of care with either a polymyxin-based or non-polymyxin-based regimen as determined by the investigator and consisting of 1 to 3 marketed antibacterial agent(s)

BAT = best available care

* 0.75 g, 1 g, 1.5 g, or 2 g based on renal function see Table 5-2.

** 6, 8, or 12 hours based on renal function see Table 5-2.

5.2.1 S-649266 Group

The preparation of the dosing solutions for S-649266 is described in the study procedure manual. The solution volume for infusion must be at least 100 mL. Under no circumstances is S-649266 to be administered in a saline solution of less than 100 mL. Dilution volumes greater than 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.

5.2.1.1 Adjunctive Antibiotic Therapy

Patients with cUTI should receive S-649266 monotherapy, ie, without combining with an additional Gram-negative antibiotic.

Patients with HAP/VAP/HCAP or BSI/sepsis randomized to treatment with S-649266 may receive a second (but not a third) Gram-negative antibiotic other than a polymyxin (colistin or polymyxin B) or a cephalosporin/carbapenem including combination with beta-lactamase inhibitor (eg, ceftazidime/avibactam or ceftolozane/tazobactam) at the initiation of study drug. This decision should be based on the investigators consideration of the patient's condition, the causative pathogen, and current best practices.

If a second Gram-negative antibiotic is administered with S-649266 at the time of randomization, the investigator must reassess the need for the second Gram-negative antibiotic upon availability of susceptibility testing to S-649266 no later than EA visit. The adjunctive antibiotic therapy should be discontinued (de-escalated) accordingly.

Examples of allowed adjuvant Gram-negative antibiotics for patients randomized to the S-649266 arm for HAP/VAP/HCAP or BSI/sepsis infections only are:

Any aminoglycoside
Any fluoroquinolone

Any macrolide
Piperacillin/tazobactam
Ampicillin/sulbactam, but not sulbactam alone
Piperacillin
Fosfomycin
Tigecycline

5.2.2 BAT Group

BAT is the standard of care as determined by the investigator based on his/her assessment of the patient's clinical condition, the site of infection and the causative organism (including available susceptibility data) as well as the totality of evidence on available medicines and his/her best clinical judgment. BAT consists of 1 to 3 antibiotics prescribed for the carbapenem-resistant, Gram-negative pathogen, without aerosolized antibiotics. BAT can be a polymyxin-based or non-polymyxin-based regimen. A second or third antibiotic could include but is not limited to an aminoglycoside, a carbapenem, a fluoroquinolones, or tigecycline. The planned standard of care regimen needs to be recorded prior to randomization (refer to Section 5.4).

If the investigator chooses to use a polymyxin (either polymyxin B or colistin [polymyxin E]), the investigator is encouraged to follow EMA's dosing recommendations [Appendix 3]. Some formulations of colistin, eg, colistimethate and colistin methanesulfonate, are pro-drugs and are hydrolyzed to colistin in situ. Since the availability of polymyxin B and colistin products vary from country to country, no standardized BAT is possible for this multinational study. Careful attention to labelled dosing recommendations including adjustments for renal function is recommended [31].

Combination therapy for BAT may include drugs to which the patient's identified pathogenic organism is non-susceptible in vitro. Various combinations of these antibiotics have been shown to be synergistic in vitro and in animal experiments [32, 33].

De-escalation is defined as the discontinuation of unnecessary antibiotics consistent with best medical practices [34, 35]. BAT regimen may be modified by reducing the number of antibiotics used to treat the carbapenem-resistant Gram-negative infections at any time, but an assessment for de-escalation is required no later than EA.

5.3 Selection and Timing of Dose for Each Patient

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

Table 5-2 provides the S-649266 dosing adjustments for patients with various degrees of renal function and ARC. The dosages for S-649266 in Table 5-2 were derived from the results of the ascending dose Phase 1 study (Study R2111) and the renal impairment study (Study R2113) examining the PK characteristics of the S-649266 in normal healthy subjects and in patients with various degrees of renal impairment including hemodialysis.

The initial dosage for each patient will be adjusted based on eGFR calculated by MDRD equation [36] and CrCl by Cockcroft-Gault equation [37] as per Table 5-2. Renal function for all patients will be assessed at EA to determine if there are changes in renal function as a result of treatment. The main purpose for this is to insure that drug levels remain in a safe and therapeutic range. If renal function is changed at EA from Screening, dose adjustment will be required as per Table 5-2. During treatment period other than EA, dose adjustment will be required on review of renal function conducted per local clinical practice.

A urinary measured CrCl will be calculated at EA for patients with eGFR $\geq$ 90 mL/min/1.73 m^2 at Screening in order to determine if an additional adjustment is required.

The adequacy of the proposed S-649266 dose regimen will be evaluated using PK data of patients treated by S-649266, if necessary.

Table 5-2 S-649266 Dosing Adjustments for Various Degrees of Renal Function and Augmented Renal Clearance

Augmented renal function (MDRD-eGFR $\geq$ 90 mL/min/1.73 m^2 and CrCl $\geq$ 120 mL/min)[a]	2 g, q6h, 3-hour infusion
Normal renal function (MDRD-eGFR $\geq$ 90 mL/min/1.73 m^2 and CrCl < 120 mL/min)[a]	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
Patient 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; ESRD = end-stage renal disease; HD = hemodialysis; MDRD-eGFR = modification of diet in renal disease-estimated glomerular filtration rate calculated with the MDRD equation; q6h = every 6 hours; q8h = every 8 hours; q12h = every 12 hours.

a A CrCl will be calculated by Cockcroft-Gault equation at Screening. A urine measured CrCl will be calculated by using timed urine collections of 2-8 hours at EA.

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 an excessive exposure and complexity of clinical operation.

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

The dosage of BAT and adjunctive antibiotic therapy is based on the country specific package insert(s) and the discretion of the investigator. Adjustments for renal impairment will be made according to each product label.

The administration schedule of study after initial administration may be adjusted gradually, within reason and based on the clinical judgement 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 patient identification numbers by the IXRS® provider in a 2:1 fashion, ie, to S-649266 and BAT, respectively. An interactive web or voice response system (IWRS/IVRS) will be used to assign patients to identification numbers for which treatment has already been randomly assigned. Randomization will be performed by the stochastic minimization method using their infection site (HAP/VAP/HCAP, cUTI, and BSI/sepsis), APACHE II score (≤ 15 and ≥ 16), and region (N. America, S. America, Europe, and Asia-Pacific) as allocation factors. To avoid deterministic allocation based on the ongoing allocation results, probabilistic allocation will be incorporated [19].

The investigator or designee will record the planned Standard of Care drug(s), drug dose, and dosing regimens, which would have been given if the patient was not participating in this clinical study, for both treatment groups (S-649266 or BAT) at the time the patient is to be randomized. Once the centralized IWRS/IVRS has accepted and randomized the patient to either treatment group, the dispensing pharmacist will prepare for administration of the allocated treatment. If BAT is allocated, please refer to Sections 5.2.2, 5.6.2, and 6.2 of protocol to confirm appropriate treatment options allowed within protocol.

The population with HAP/VAP/HCAP will be approximately 50% of randomized patients; cUTI is limited to no more than 30% of randomized patients, and the remainder of patients will be enrolled under the BSI/sepsis diagnosis. The randomization ratio of patients between treatment groups based on clinical diagnosis will be maintained through the allocation factor of clinical diagnosis at the time of randomization. The process for patient number assignment and treatment assignment is described in the study procedure manual.

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

5.5 Blinding

This is an open-label study.

The number of approved drugs for treating carbapenem-resistant Gram-negative bacterial infection is very limited. Choice of treatment is determined by multiple factors. Because BAT cannot be defined in the protocol, blinding of this study is not possible.

5.6 Packaging and Labeling, Storage and Accountability

The investigator/site pharmacist will ensure that S-649266 drug supply is stored and dispensed in accordance with local health regulations concerning the storage and administration of investigational drugs. All S-649266 drug supplies must be kept in a secure area at specified refrigerated temperatures with access limited to those authorized by the investigator.

The investigator or pharmacist will maintain accurate records on the following information: receipt and condition of S-649266 drug supplies, date of the receipt, when and how much S-649266 is dispensed and used by each patient in the study, and any reasons for departure from the protocol-dispensing regimen. The drug accountability records and the spent dosage vials of S-649266 will be available for verification by the Shionogi monitor, contract research organization (CRO) or designee at each monitoring visit. If 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 S-649266 drugs will be performed. S-649266 must not be used for any purpose other than the present study.

5.6.1 S-649266

S-649266 will be supplied to the study sites in containers which identify the contents, ie, not blinded. The pharmacist or qualified designee who will prepare the infusion solutions will also adjust the dosages as described in Section 5.3. The individual vials for S-649266 will be labeled with the name of active ingredient, protocol number, lot number, dosage form, strength, dosing instructions, medication ID number, storage conditions, caution statements, name and address of the manufacturer or sponsor as appropriate for a given country labeling requirements.

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.

Adjunctive antibiotic therapy for HAP/VAP/HCAP or BSI/sepsis patients will be locally sourced by study sites and will include only marketed drug products available through the investigator’s site pharmacy. Investigational agents, a polymyxin (colistin or polymyxin B), and a cephalosporin/carbapenem including combination with beta-lactamase inhibitor (eg, ceftazidime/avibactam or ceftolozane/tazobactam) are not permitted as part of Adjunctive antibiotic therapy. Adjunctive antibiotic therapy will be stored as specified by the label.

5.6.2 BAT

BAT will be locally sourced by study sites and will include only marketed drug products available through the investigator's site pharmacy. Investigational agents, including S-649266 are not permitted as part of BAT. BAT will be stored as specified by the label.

5.7 Investigational Product Retention at Study Site

All unused study drug supplies (S-649266 only) 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 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.

5.8 Treatment Compliance

Dose, start times, and end times of the administration of intravenous treatments, and the approximate extent of completion of all infusions of S-649266, antibacterial agents used as BAT, and adjunctive antibiotics will be recorded in the electronic case report form (eCRF). Any interruption or adjustment of the rate of an infusion will be noted in the eCRF. The reason for interruption or adjustment will also be noted in the eCRF.

5.8.1 Changes in Treatment Regimen

After initial administration of S-649266 or BAT, patients who have their treatment regimen altered for reasons of either 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 which were taken prior to randomization of the study.

Systemic antibiotic treatment or prophylaxis for Gram-negative pathogens including aerosolized antibiotics in patients with HAP/VAP/HCAP must be stopped before administration of study drug.

Prior antibiotic therapy (oral or intravenous) taken by patient during the current during the current hospitalization until randomization into the study will be recorded in the eCRF and the information will include the name of drug used or procedures done, start and end dates, route of administrations and reason.

Similarly, any prior therapy other than systemic antibiotics (prescription drugs, over-the-counter drugs, procedures [eg, surgical or non-surgical related to infection treatment or treatment-related complications such as dialysis] with or without any medication) taken by patient within 2 weeks prior to randomization of the study will be recorded in the eCRF.

6.2 Concomitant Therapy during the Study

6.2.1 Antibiotic Therapies

Concomitant antibiotic therapies are defined as therapies taken after randomization in the study.

Additional antibiotics may be added to both S-649266 and BAT groups for concomitant Gram-positive or anaerobic infection or for infection prevention (prophylaxis). Only narrow-spectrum agents lacking substantial Gram-negative activity are permitted (eg, vancomycin, daptomycin, linezolid, metronidazole, or clindamycin). Topical antibiotics excluding aerosolized antibiotics will be permitted.

The investigator, sub-investigator, or designee will record the following information for all therapies (prescription drugs, over-the-counter drugs, herbal preparation, and procedures without any medication) used during the study (from randomization 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

6.2.2 Nonantibiotic Therapies and Procedures

Concomitant therapies are defined as therapies including concomitant drugs to support blood pressure or renal output, antiviral agents, or antifungal therapy which 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, sub-investigator, or designee will record the following information for all therapies (prescription drugs, over-the-counter drugs, herbal preparation, and procedures without any medication) used during the study (from randomization 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

6.2.3 Prohibited Therapy

For patients randomized to S-649266

- Systemic antibiotics with Gram-negative activity, other than a single adjunctive Gram-negative antibiotic therapy for HAP/VAP/HCAP or BSI/sepsis patients initiated with the study drug, are not permitted until TOC
- Aerosolized antibiotics are not permitted until TOC
- Refer to the label of any adjunctive antibiotic therapy being used in combination with S-649266 for information about contraindicated therapies to those adjunctive antibiotic therapies

For patients randomized to BAT

- More than 3 systemic antibiotics with Gram-negative activity are not permitted until TOC
- Aerosolized antibiotics are not permitted until TOC
- Refer to label of BAT drugs for contraindicated therapies

6.2.4 Rescue Therapy

There is no identified rescue treatment regimen. No addition or substitution of any antibiotic after randomization is allowed unless the patient is assessed as a microbiologic or clinical failure in which case an EOT assessment should occur. If a patient needs to be treated for longer than 21 days, an EOT visit should be performed as soon as possible after last dose (same calendar day) and the patient should be discontinued from the study treatment: 1) in the case of S-649266 (and the adjunctive antibiotic), treatment should

follow local clinical practice; 2) in the case of BAT, it should be continued or changed per local clinical practice. All antibiotics 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 patient is screened and enrolled on the same day, the information requirements for the Screening (Day −2 to Day 1) and for Randomization (Day 1) are to be completed. The requirements for the complete physical examination, vital signs, and clinical laboratory tests will be limited to only one set of tests.

7.1 Informed Consent

The investigator or sub-investigator will fully explain the nature of the study to a patient or if unable to give consent him/herself, his/her legal guardian using the Institutional Review Board (IRB)/Institutional Ethics Committee (IEC)-approved informed consent document. When the patient or his/her legal guardian agrees that he/she can participate in the study, the patient or his/her legal guardian 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 patient. The signed and dated original consent form will be retained by the investigator. Informed consent will be obtained from all patients. A patient 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 patient who can only be enrolled with the consent of his/her legal guardian should be informed about the study when the patient is able to sign a consent during the study and, if capable, the patient should sign and personally date the written informed consent. (Note: Country specific rules and local Ethics Committee approval for legal guardian informed consent will determine whether or not a patient unable to comprehend or sign the informed consent is allowed to be enrolled in the study).

The investigator or sub-investigator is responsible for ensuring that the patient understands the risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing any new information in a timely manner that may be relevant to the patient's willingness to continue his/her participation in the study.

Patient's eligibility for the study may be determined through the use of diagnostics, some of which are investigational in the country where the protocol will be used. The use of investigational diagnostics or diagnostics that are not the local standard of care for determination of carbapenem resistance will require that the investigational diagnostics section of the informed consent be signed by the patient or legal guardian.

7.2 Baseline Patient Characteristics and Medical History

The following baseline patient characteristics will be obtained upon entrance into the study and entered in the eCRF: age, sex, ethnicity, race, onset of infection, severity of infection, prior therapy, and medical history. Medical history will include the following:

- The detailed reason for current hospitalization
- History of study qualifying infection and the cause of the infection if known at the time of enrollment (eg, recurrent pneumonia, BSI, cUTI, etc) with

microbiological information

- Any previous, concurrent, or concomitant medical conditions meaningful to the current infection (eg, cancer, stroke, and myocardial infarction)
- Conditions that required antibiotic treatment during current hospitalization, and the name and duration (calendar dates) of antibiotic treatment as well as relevant microbiological information
- Tracheostomy during the hospitalization
- History of other relevant surgical procedures that relate to the patient's study infection
- History of other major, clinically important infections (not same as study infection) during the current hospitalization, including fungal or viral infections, with relevant microbiological information

All patients must receive a clinical diagnosis of serious bacterial infection (cUTI, HAP/VAP/HCAP, or BSI/sepsis) presumably caused by a carbapenem-resistant Gram-negative pathogen at the time of randomization.

Screening/baseline assessments as part of the standard of care, eg, chest radiographs performed within 48 hours prior to randomization and safety laboratory tests obtained within 24 hours prior to randomization may be accepted for Screening/baseline.

7.3 Hospitalization

Additional information to be entered into the eCRF to assist in the pharmacoeconomics evaluation are the date of hospitalization from 90 days prior to enrollment or current hospitalization date if the date of hospitalization is before 90 days of enrollment, throughout 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 ICU admission or isolation, initial/end date of treatment with ventilator, and status at EOS.

7.4 Physical Examination

A complete physical examination will be performed at Screening. A limited physical examination relevant to the patient's current condition will be performed at the specified evaluation points (See Section 8 or Appendix 1). 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 sub-investigator. Clinically significant findings on physical examination will be recorded as an AE. Weight and height will be entered in the eCRF.

7.4.1 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 Glasgow Coma Scale (GCS) according to Appendix 5, 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 patients, the GCS cannot be properly assessed, and a normal score of 15 could be used to complete the APACHE II and SOFA scores.

7.4.2 APACHE II

The components measurements, observations, and calculation of APACHE II system will be collected and used as a method to establish the severity of disease for a given patient. The APACHE II score will be collected and entered in the eCRF at Screening by the investigator or qualified designee based on Appendix 6. If APACHE II components are measured multiple times, the highest APACHE II score recorded during the Screening period will be entered in the record. If core temperature measurement is not available (ie, tympanic, rectal, esophageal), oral and axillary temperatures could be adjusted by adding 0.5 °C or 1 °C, respectively.

7.5 Vital Signs

Blood pressure (systolic/diastolic pressures), 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 the 24-hour day starting on Day 1 (calendar date) of the infusions and continuing while the patient is hospitalized and receiving treatment.

For patients 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 sub-investigator will consider whether changes from baseline are clinically significant (See also Section 7.12.6). Results of blood pressure, temperature, pulse rate, and respiratory rate will be entered in the eCRF.

7.6 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 patient has been in a supine or semi-recumbent position for several minutes. Electrocardiograms obtained by the site within the 48 hours prior to signing 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. QTc interval data will be calculated using Fridericia's correction (QTcF) by the electronic data capture system once the basic ECG data are entered therein.

The investigator or sub-investigator will assess whether the ECG is normal or abnormal, the investigator or sub-investigator will consider further whether the abnormal ECG is clinically significant (See also Section 7.12.6). Results of the ECG 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 be reported as an AE.

7.7 Clinical Laboratory Tests

7.7.1 Microbiologic Cultures

Appropriate clinical specimens will be obtained from all patients within 48 hours prior to the start of the infusion of the first dose of study treatment or clinical specimens obtained by the site within the 48 hours prior to signing ICF could be acceptable as screening/baseline cultures for this study.

For patients who failed empiric treatment (as defined in general inclusion No. 4), clinical specimens obtained within 72 hours of randomization in this study could be used as screening/baseline cultures. A culture should be done again upon randomization and the pathogen isolated sent to central lab.

Biologic tissue or fluids for microbiologic cultures will be sent to the local laboratory for identification of all pathogens causing the infection. After initiation of study treatment, appropriate clinical specimens will be obtained at the specified assessment time points (EA, EOT, TOC, FUP. If it is not possible to obtain an appropriate clinical specimen after randomization, the reason (eg, no material available to culture) must be documented in the eCRF.

In addition, 2 blood samples from separate venipunctures will be obtained from all patients regardless of the site of infection, within 48 hours prior to the start of study treatment and sent to the local laboratory. Subsequent blood cultures are to be repeated only if the baseline blood culture is positive.

Culture results should be recorded in the eCRF with the date of sampling and the reporting date and identified isolates sent to the central lab.

In general, all specimens should also have Gram stain of infected material (not swab). A report of both inflammatory cells and bacteria is necessary.

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

Detailed procedures (Gram stain, quantitative or semi-quantitative cultures) per infection type are provided in Appendix 4.

All isolated pathogens (Gram-positives, Gram-negatives, fungi and yeast) 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 procedure manual. Shipping labels, instructions for shipping, and courier service will be provided from the sponsor or CRO.

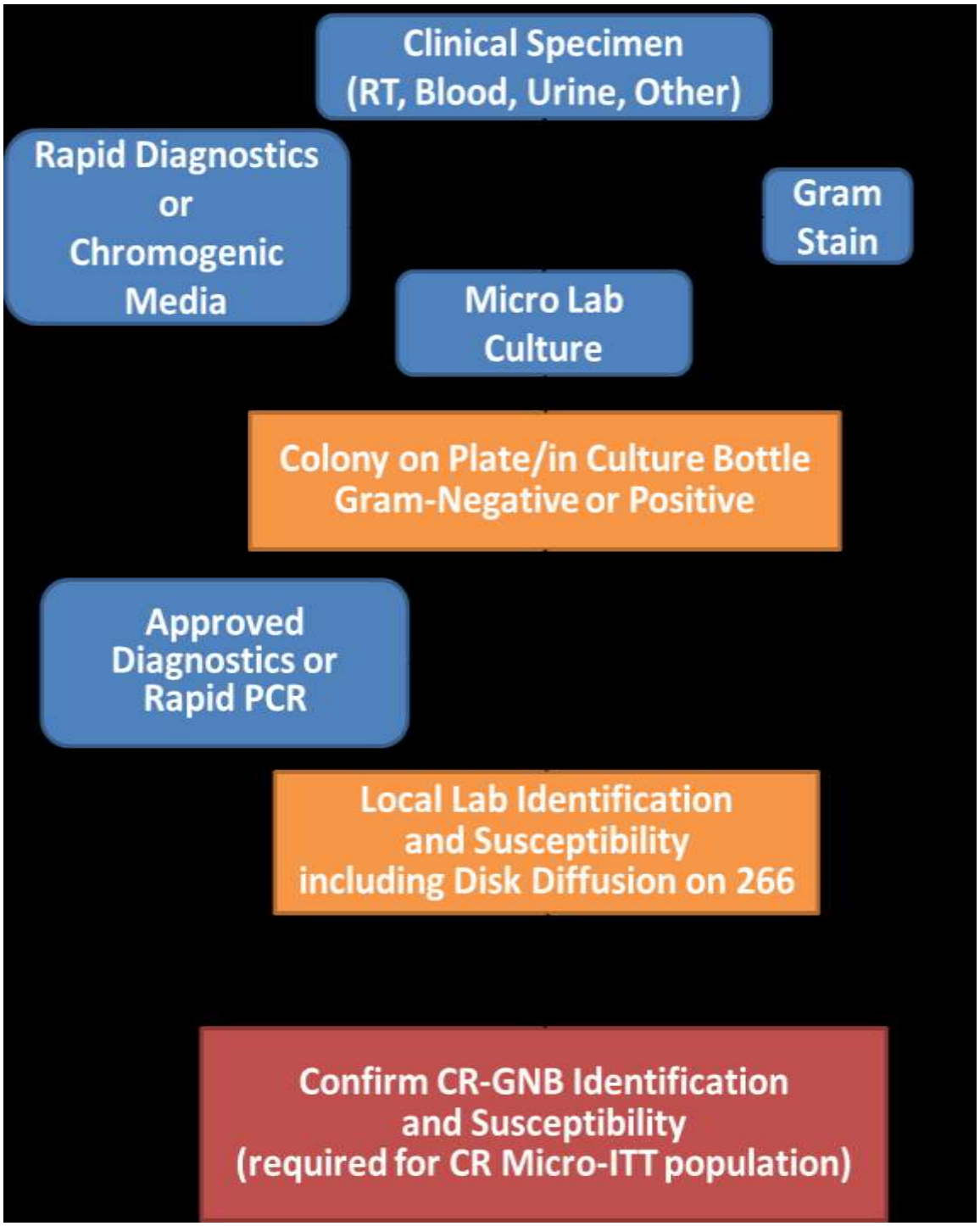
7.7.1.1 Diagnostics for Initial Patient Qualification

Patients are eligible for randomization only if there is documented evidence of a carbapenem-resistant Gram-negative pathogen from a suitable infection source. Routine culture methods with susceptibility phenotype determination (MIC, Etest, or disc diffusion) using standard determination of susceptibility (breakpoints) based on local regulations would meet eligibility criteria. Isolates considered intermediate, but not fully susceptible, will be considered carbapenem-resistant.

In order to expedite appropriate treatment for the patient before the availability of standard susceptibility results, rapid diagnostic methods, or selective chromogenic media may be used to identify patients with carbapenem-resistant pathogens. These may include marketed tests to determine the presence of carbapenem hydrolyzing enzymes (carbapenemases) or tests to determine the presence of genes indicating the presence of carbapenemases (polymerase chain reaction [PCR]) (Figure 7-1). Tests available to the investigator through their local microbiology laboratory may be used. Investigational rapid diagnostics may be provided and can be used to determine a patient's eligibility for inclusion into this study. A manual with details on investigational rapid diagnostics that may be provided along with instructions for use will be provided separately. Rapid diagnostic result should be recorded in the eCRF.

Although the rapid diagnostic tests may provide evidence of eligibility of patients for this study, all patients will require subsequent confirmation through microbiologic isolation and susceptibility testing of isolates obtained from appropriate clinical specimens. The final study analysis will use the pathogen identification and susceptibility data provided by the central microbiology laboratory.

Figure 7-1 Schematic of Clinical Specimen Handling



CR-GNB = carbapenem-resistant Gram-negative bacilli; CR Micro-ITT = Carbapenem-resistant Microbiological Intent-to-treat; lab = laboratory; PCR = polymerase chain reaction; RT = respiratory specimen

7.7.2 Clinical Laboratory Parameters

7.7.2.1 Clinical Laboratory Tests

Clinical laboratory tests are shown in Table 7-1.

Table 7-1 Clinical Laboratory Tests

Category	Evaluation Items
Hematology Tests	Hematocrit, Hemoglobin, Platelet count, RBC count, WBC count with differential and morphology indices INR and PTT
Blood Chemistry Tests	ALP, ALT, AST, GGT, LDH, CPK, CRP, and Amylase BUN, Creatinine, TBL Sodium (Na), Potassium (K), Bicarbonate (HCO_3), Chloride (Cl), Calcium (Ca), Magnesium (Mg) Glucose, Total protein, Albumin, Uric acid, Total cholesterol
Urinalysis	Glucose, Blood, Protein, Ketones, Bilirubin, Urobilinogen, Leukocyte esterase, Microscopic[a] (WBC, RBC, Crystal and casts)
Specialized Tests	Iron, TIBC, Transferrin iron saturation, and Hepcidin at Screening and TOC
Others	Serum or urine pregnancy: at Screening CrCl and eGFR at Screening and EA CrCl determined from a timed urine collection at EA[b]

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

a If sediment is present

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

Blood and urine samples for clinical laboratory tests will be collected at specified times. Blood samples for all clinical laboratory tests will be collected in the fasted state, if possible.

The samples other than some specialized tests will be measured at a local laboratory and results will be entered in the eCRF. The samples for serum iron, TIBC, transferrin iron saturation, and hepcidin will be shipped to a central laboratory. Details procedures for sample collection, handling, labeling, storage, and shipping will be provided in the separate study procedure manual. Shipping labels, instructions for shipping and courier service will be provided from the sponsor or CRO.

The investigator or sub-investigator will assess whether any abnormal changes from baseline are clinically significant (See also Section 7.12.6).

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.

7.7.2.2 Pregnancy Tests

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

7.7.2.3 Creatinine Clearance

Renal function measured by urinary clearance of creatinine may be monitored per local clinical practice and study drug dose adjustments made accordingly and recorded in the eCRF.

7.7.2.3.1 Creatinine Clearance Estimate 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 patients at Screening and EA and serum creatinine will be recorded in the eCRF. If renal function has changed at EA from Screening, dose adjustment will be required as per Table 5-2. The MDRD equation and the Cockcroft-Gault equation are as follows [36-38]:

- 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 American)
- Cockcroft-Gault equation

  Creatinine clearance (mL/min) = Weight × (140 − age in years)/(72 × sCr) × (0.85 if female)

  where sCr is serum creatinine concentration (mg/dL) and Weight is body weight (kg).

7.7.2.3.2 Urine-Measured Creatinine Clearance

For patients with eGFR ≥ 90 mL/min/1.73 m^2 at baseline, urine samples will be collected for a time interval as short as 2 hours or up to 8 hours at EA. Total volume of urine and urinary creatinine concentration or CrCl, which will be derived from the following calculation formula, will be measured and will be recorded in the eCRF.

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

Creatinine clearance (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 (hour).

7.8 Efficacy, and Safety Evaluations

7.8.1 General Evaluations

7.8.1.1 Vital Status

The investigator or qualified designee will enter the date and cause of death in the eCRF if the patient dies during this study.

The investigator or qualified designee will enter vital status (survival or death) in the eCRF at EOS.

7.8.1.2 SOFA

The SOFA score is a scoring system to determine the extent of a patient's organ function or rate of failure. The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems. The investigator or qualified designee will collect and enter the SOFA scores in the eCRF at the specified evaluation points based on Appendix 7. In non-ventilated patients, a respiration score of zero may be assigned.

7.8.1.3 Oxygenation Status

For patients receiving an oxygen inhalation treatment, the patient's oxygenation status including PaO_2, $PaCO_2$, FiO_2 and O_2 saturation, will be determined by either pulse oximetry or by arterial blood gas measurements as relevant at the specified evaluation points and entered in the eCRF.

7.8.1.4 Ventilator Parameters

For ventilated patients treated with S-649266, specified ventilator parameters (FiO2, PEEP, and pressure support [PS]) will be captured at the start of the infusion during which PK sampling will be taken (acceptable time window: 0 hours to end of infusion). The results will be entered in the eCRF.

7.8.1.5 Clinical Assessment of Signs and/or Symptoms

General signs and/or symptoms of infection, including fatigue, chills/rigors, malaise, nausea, vomiting 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 patient during the course of the study will also be assessed. The results will be entered in the eCRF.

7.8.2 HAP/VAP/HCAP Specific Evaluations

7.8.2.1 Clinical Assessment of Signs and/or Symptoms

Signs and symptoms specific to HAP/VAP/HCAP 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 patient during the course of the study will also be assessed. The results will be entered in the eCRF.

7.8.2.2 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 including body temperature, WBC, tracheal secretion, PaO_2/FiO_2 and chest radiograph. For non-ventilated patients who, based on local practice, do not have blood gasses done, a CPIS point value of zero may be assigned for the PaO_2/FiO_2 evaluation. The total score will be entered in the eCRF at the specified evaluation points based on Appendix 8.

7.8.2.3 Chest Radiographs

A chest x-ray (lateral and posterior/anterior [PA], or portable [when the patient's condition does not permit transport to the radiology department]) will be performed at the specified evaluation points 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, preferably by a certified radiologist, will be entered in the eCRF.

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.

7.8.3 Complicated Urinary Tract Infection Specific Evaluation

7.8.3.1 Clinical Assessment of Signs and/or Symptoms

Specific signs and/or symptoms of infection, including dysuria, frequency, suprapubic pain, urgency, or flank pain/costovertebral angle tenderness, 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 patient during the course of the study will also be assessed. The results will be entered in the eCRF.

7.8.4 Blood Stream Infection/Sepsis Specific Evaluations

7.8.4.1 Clinical Assessment of Signs and/or Symptoms

Clinical signs and/or symptoms of the infection which caused the BSI/sepsis 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 patient during the course of the study will also be assessed. The results including negative blood culture at Screening will be entered in the eCRF with the relevant sampling and reporting dates.

7.9 Pharmacokinetic Sample Collection, Storage, and Shipping

7.9.1 Pharmacokinetic Blood Sampling

All patients treated with S-649266 will have blood drawn for sparse PK sampling of plasma concentrations of study drug. The actual sampling date and time will be recorded. PK blood sampling will occur on Day 3 (after at least 6 doses of drug) at 4 timepoints: (1) just prior to the start of infusion, (2) 1 hour after start of infusion, (3) at the end of infusion, and (4) 1 hour after the end of the infusion.

The date, actual time, and site of the PK sampling will be recorded in the eCRF.

Patients with nonstable renal function resulting in a dosage adjustment (dose or interval) at EA will undergo another blood PK sampling (4 samples at the above specified timepoints) within 24 to 72 hours after their dosing adjustment. The timing for PK blood draws is the same as timing on Day 3.

If possible, a single blood sampling should be performed as soon as possible at EOT in the case of premature EOT (within 24 hours of last dose).

Blood 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 study procedure manual. Shipping labels, instructions for shipping and courier service will be provided from the sponsor or CRO.

7.9.2 Other Tissue or Body Fluid Sampling for Pharmacokinetics

A sub-study may be developed to determine drug concentrations in ELF in patients with VAP receiving S-649266. In addition, the sponsor may choose to initiate a sub-study to determine S-649266 tissue concentrations in body sites other than lung, eg, peritoneal fluid. Any sub-study designed to determine drug concentrations of S-649266 would require a separate written informed consent by the patient or representative.

7.10 Enrollment in the Study and Dispensing Study Drug

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

- Clinical diagnosis (HAP/VAP/HCAP, cUTI, or BSI/sepsis)
- Calculated APACHE II score (≤ 15 and ≥ 16)
- Region (North America, South America, Europe, and Asia-Pacific; automatically added by the IXRS system according to the site number)

If the registration is accepted, the patient will be randomized to either treatment group.

7.11 Efficacy Assessments

7.11.1 Efficacy Criteria for Infection Site Specific Clinical Outcomes for EA, EOT, and TOC

The clinical outcomes will be assessed by the investigator according to the following criteria established for each infection site 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.

7.11.1.1 HAP/VAP/HCAP

- **Clinical Cure:** Resolution or substantial improvement of baseline signs and symptoms of pneumonia including a reduction in SOFA and CPIS scores, and improvement or lack of progression of chest radiographic abnormalities such that no antibacterial therapy is required for the treatment of the current infection.
- **Clinical Failure:** No apparent response to therapy; persistence or worsening of baseline signs and/or symptoms of pneumonia; reappearance of signs and/or symptoms of pneumonia; development of new signs and/or symptoms of pneumonia requiring 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.

Applicable only to Germany due to local requirements: If a chest X-ray is not performed because of standard of care at the site, clinical assessment will be done without chest X-ray.

7.11.1.2 cUTI

- **Clinical Cure:** Resolution or substantial improvement of baseline signs and symptoms of cUTI, or return to pre-infection baseline if known, such that no antibacterial therapy is required for the treatment of the current infection.
- **Clinical Failure:** No apparent response to therapy; persistence or worsening of baseline signs and/or symptoms of cUTI; or reappearance of signs and/or symptoms of cUTI; development of new signs and/or symptoms of cUTI requiring antibiotic therapy other than, or in addition to, study treatment therapy; or death due to cUTI.

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

7.11.1.3 BSI/Sepsis

- **Clinical Cure:** Resolution or substantial improvement of baseline signs and symptoms including a reduction in SOFA score, such that no antibacterial therapy is required for the treatment of BSI/sepsis. Patients with bacteremia must have eradication of bacteremia caused by the Gram-negative pathogen.
- **Clinical Failure:** No apparent response to therapy; persistence or worsening of baseline signs and/or symptoms, reappearance of signs and/or symptoms; development of new signs and/or symptoms requiring antibiotic therapy other than, or in addition to, study treatment therapy; or death due to BSI/sepsis.
- **Indeterminate:** Lost to follow-up such that a determination of clinical cure/failure cannot be made.

7.11.2 Clinical Outcomes for FUP

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

7.11.2.1 HAP/VAP/HCAP

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

7.11.2.2 cUTI

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

7.11.2.3 BSI/Sepsis

- **Sustained Clinical Cure:** Continued resolution or substantial improvement of baseline signs and symptoms associated with reduction in SOFA score, such that no antibacterial therapy is required for the treatment of the patients original BSI/sepsis in a patient assessed as cured at TOC.
- **Relapse:** Recurrence of signs and/or symptoms of BSI/sepsis, appearance of new signs and/or symptoms of the patients original BSI/sepsis, or death due to BSI/sepsis in a patient assessed as cured at TOC.
- **Indeterminate:** Lost to follow-up such that a determination of clinical sustained cure/relapse cannot be made, or patient received additional antibacterial therapy for the treatment of the current infection.

7.11.3 Microbiological Outcomes for EA, EOT, and TOC

An overall per-patient microbiological outcome will be determined based on the individual microbiological outcomes for each baseline pathogen. The microbiological outcomes determined by investigator will also be entered in the eCRF. Emergent (ie, non-baseline) pathogens are considered separately, and do not affect the per-patient microbiological outcome.

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

7.11.3.1 HAP/VAP/HCAP

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

7.11.3.2 cUTI

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

7.11.3.3 BSI/Sepsis

- **Eradication:** Absence of the baseline Gram-negative pathogen from a blood culture and/or other primary source as applicable. In the case of sepsis, if the patient has a successful clinical outcome and it is not possible to obtain an appropriate clinical culture, the response will be presumed to be eradication.
- **Persistence:** Continued presence of the baseline Gram-negative pathogen from a blood culture or other primary source.
- **Indeterminate:** No culture obtained or additional antibacterial therapy for the treatment of the current infection including missed sampling.

7.11.4 Microbiological Outcomes for FUP

An overall per-patient microbiological outcome will be determined based on the individual microbiological outcomes for each baseline pathogen. The microbiological outcomes determined by investigator will also be entered in the eCRF.

Separately, the microbiological outcomes by baseline pathogen will be determined by the sponsor according to the following criteria established for each infection site at FUP.

7.11.4.1 HAP/VAP/HCAP

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

7.11.4.2 cUTI

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

7.11.4.3 BSI/Sepsis

- **Sustained Eradication:** Absence of the baseline Gram-negative pathogen from a blood culture or other primary source after TOC as applicable. In the case of sepsis, if the patient has a successful clinical outcome after TOC and it is not

possible to obtain an appropriate clinical culture, the response will be presumed to be sustained eradication.

- **Recurrence:** Recurrence of the baseline Gram-negative pathogen from a blood culture or other primary source after TOC, and the TOC culture is negative.
- **Indeterminate:** No culture or patient received additional antibacterial therapy for the treatment of the current infection including missed sampling.

7.11.5 New Pathogens

New pathogens that emerge after study therapy is started will be categorized as either superinfection or new infection as follows:

- **Superinfection:** The identification from an appropriate clinical specimen of a new pathogen from the original infection site. This new pathogen must be associated with new or persisting signs and symptoms of infection.
- **New Infection:** The identification from an appropriate clinical specimen of a new pathogen from an infection site different from the original infection site. This new pathogen must be associated with new or persisting signs and symptoms of infection.

7.12 Adverse Events Assessments

7.12.1 Performing Adverse Events Assessments

An AE is defined as any untoward medical occurrence in a patient 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 patient's spontaneous complaint, patient comment cards, or as a result of nonleading questions, physical examination, vital signs, or laboratory tests. AEs 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 which are reported at the baseline and worsen will be considered as AEs. Lack of efficacy, aggravation, or relapse of current infection are not an AE in the study and therefore also not an SAE (except death).

The investigator or sub-investigator is responsible for assessing AEs. AEs should be fully investigated and recorded in detail including 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.

7.12.2 Timing

AEs will be collected from the time of having signed informed consent through 28 days after the last dose of the study treatment for randomized patients. If a patient withdraws early from the study, the investigator or sub-investigator will make an effort to collect AEs for 28 days after the last dose of the study treatment. Any ongoing AE 28 days after the last dose of study treatment will be followed until resolution, stabilization, the condition becomes chronic, or the patient is lost to follow-up.

7.12.3 Severity

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

- **Mild:** A finding or symptom is minor and does not interfere with usual daily activities.
- **Moderate:** The event causes discomfort and interferes with usual daily activity or affects clinical status.
- **Severe:** The event causes interruption of the patient'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.

7.12.4 Relationship

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

- **Related:** An AE which can be reasonably explained as having been caused by the study treatment.

  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 which cannot be reasonably explained as having been caused by the study treatment.

7.12.5 Expectedness

Expected AEs for S-649266 are listed under Expected Adverse Reactions in Section “Undesirable Effects” of the “Summary of Data and Guidance for Investigators” in the current Investigator's Brochure for S-649266. The expected AEs for the drugs that are a part of the BAT will be those found in the EMA Summary of Product Characteristics

(SmPCs) for those products. The US Package Insert will be used if the SmPC is not available. Expectedness will be assessed by the sponsor.

7.12.6 Clinical Laboratory Adverse Events

For any abnormal laboratory test results (hematology, blood chemistry, or urinalysis) or other safety assessments (eg, physical examination, vital signs, ECG) that are worsening from baseline or occur thereafter in the course of the study, the investigator or sub-investigator will consider whether these results are clinically significant. Abnormal laboratory test results are defined as values outside the reference range. Any test results which are considered to be clinically significant by the investigator or sub-investigator 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 sub-investigator 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 drug 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 Appendix 9.

7.12.6.1 Liver Abnormalities

Management and Discontinuation Criteria for Abnormal Liver Function tests have been designed to ensure patient safety and evaluate liver event etiology. The investigator or sub-investigator must review study patient laboratory results as they become available to identify if any values meet the criteria in Appendix 9. 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.

7.12.7 Serious Adverse Events

7.12.7.1 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
- 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 patient and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. Test results that meet the criteria of Hy's law are considered SAEs (Appendix 9). The investigator or sub-investigator 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 is met). A hospitalization or prolongation of hospitalization for reasons other than an AE would not be considered an SAE.

7.12.7.2 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 of 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 (EDC) or by phone or fax if EDC is not available.

CRO SAE hotline – North America and South America:

Telephone: [redacted]

Fax: [redacted] **or** [redacted]

[redacted]

OR

CRO SAE hotline – Europe and Asia-Pacific:

Telephone: [redacted]

Fax: [redacted]

[redacted]

If the sponsor requires a follow-up assessment, the investigator should provide new information as it becomes available and then report to 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 patient'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 AE assessment period specified in Section 7.12.2, that is considered to be related to study drug by the investigator must be reported to CRO or the sponsor.

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

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

Abuse, misuse, overdose, or medication errors (as defined below) in patients treated with S-649266 must be reported by the investigator to CRO or sponsor via fax using a Special Situations Report Form within 24 hours of becoming aware (Refer to Section 7.12.7.2 for reporting destination). If there are associated SAEs, the investigator will report an SAE as well.

- **Abuse:** Persistent or sporadic, intentional excessive use of an investigational product(s), which is accompanied by harmful physical or psychological effects.
- **Misuse:** Intentional and inappropriate use of an investigational product(s) other than as directed or indicated at any dose.
- **Overdose:** Intentional or unintentional intake of a dose of investigational product(s) 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(s). Medication errors are reportable only as defined below.

  The administration or consumption of the unassigned treatment is always reportable as a medication error.

  Administration of an expired product should be considered as a reportable medication error.

7.12.9 Pregnancy

Women of child bearing potential will be screened for pregnancy at the time of study enrollment. A positive test is reason for exclusion. Patients will be instructed to avoid conception until 28 days (EOS) following treatment (EOT) or according to country specific requirements, whichever is longer.

If a female patient in S-649266 group becomes pregnant during the study, investigator or sub-investigator will immediately discontinue study drug. All pregnancies that occur after the first dose of the study treatment through the follow-up period (EOS) must be reported within 24 hours of becoming aware of the pregnancy and the Pregnancy Form will be reported to CRO or the sponsor by the investigator (Refer to Section 7.12.7.2 for reporting destination). Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE 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, to CRO or the sponsor.

7.12.10 Treatment-Emergent Adverse Events

AEs reported after the initial dose of randomized study or control treatment will be considered treatment-emergent adverse events (TEAE).

7.13 Withdrawal or Discontinuation of Patients from the Study or Study Treatment

The investigator will make every reasonable attempt to complete the study for each enrolled patient. A patient 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 patient from the study by using the IWRS/IVRS.

The investigator or sub-investigator will discontinue a patient from the study treatment for any of the following reasons. Please note that unless the patient withdraws consent to participate in the study, all randomized patients should be followed for the entire duration of the study:

- A serious or intolerable AE occurs and the investigator considers that the patient 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 patient should be withdrawn.
- The patient requests to be withdrawn from the study.
- The patient is lost to follow-up.
- The investigator determines that the patient should be withdrawn because of other reasons.

For patients who withdraw or are discontinued by the investigator or sub-investigator at any time after the start of treatment, they are still considered to be in the study, and they

should still be followed through to the completion of all study activities, ie, EOT, TOC, FUP, and EOS, if at all possible. All withdrawn or discontinued patients will remain in the study for safety and clinical outcome purposes.

All patients 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 patient is lost to follow-up.

Patients who withdraw or are 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).

7.14 Appropriateness of Measurements

The measures of efficacy selected in the study differ for each of the 3 groups of infection, but in general includes both clinical and microbiologic outcome. The specific endpoints based on the EMA guidance [17] have been discussed with regulatory agencies.

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

7.15 Acceptable Time Windows

Measurements for efficacy or safety endpoints will be performed according to the schedule of assessments as shown in Appendix 1. The following time window, as 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 Blood PK Sampling	Day 3	+ 2 days
Day 3 Blood PK Sampling (This sample should be drawn after the patient had at least 6 infusions)	Just prior to the next infusion	–1 to 0 hours
	One (1) hour into the infusion	± 15 minutes
	At the end of infusion	–15 minutes to end of infusion
	One (1) hour after end of infusion (four [4] hours after the start of infusion)	± 0.5 hours
EA	Day 3 to 4	+ 1 day
EOT	Last day of study treatment	As soon as possible after last dose (within 24 hours after the last dose)
TOC	EOT + 7	± 2 days
FUP	EOT +14	± 3 days
EOS	EOT +28	± 3 days

8. STUDY ACTIVITIES

The overall schedule of events for the study is presented in Appendix 1.

8.1 Screening (Day –2 to Randomization)

- Informed consent
- Appropriate clinical specimens will be obtained from all patients within 48 hours prior to the start of the infusion of the first dose of study treatment including blood for culture. Clinical specimens obtained by the site within the 48 hours prior to signing ICF could be acceptable as screening/baseline cultures for this study.
- Rapid diagnostics for the presence of a carbapenemase (if necessary)

  If any diagnostics provided by the sponsor are considered investigational in the country where the protocol is implemented are to be used, or diagnostics that are not the local standard of care for determination of carbapenem resistance are to be used, the investigational diagnostics section of the informed consent form will be required. (See Section 7.1)
- Inclusion and exclusion criteria assessments
- Baseline patient characteristics
- Medical history
- Physical examination including height and body weight
- Vital signs (including blood pressure, body temperature, pulse rate, and respiratory rate)
- 12-lead ECG
- Pregnancy test if applicable
- Clinical laboratory tests (hematology, blood chemistry, urinalysis, specialized tests and others; see Table 7-1)
- Glasgow Coma Scale
- Calculate APACHE II score
- Calculate SOFA score
- Provide parameters for CPIS score (HAP/VAP/HCAP patients)
- Clinical assessment of signs and/or symptoms
- Oxygenation status (patients receiving an oxygen inhalation treatment)
- Chest radiographs (HAP/VAP/HCAP patients)
- Biologic tissue or fluids (including blood) for microbiological culture
- AE assessment (begins with the signing of the informed consent form and continues through to the EOS)
- Prior and concomitant therapies
- Hospitalization

8.2 Treatment Period (Day 1 to up through Day 14)

8.2.1 Randomization and Treatment Initiation Day 1

- Randomize patient via IWRS or IVRS
- Initiate treatment based on eGFR and CrCl by Cockcroft-Gault equation

8.2.2 All Treatment Days

- Continue randomized treatment
- Vital signs including body temperature
- Concomitant therapy
- AE assessment
- Hospitalization
- Vital status (survival)
- Dose adjustment considered on review of renal function conducted per local clinical practice (If necessary)

8.2.3 Treatment Day 3

- Activities for all treatment days (See Section 8.2.2)
- Blood PK samples (after at least 6 infusions) for patients receiving S-649266
- Ventilator parameters at the timing of blood PK sampling for ventilated patients (See Section 7.8.1.4)

8.2.4 Early Assessment (EA) (Occurs once at investigator's discretion during Days 3 to 4)

- Activities for all treatment days (See Section 8.2.2)
- Limited physical examination relevant to the patient's current condition
- Clinical laboratory tests (hematology, blood chemistry, urinalysis, and others; see Table 7-1)
- Glasgow Coma Scale
- Calculate SOFA score
- Provide parameters for CPIS score (HAP/VAP/HCAP patients)
- Clinical assessment of signs and/or symptoms
- Oxygenation status (patients receiving an oxygen inhalation treatment)
- Chest radiographs (HAP/VAP/HCAP patients)
- Biologic tissue or fluids (including blood until result is negative) for microbiological culture
- Assess clinical outcome
- Assess microbiological outcome
- Dosing adjustment if renal function is changed
- Blood PK samples for patients with nonstable renal function resulting in a dosing

adjustment at EA (S-649266 group only) (See Section 7.9.1)
- Ventilator parameters at the timing of blood PK sampling for ventilated patients (See Section 7.8.1.4)

8.2.5 Treatment Day 14

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 patient's current condition
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis; see Table 7-1)
- Glasgow Coma Scale
- Calculate SOFA score
- Provide parameters for CPIS score (HAP/VAP/HCAP patients)
- Clinical assessment of signs and/or symptoms
- Oxygenation status (patients receiving an oxygen inhalation treatment)
- Chest radiographs (HAP/VAP/HCAP patients)
- Biologic tissue or fluids (including blood until result is negative) for microbiological culture
- Assess clinical outcome
- Assess microbiological outcome

8.2.6 Last Day of Study Treatment (EOT)

- Activities for all treatment days (See Section 8.2.2)
- Limited physical examination relevant to the patient's current condition
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis; see Table 7-1)
- Glasgow Coma Scale
- Calculate SOFA score
- Provide parameters for CPIS score (HAP/VAP/HCAP patients)
- Clinical assessment of signs and/or symptoms
- Oxygenation status (patients receiving an oxygen inhalation treatment)
- Chest radiographs (HAP/VAP/HCAP patients)
- Biologic tissue or fluids (including blood until result is negative) for microbiological culture
- Assess clinical outcome
- Assess microbiological outcome

8.3 Test of Cure (TOC [EOT + 7 days])

- Limited physical examination relevant to the patient's current condition
- Vital signs (including blood pressure, body temperature, pulse rate, and respiratory rate)
- Clinical laboratory tests (hematology, blood chemistry, urinalysis, and specialized tests; see Table 7-1)
- Clinical assessment of signs and/or symptoms
- Oxygenation status (patients receiving an oxygen inhalation treatment)
- Chest radiographs (HAP/VAP/HCAP patients) (if indicated)
- Biologic tissue or fluids (including blood until result is negative) for microbiological culture
- Glasgow Coma Scale
- Calculate SOFA score
- Provide parameters for CPIS score (HAP/VAP/HCAP patients)
- AE assessment
- Concomitant therapy
- Assess clinical outcome
- Assess microbiological outcome
- Hospitalization

8.4 Follow-up (FUP [EOT + 14 days])

- Limited physical examination relevant to the patient's current condition
- Vital signs (including blood pressure, body temperature, pulse rate, and respiratory rate)
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis; see Table 7-1)
- Clinical assessment of signs and/or symptoms
- Oxygenation status (patients receiving an oxygen inhalation treatment)
- Chest radiographs (HAP/VAP/HCAP patients) (if indicated)
- Biologic tissue or fluids (including blood until result is negative) for microbiological culture (if indicated)
- Glasgow Coma Scale
- Calculate SOFA score
- Provide parameters for CPIS score (HAP/VAP/HCAP patients)
- AE assessment
- Concomitant therapy
- Assess clinical outcome
- Assess microbiological outcome
- Hospitalization

8.5 End of Study (EOS [EOT + 28 days])

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

EOS assessments may be performed by phone to document current patient status, in which case, the physical examination, vital signs, and laboratory tests will not be performed. Any AEs ongoing at EOS (28 days after the last dose of study treatment) will be followed as specified in Section 7.12.2. Continuing laboratory changes that are considered significant and symptoms related to AEs should be followed until resolution, AEs are judged by the investigator to have stabilized, or the patient is lost to follow-up. Pregnancies should be followed as specified in Section 7.12.9.

9. PLANNED STATISTICAL METHODS

9.1 General Considerations

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

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

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

If statistical tests are performed, they will be performed at the 0.05 significance level using 2-sided tests, except where otherwise noted. No multiplicity adjustment of statistical tests will be applied in this study.

9.2 Determination of Sample Size

Given the challenges involved in recruiting patients meeting the criteria for inclusion in this study, and, after discussions with the EMA, it was agreed that approximately 150 patients will be enrolled and randomized 2:1 to S-649266 and BAT, respectively. This sample size will ensure that approximately 100 patients are treated with S-649266.

9.3 Analysis Populations

The following analysis populations will be examined in this study:

- Intent to Treat (ITT) population: All randomized patients who received at least 1 dose of the study treatment.
- Microbiological Intent to Treat Population (Micro-ITT): All ITT patients who have a baseline Gram-negative pathogen from an appropriate clinical specimen. Patients should not be excluded from this population based upon events that occurred post randomization (eg, loss to follow-up).
- Carbapenem-Resistant Microbiological Intent to Treat Population (CR Micro-ITT): All Micro-ITT patients whose baseline Gram-negative pathogen is carbapenem-resistant.

- Carbapenem-Resistant Microbiologically Evaluable Population (CR-ME): includes all CR Micro-ITT patients who follow important components of the study as specified in the protocol with no major protocol violations.
  Criteria for inclusion are:
  - ≥ 5 days of intravenous (IV) study treatment unless treatment was a failure
  - Underwent TOC assessment
  - Patients without any major protocol inclusion or exclusion violations
  - Patients with no violations of restrictions for concomitant therapy including concomitant antibiotic(s) effective against Gram-negative bacteria
- Safety population includes all randomized patients who receive at least 1 actual dose of the study treatment (ITT population). The population will be analyzed according to the treatment that the patients actually received, rather than the treatment to which the patients were randomized.
- The PK concentration population includes all patients who undergo plasma sampling and have at least one evaluable PK assay result for S-649266. This population will be used for the concentration listing, plotting of the concentration-time data and the concentration summary.

9.4 Handling of Missing Data

Missing data will not be replaced. Details will be defined in SAP.

9.5 Patient Disposition

Among the randomized patients in the safety population, and the ITT population, and the Micro-ITT population, the number and percentage of patients who complete the study and those of patients who prematurely discontinue 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 patients for the randomized patients included in each analysis population will also be presented.

9.6 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized with descriptive statistics for the ITT population, the CR Micro-ITT population.

9.7 Prior Therapies

Prior therapies for drugs will be coded using the World Health Organization Drug Dictionary (WHO-DD). Patients who received prior therapy(ies) will be listed and summarized for the safety population and the CR Micro-ITT population.

9.8 Concomitant Therapies

Concomitant therapies for drugs will be coded using WHO-DD. Patients who received concomitant therapy(ies) will be listed and summarized for the safety population and the CR Micro-ITT population.

9.9 Efficacy Analyses

The CR Micro-ITT population will be the primary population for efficacy analyses (primary and secondary efficacy analyses). The CR-ME population and the Micro-ITT population will be used for assessing the robustness of the conclusions.

9.9.1 Primary Efficacy Endpoint

- Clinical outcome per patient at TOC in patients with HAP/VAP/HCAP or BSI/sepsis
- Microbiologic outcome (for Gram-negative pathogen) per patient at TOC in patients with cUTI

9.9.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following variables:

- Clinical outcome per patient at EOT and FUP (HAP/VAP/HCAP or BSI/sepsis)
- Clinical outcome per pathogen at EOT, TOC, and FUP (HAP/VAP/HCAP or BSI/sepsis)
- Clinical outcome per patient/pathogen at EOT, TOC, and FUP (cUTI)
- Microbiologic outcome (for Gram-negative pathogen) per patient/pathogen at EOT, TOC, and FUP (HAP/VAP/HCAP or BSI/sepsis)
- Microbiologic outcome (for Gram-negative pathogen) per patient at EOT, and FUP (cUTI)
- Microbiologic outcome (for Gram-negative pathogen) per pathogen at EOT, TOC, and FUP (cUTI)
- Microbiologic outcome with documented carbapenem-resistant Gram-negative bacteremia (regardless of primary infection diagnosis) at EOT, TOC, and FUP
- Composite clinical and microbiologic outcome at EOT, TOC, and FUP
- All-cause mortality at Day 14 and Day 28 for HAP/VAP/HCAP and BSI/sepsis
- Composite endpoint of survival and no change in antibiotic treatment due to either lack of therapeutic benefit or drug-related toxicity at TOC
- Survival time (HAP/VAP/HCAP, BSI/sepsis)
- CPIS parameters at EOT and TOC (HAP/VAP/HCAP only)
- SOFA Score at EOT, and TOC

9.9.2.1 Composite Clinical and Microbiologic Outcome for cUTI

The composite clinical and microbiologic outcome for cUTI will be determined by the sponsor based on both the clinical and microbiologic outcomes:

Clinical and microbiologic response: Clinical cure/Sustained clinical cure in clinical outcomes (resolution or improvement of the signs and symptoms of cUTI or return to pre-infection baseline if known) and **Eradication/Sustained eradication** in microbiological outcomes (microbiological success) at each scheduled timepoint.

Clinical or microbiologic failure: Clinical failure/Relapse in clinical outcomes, or **Persistence/Recurrence** in microbiological outcomes.

9.9.2.2 Per Patient Microbiological Outcome

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

9.9.3 Primary Efficacy Analyses

Descriptive statistics will be provided. For patients with HAP/VAP/HCAP or BSI/sepsis, the clinical response rates by treatment group and the 95% CIs will be calculated. Also for the patients with cUTI, microbiological response rates by treatment group and the 95% CIs will be calculated.

Details for the primary efficacy analyses will be discussed in the SAP.

9.9.4 Secondary Efficacy Analyses

The secondary endpoint of clinical response rates and microbiological response rates by treatment group and the 95% CIs will be calculated.

Composite clinical and microbiologic response rates by treatment group and the 95% CIs will be calculated.

Survival analysis of all-cause mortality will be performed.

The response rate of a composite endpoint of survival and no change in antibiotic treatment due to either lack of therapeutic benefit or drug-related will be compared between treatment groups by infection site (HAP/VAP/HCAP, cUTI, or BSI/sepsis) at TOC.

SOFA and CPIS (ventilated only) scores by infection site as relevant will be summarized by timepoint.

Descriptive statistics for all efficacy parameters will be provided.

Details for the secondary efficacy analyses will be discussed in the SAP.

9.10 Safety Analyses

Safety assessments include AEs, mortality for up to EOS, clinical laboratory tests (hematology, chemistry, and urinalysis), and vital signs. Safety analyses will be performed for the safety population.

9.10.1 Adverse Events

AEs will be classified by system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA). Of reported AEs on the eCRF, TEAEs will be used for safety analyses. The definition of TEAE is described in Section 7.12.10.

The number and the percentage of patients who experienced TEAEs will be summarized by treatment group. Treatment-emergent SAEs and AEs related to study treatment 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 TEAE by system organ class and preferred term, the number of patients who experienced AEs will be presented for each treatment group with the percentage of patients. 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

Vital signs measured at the time when highest body temperature is observed will be included in the analysis. Summary statistics for vital signs will be presented for EOT, TOC and for the change from baseline to each timepoint. 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 timepoint and for the change from baseline to each timepoint. Baseline will be the last value obtained before randomization.

9.11 Pharmacokinetic Analysis

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

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

9.12 Pharmacokinetic/Pharmacodynamic Analysis

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

For each patient 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 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 Stay (LOS) attributable to the infection
- Days in ICU
- Hours on assisted mechanical ventilation
- Days in isolation for infection control (ICU or ward)
- Discharge status, eg, to home, hospice, or general ward
- Monitoring for renal toxicity or renal replacement therapy utilization

9.14 Interim Analysis

No interim analysis is planned. The study is open-label, and monitoring of patient safety and efficacy by the sponsor will be continuous. In addition, a data safety monitoring board (DSMB) will periodically review the efficacy and safety. The sponsor reserves the option to submit preliminary data to competent regulatory authorities.

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:	Shionogi Ltd. 33 Kingsway, Holborn, London WC2B 6UF, United Kingdom
Sponsor for Asia-pacific:	Shionogi & Co., Ltd. (Head Office) 3-1-8 Doshomachi, 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 Tel: [redacted] [redacted] Shionogi Ltd. 33 Kingsway, Holborn, London WC2B 6UF, United Kingdom Tel: [redacted] [redacted] Clinical Research Department, Shionogi & Co., Ltd. 1-1-4, Shibata, Kita-ku, Osaka 530-0012, Japan Tel: [redacted]
[redacted]:	[redacted]
[redacted]:	[redacted]
[redacted]:	[redacted] Shionogi Inc. 300 Campus Drive, Florham Park, NJ 07932 USA Tel: [redacted] E-mail: [redacted]
Medical Monitor [redacted] – North America and South America:	[redacted] Medical Monitor [redacted] North America - Tel: [redacted] North America - Fax: [redacted] South America - Tel: [redacted]

	South America - Fax: [redacted]
Medical Monitor [redacted] Europe and Asia-Pacific:	[redacted] Tel: [redacted] Fax: [redacted]
Investigator and Study Center:	Multicenter
Study Monitoring:	[redacted] Tel: [redacted] Fax: [redacted]
	[redacted] Tel: [redacted] Fax: [redacted]
Clinical Laboratory for North America and South America:	[redacted] Tel: [redacted] Fax: [redacted]
Clinical Laboratory for Europe:	[redacted] Tel: [redacted] Fax: [redacted]
Clinical Laboratory for Asia-Pacific:	[redacted] Tel: [redacted] Fax: [redacted]
Bioanalytical Laboratory:	[redacted] Tel: [redacted] Fax: [redacted]
Microbiological Laboratory:	[redacted] Tel: [redacted] Fax: [redacted]

10.2 Institutional Review Board or Institutional Ethics Committee Approval

Relevant IRBs/IECs will safeguard the rights, safety, and well-being of the patients by reviewing the following study documents: the protocol, informed consent form, written information on patient recruitment procedures (if applicable), other written information given to the patients, 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 International Council for Harmonisation (ICH) good clinical practice (GCP), and local requirements, as applicable. The study will be undertaken only after 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 protocol approved by an IRB/IEC. The study will be conducted in accordance with current ICH GCP, all appropriate patient privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki.

10.4 Patient 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 sub-investigator will explain the nature, purpose and methods, reasonable anticipated benefits and potential hazards of the study to the patient or his/her legally qualified representative if incapacitated in simple terms by using the consent form before the patient is entered into the study. The method of obtaining and documenting informed consent will comply with ICH GCP and all applicable regulatory requirement(s).

10.5 Patient Confidentiality

Procedures for protecting patient privacy must adhere to applicable data privacy laws and regulations. In order to maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by the patient

number. The investigator will grant site monitor(s) and auditor(s) of the sponsor or designee and regulatory authority(ies) access to all source documents for verification of data collected on the eCRFs and for verification of the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations. The investigator and the sponsor are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, Health Insurance Portability and Accountability Act [HIPAA]). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

Data on patients collected on eCRFs during the study will be documented in an anonymous fashion and the patient will only be identified by the patient number. In the emergent or rare event that for safety or regulatory reasons it is necessary to identify a patient, 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 frequent communications (e-mail, letter, telephone, and fax). The site monitor will review data recorded on the eCRFs, verify the eCRF entries with direct access to source documents, collect any safety/efficacy information on patients, verify that amounts of unused study drug are accurate, and check retention of source documents and essential documents.

10.7 Case Report Forms and Source Documents

10.7.1 Case Report Forms

The sponsor or designee will supply eCRFs. The eCRFs for each patient signed informed consent will be provided and historical information and study data, which are specified by the protocol, will be recorded on eCRFs by the investigator. All patient data from the study evaluations must be collected on source documents and are promptly entered in the eCRFs in accordance with the specific instructions. The eCRF entries will be performed by an investigator, sub-investigator, 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 is 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 patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status. However, the following data will be allowed as data which can be directly recorded on eCRF:

- 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
- Automatically-calculated data in eCRF (eg, QTc)

The investigator must maintain source documents such as laboratory reports, and complete medical history and physical examination reports. All the source documents are accessible for verification by the site monitor, auditor, IRB/IEC, and inspectors form regulatory authorities. Direct access to these documents must be guaranteed by the investigator, sub-investigator, 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 document within the medical institution.

10.7.3 External Data

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

- Drug concentration of S-649266 determined by bioanalytical laboratory, according to procedures specified in a separate document
- Pharmacokinetic parameter data
- Microbiological results from central laboratory
- Clinical laboratory results from central laboratory

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, responsibilities, and processes will be documented in a separate DSMB charter. The DSMB will review patient information periodically and immediately in the event of a death. However, the timing and the frequency of DSMB reviews and meetings will be adjusted as needed, as decided by the DSMB members.

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 patient safety becomes difficult due to safety concerns (eg, occurrence of many serious treatment-related AEs)
- Achieving the purpose of the study is considered impossible (eg, data suggests lack of efficacy/safety, inadequate recruitment of patients)

If the study is prematurely terminated or suspended, the sponsor should promptly inform the investigators. The investigator or sub-investigator should promptly inform the participating patients and change the study treatment to other appropriate therapy(ies).

For withdrawal criteria for individual patients, see Section 7.13.

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, 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 protocol, other procedures, and ICH GCP guidelines.

If the study is prematurely terminated or suspended, the investigator or sub-investigator should promptly inform the corresponding IRB/IEC and participating patients and change the study treatment to other appropriate therapy(ies).

10.10 Protocol Deviations and Modifications

The investigator will conduct the study in compliance with the protocol provided by the sponsor and approval/favorable opinion given by the IRB/IEC and the regulatory authority(ies). 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(s) to patients.

The investigator or sub-investigator 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(s) to patients, 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 deviation from the protocol is required to eliminate immediate hazard(s) to patients, 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 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 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
- Two years after formal discontinuation of the clinical development of the investigational product
- Other period according to applicable country regulatory requirement(s), 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 the 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 authority(ies), other investigators, corporate partners, or consultants as required.

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

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

10.15 Financial Disclosure

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

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Appendix 1 Time and Events Schedule

Evaluation	Screening\Baseline	Randomization	Treatment					Test of Cure (TOC)	Follow-Up (FUP)	End of Study (EOS)
	Day −2 to Same Day Prior to Randomization[a]		Day 1	Day 3	Early Asses. (EA) Day 3 to 4	(Day 14)[b]	End of Treat. (EOT)[c]	EOT + 7 (± 2)	EOT + 14 (± 3)	EOT + 28 (± 3)
Rapid Diagnostic for the Presence of a Carbapenemase	X[d]									
Informed Consent	X									
I/E Criteria	X									
Demographics	X									
Medical History[e]	X									
Physical Examination	X[f]				X[g]	X[g]	X[g]	X[g]	X[g]	X[g,h]
Glasgow Coma Scale	X				X	X	X	X	X	
APACHE II	X									
SOFA Score	X				X	X	X	X	X	
Clinical Assessment of Signs and/or Symptoms	X				X	X	X	X	X	
Oxygenation Status[i]	X				X	X	X	X	X	
Ventilator Parameters (Ventilated Patients Treated with S-649266)				X[j]	X[j]					
Chest Radiographs[k] (HAP/VAP/HCAP)	X				X	X	X	X	X	
CPIS Parameters (HAP/VAP/HCAP)	X				X	X	X	X	X	
Pregnancy Test[l]	X									

Evaluation	Screening\Baseline	Randomization	Treatment					Test of Cure (TOC)	Follow-Up (FUP)	End of Study (EOS)
	Day −2 to Same Day Prior to Randomization[a]		Day 1	Day 3	Early Asses. (EA) Day 3 to 4	(Day 14)[b]	End of Treat. (EOT)[c]	EOT + 7 (± 2)	EOT + 14 (± 3)	EOT + 28 (± 3)
Hematology Tests, Blood Chemistry Tests, and Urinalysis (Table 7-1)	X				X	X	X	X	X	X[h]
TIBC, Transferrin Iron Saturation, Hepcidin	X							X		
CrCl from Serum Creatinine[m]	X	Randomization			X					
CrCl from Urinary Creatinine[l]					X					
Vital Signs[n]	X		X ←	———	———	———	→ X	X	X	X[h]
12-lead ECG	X									
Drug Administration			X ←	———	———	———	→ X			
Clinical Outcome					X	X	X	X	X	
Biologic Tissue or Fluids for Microbiologic Cultures[o]	X				X	X	X	X	X	
Microbiological Outcome					X	X	X	X	X	
Blood PK Samples (S-649266 Group)				X[p]	X[p]					
AE Assessment	X ←	———	———	———	———	———	———	———	———	→ X
Concomitant Therapy	X ←	———	———	———	———	———	———	———	———	→ X
Hospitalization	X ←	———	———	———	———	———	———	———	———	→ X
Vital Status	X ←	———	———	———	———	———	———	———	———	→ X

a. If Screening and Randomization (Day 1) occur on the same day, the activities of Screening and Day 1 should be completed, without duplication of assessments.
b. In case treatment duration is extended beyond 14 days, an additional assessment will be conducted on Day 14.
c. EOT evaluations occur on the last day of study treatment. EOT can be any time after the patient had at least one dose of study treatment, duplication of assessments for a given day and EOT is not necessary.
d. The use of investigational diagnostics or diagnostics that are not the local standard of care for determination of carbapenem resistance will require that the investigational diagnostics section of the informed consent be signed by the patient or legally authorized representative.
e. Include a review of prior/concomitant therapies.
f. A complete physical examination including measurement of body weight and height will be performed at Screening only.
g. A limited physical examination relevant to the patient's current condition will be performed.
h. If end of study evaluation is by phone, physical examination, laboratory tests, and vital signs will not be performed.
i. Patients receiving an oxygen inhalation treatment.
j. For ventilated patients treated with S-649266, specified ventilator parameters will be captured at the start of the infusion (acceptable time window; 0 hours to end of infusion) which PK sampling will be taken.
k. **At German sites,** in sites where chest radiographs after screening are part of the standard of care, ie, a chest radiograph is clinically indicated by the treating physicians, it can be performed as usual without a special informed consent. If a chest radiograph is not standard of care (no clinical indication), and is planned based on the study protocol, an informed consent from a conscious patient is mandatory. Chest radiographs without clinical indication cannot be performed in unconscious patients.
l. Urine or serum pregnancy test only for females who are not diagnosed as postmenopausal or surgically sterile.
m. The CrCl (the Cockcroft-Gault equation) and eGFR (the MDRD equation) will be calculated from the serum creatinine. For patients with eGFR ≥ 90 mL/min/1.73 m^2 at baseline, urine samples will be collected a time interval as short as 2 hours or up to 8 hours.
n. Blood pressure (systolic/diastolic pressures), body temperature, pulse rate, and respiratory rate.
o. Biologic tissue or fluids (including blood regardless of the infection site) for microbiologic cultures will be obtained with 48 hours of the start of treatment, and at specified times and at the investigator's discretion. Two blood samples from separate venipunctures will be collected within 48 hours prior to start of the first dose of study treatment. Subsequent blood cultures are to be completed only if the first culture is positive.
p. PK blood samples will be drawn on Day 3 after at least the sixth dose of study drug; one draw just prior to the infusion of the dose, 1 hour after start of infusion, at the end of infusion, and at 1 hour after the end of infusion. Patients with non-stable renal function resulting in a dosage adjustment at EA will undergo another blood PK sampling (4 samples at the above specified timepoints) within 24 to 72 hours after their dosing adjustment. If possible, a single blood draw should be performed as soon as possible at EOT in case of premature EOT.

Appendix 2 SIRS Criteria

Patient exhibits 2 or more of the following responses:

1. Temperature greater than 38°C (100.4°F) or less than 36°C (96.8°F)
2. Heart rate greater than 90 beats/minute
3. Respiratory rate greater than or equal to 20 breaths/minute or $PaCO_2$ less than 32 mmHg
4. WBC greater than 12,000/mm^3 or less than 4000/mm^3 or > 10% immature (band) forms

Reference:

Bone RC, Balk RA, Cerra FB. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101:1644-55.

Appendix 3 European Medicines Agency Completes Review of Polymyxin-based Medicines

Information to Healthcare Professionals

The recommendations of European Medicines Agency (EMA) are based on a review of the available clinical, pharmacological, and pharmacokinetic data, although significant gaps still exist, particularly with regard to the pharmacokinetics in special populations such as children and patients with renal impairment. Research currently underway may provide further information on pharmacodynamics and pharmacokinetics of these medicines to improve the evidence-base behind any dose recommendations. However, it was considered that in the interim the product information should be updated throughout the EU to reflect what was currently known.

- Doses should always be expressed in IU of colistimethate sodium. To address the differences in the way in which the strength of colistimethate sodium and colistin are expressed in the EU and in other regions such as the USA and Australia, which has led to errors in reporting in the medical literature and could potentially lead to serious medication errors, the following table has been recommended for inclusion in product information:

Colistimethate sodium (IU)	Colistimethate sodium (mg)	Colistin-base activity (CBA) (mg)[1]
12,500	1	0.4
150,000	12	5
1,000,000	80	34
4,500,000	360	150
9,000,000	720	300

1 Based on a nominal potency of the drug substance of 12,500 IU/mg or 0.424 mg CBA/mg: both IU and mg CBA are expressions of potency and have only approximate relation to the mass of drug substance.

- Intravenous colistimethate sodium is indicated in adults and children including neonates for the treatment of serious infections due to aerobic Gram-negative pathogens in patients with limited treatment options. Consideration should be given to coadministration with another antibacterial agent whenever this is possible.
- Dosage should be in line with relevant treatment guidelines. Based on the limited available evidence the recommended dose in adults is 9 million IU daily in 2 or 3 divided doses as a slow intravenous infusion; in critically ill patients, a loading dose of 9 million IU should be given. Doses should be reduced according to creatinine clearance in patients with renal impairment.
- Intravenous colistimethate sodium does not cross the blood-brain barrier to a significant extent. Where appropriate, adult doses of 125,000 IU for intraventricular administration and no more than this for intrathecal administration are recommended.

- Use of intravenous colistimethate sodium together with other medications that are potentially nephrotoxic or neurotoxic should be undertaken with great caution.

Reference:

European Medicine Agency. European Medicines Agency completes review of polymyxin-based medicines. Recommendations issued for safe use in patients with serious infections resistant to standard antibiotics. October 2014.

Appendix 4 Microbiology Tests

Appropriate clinical specimens will be obtained from all patients within 48 hours prior to the start of the infusion of the first dose of study treatment therapy. Biologic tissue or fluids for microbiologic cultures will be sent to the local laboratory for identification of all pathogens causing the infection. Two blood samples from separate venipunctures will be obtained from all patients and sent to the local laboratory. After initiation of study treatment, appropriate clinical specimens including blood culture will be obtained at the specified evaluation points (Appendix 1).

Identified isolates in unscheduled cultures should be sent to the central lab.

In general, all specimens should also have Gram stain of infected material (not swab). A report of both inflammatory cells and bacteria is necessary.

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

1. HAP/VAP/HCAP Specific Procedures

Patients enrolled in a HAP/VAP/HCAP study should have a baseline respiratory specimen obtained for Gram stain and culture [1]. In addition to defining the bacterial etiology for HAP/VAP/HCAP, the Gram stain and culture are important considerations because they may be used to define analysis populations and to characterize the quality and findings of the respiratory specimen sent for culture. More specifically, 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 (eg, fewer than 10 squamous epithelial cells and greater than 25 neutrophils is an example of an adequate expectorated sputum specimen). 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). When bacterial growth is obtained on culture of the respiratory specimen, in vitro susceptibility tests should be performed by using standardized methods unless otherwise justified.

Endobronchial culture specimens collected by BAL or protected specimen brush (PSB) should be grown quantitatively with appropriate method specific dilutions.

2. cUTI Specific Procedures

Clean-Catch Mid-Stream Urine Specimen: After appropriate patient preparation, a specimen should be collected and immediately sent to the microbiology laboratory or properly stored for no longer than 24 hours.

Urine Specimen from Patients with Indwelling Urinary Catheters: Because biofilms on indwelling catheters (eg, Foley catheters) are more likely to be present after the catheter has been in place for a period of time, samples should be collected following the placement of a new catheter. If the placement of a new catheter is contraindicated or is

not feasible, specimens should be collected using aseptic techniques with the urine obtained through a properly disinfected collection port. Urine samples should never be obtained from the collection bag.

Urine Evaluations: A microscopic evaluation (eg, Gram stain) or dipstick analysis for leukocytes, nitrates, or a catalase test should be performed and the specimen cultured. In general, bacteria identified at 1 x 10^5 CFU/mL or greater should be considered a bacterial pathogen (probability of true pathogen is greater than that of contamination). Quantitative urine culture by appropriate methods should be performed using a calibrated loop that would identify bacteria at a lower limit of 10^3 CFU/mL. In vitro antibiotic susceptibility testing of the isolates to the investigational drug and to other antibiotic drugs that may be used to treat cUTIs should be performed using standardized methods unless otherwise justified.

If possible, the identity of bacteria that are demonstrated in culture between 10^3 CFU/mL and 10^4 CFU/mL should be determined as these may be background bacteria associated with the method of collection.

3. Bloodstream and Sepsis Infections: Specific Procedures

For infections categorized as BSI/sepsis, the following guidelines are provided (for details see reference infectious disease society of America/ American society for micobiology (IDSA/ASM) guidelines [2]). These guidelines apply to blood cultures and infection site tissue or fluids cultures for patients with infections other than HAP/VAP/HCAP or cUTI.

Culture Procedures

Infection Site	Culture Method (Gram Stain Required for All Cultures or Appropriate Specimen)
Blood Stream Infection (Bacteremia)	
Primary (Not Endocarditis)	2-3 separate "sets" of blood cultures (10 mL/bottle) drawn from peripheral vein
Secondary	2-3 separate "sets" of blood cultures (10 mL/bottle) drawn from peripheral vein
Line Related	2-3 separate "sets" of blood cultures (10 mL/bottle) drawn from peripheral vein
Skin/Skin Structure Infections	
Primary Skin Infection (eg, Necrotizing Fasciitis)	Quantitative, semi-quantitative tissue culture (not swab)
Burn Wound Infection	Quantitative, semi-quantitative tissue culture (not swab)
Human/Animal Bite Infection	Tissue culture or aspirate (not swab)
Surgical Site Infection	Tissue culture or aspirate (not swab)
Trauma Associated Skin Infection	Post debridement tissue culture or aspirate (not swab)
Intra-Abdominal Infections	
Spontaneous Bacterial Peritonitis	Culture aspirate or inoculate blood culture bottle
Tertiary Peritonitis (Post-Surgical)	Fluid aspirate or tissue culture
Abscess of Liver	Lesion aspirate
Biliary Tract Infection	Lesion aspirate
Secondary Pancreatic Infection	Lesion aspirate
Respiratory Tract other than HAP/VAP/HCAP	
Community Acquired Pneumonia	Expectorated sputum, or bronchoscopic specimen
Lung Abscess	Lesion aspirate or bronchoscopic specimen
Pleural Space, Empyema	Culture aspirate or inoculate blood culture bottle
Pelvic Infection (Post-Surgical)	Fluid aspirate or tissue culture

References:

1. Guidance for Industry Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). May 2014 (revision 2).
2. Baron EJ, Miller JM, Weinstein MP, et al. A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2013 Recommendation by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM). Clinical Infectious Diseases 2013;57(4):e22-e121.

Appendix 5 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
	Localising	5
	Normal flexion	4
	Flexing	3
	Extension	2
	None	1

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. The Lancet Neurology. 2014;13:844-54.

Appendix 6 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)									

Chronic Health Points: If the patient 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 patients and 2 points for elective postoperative patients.

***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 (GI) 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 (ie, 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 patient 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 7 SOFA Score

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

* Norepi indicates norepinephrine; dob, dobutamine; Dop, dopamine; epi, epinephrine; and FiO_2, fraction of inspired oxygen.

† Values are with respiratory support.

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

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

‖ 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 8 Clinical Pulmonary Infection Score (CPIS) Parameters

CPIS Points	0	1	2
Tracheal Secretions*	Few	Moderate	Large
Chest X-Ray Infiltrates†	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) †	≥ 4000 and ≤ 11,000	< 4000 or > 11,000	
PaO_2/FiO_2 (mmHg)‡	> 240 or evidence of Acute Respiratory Distress Syndrome (ARDS)		≤ 240 and no evidence of ARDS

* If purulent: +1

† For post baseline CPI scores where the radiograph or leukocytosis has improved: −1

‡ Use first blood gas measure in morning. For non-ventilated patients who, based on local practice, do not have blood gasses done, a PaO_2/FiO_2 point value of zero may be assigned.

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 9 Management Criteria for Abnormal Liver Function Tests

Management Criteria for Abnormal Liver Function tests have been designed to ensure patient safety and evaluate liver event etiology.

Abnormal Liver Chemistry Criteria:

The investigator or sub-investigator must review study patient laboratories to identify if any levels meet the following criteria a.-e.:

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

   OR

e. AST or ALT > 3 × increase from baseline ALT 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%]);

Patients who develop AST or ALT > 5× ULN (if baseline ALT is > ULN) should be followed weekly until resolution or stabilization.

Action to Be Taken by Investigator:

If any one of abnormal liver chemistry criteria is met, the investigator or sub-investigator must do the following:

- Following the initial observed elevation, every effort should be made to have the patient reassessed within 48 to 72 hours to repeat liver function chemistries and for further hepatic evaluation.
- Patients must be monitored 2 to 3 times per week until liver function chemistries (ALT, AST, ALP, total bilirubin) resolve, stabilize or return to within the normal range or to baseline levels.
- This event must be reported to the sponsor within 48 to 72 hours of learning after its occurrence on the Liver Event Form.
- Consultation with a specialist such as a hepatologist is considered.
- Liver imaging (ie, ultrasound, magnetic resonance imaging [MRI], computerized tomography (CT) is considered.

- For criteria c, termed “Hy’s law,” the case must be reported as an SAE (if baseline AST or ALT is ≤ ULN).
  If baseline AST or ALT is > ULN, the case that meets the following criteria must be reported as an SAE.
  AST or ALT > 3 × increase from baseline AST or ALT and TBL > 2 × increase from baseline TBL

Follow-up Examination:

If any of abnormal liver chemistry criteria are met, the following assessments should be obtained at FUP and documented in the Liver Event Form:

- Clinical signs and symptoms course
- Concomitant medications: OTC/herbal/dietary supplements (start and stop dates)
- Alcohol use
- Risk factors for nonalcoholic steatohepatitis (NASH) such as diabetes, obesity and hypertriglyceridemia
- Autoimmune hepatitis/cholangitis
- Wilson's disease
- Laboratory Assessments

  Viral hepatitis serology
  - Hepatitis A 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 patients with total bilirubin of > 1.5 ULN, conjugated bilirubin should be measured

  Complete blood count with differential

Appendix 10 Sponsor Signature

Form 510-01

Approval of the Protocol

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

Study Protocol Number: 1424R2131

Edition Number: 3

Issue Date of Original: 11 November 2015

Issue Date of Latest Version 4: 16 November 2017

Sponsor signatory:

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

[redacted]

Date: day-month-year

Appendix 11 Investigator's Signature

Study Title:	A Multicenter, Randomized, Open-label Clinical Study of S-649266 or Best Available Therapy for the Treatment of Severe Infections Caused by Carbapenem-resistant Gram-negative Pathogens
Study Number:	1424R2131
Date of Original:	11 November 2015
Date of Version 4	16 November 2017

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: _____