CLINICAL STUDY PROTOCOL

A Phase 3, Multi-Center, Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Cefepime/Nacubactam or Aztreonam/Nacubactam Compared to Imipenem/Cilastatin in the Treatment of Complicated Urinary Tract Infections or Acute Uncomplicated Pyelonephritis, in Adults

Investigational Product: 1 g Nacubactam for injection
Protocol Number: OP0595-5
EudraCT Number: 2021-001441-12

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SIGNATURE PAGE

STUDY TITLE: A Phase 3, Multi-Center, Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Cefepime/Nacubactam or Aztreonam/Nacubactam Compared to Imipenem/Cilastatin in the Treatment of Complicated Urinary Tract Infections or Acute Uncomplicated Pyelonephritis, in Adults

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature	Date
Takeshi Minamida	20 Dec. 2023

Takeshi Minamida
General Manager
Clinical Development Department
Meiji Seika Pharma Co., Ltd.

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Meiji Seika Pharma Co., Ltd. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Meiji Seika Pharma Co., Ltd. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Meiji Seika Pharma Co., Ltd., with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with the laws and regulations of the country in which the study is conducted, Institutional Review Board/Ethic Committee Regulations, International Council for Harmonisation Guidelines for Good Clinical Practices, current Declaration of Helsinki, and the Regulation (EU) No. 536/2014 or applicable regulatory requirements.

_____ _____

Principal Investigator's Signature Date

_____

Principal Investigator's Printed Name

SYNOPSIS

TITLE: A Phase 3, Multi-Center, Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Cefepime/Nacubactam or Aztreonam/Nacubactam Compared to Imipenem/Cilastatin in the Treatment of Complicated Urinary Tract Infections or Acute Uncomplicated Pyelonephritis, in Adults

SHORT TITLE: A Phase 3 Study to Evaluate the Efficacy and Safety of Cefepime/Nacubactam or Aztreonam/Nacubactam Compared to Imipenem/Cilastatin in the Treatment of Complicated Urinary Tract Infections or Acute Uncomplicated Pyelonephritis in Adults

PROTOCOL NUMBER: OP0595-5

INVESTIGATIONAL PRODUCT: 1 g Nacubactam for injection

PHASE: 3

INDICATION: Complicated urinary tract infection (cUTI) and acute uncomplicated pyelonephritis (AP)

OBJECTIVES:

The primary objective of this study is to assess the efficacy and safety of cefepime/nacubactam and to assess the safety of aztreonam/nacubactam administered by intravenous (IV) infusion compared to imipenem/cilastatin in patients with cUTI or AP.

The secondary objectives of this study are the following:

- To assess the efficacy of aztreonam/nacubactam administered by IV infusion in patients with cUTI or AP;
- To assess the efficacy of cefepime/nacubactam and aztreonam/nacubactam administered by IV infusion in patients with secondary bacteremia due to cUTI or AP;
- To assess the pharmacokinetics (PK) of cefepime/nacubactam and aztreonam/nacubactam administered by IV infusion in patients with cUTI or AP; and
- To assess clinical and microbiological response of cefepime/nacubactam and aztreonam/nacubactam administered by IV infusion per type of pathogen, type of resistance, and antimicrobial susceptibility.

POPULATION:

Inclusion criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Male or female patients ≥ 18 years of age (or age of legal consent, whichever is older) at the time of obtaining informed consent and who can be hospitalized throughout the Treatment Period;
2. Weight ≤ 140 kg;
3. Expectation, in the opinion of the Investigator, that the patient's cUTI or AP will require treatment with at least 5 days of IV antibiotics;
4. Diagnosis of cUTI or AP as defined in the tables below:

   Note: If a patient meets the criteria for cUTI below and also has flank pain or costo-vertebral angle tenderness, the patient will be randomized as cUTI instead of AP.

cUTI		
Signs or symptoms evidenced by at least 2 of the following	**Pyuria evidenced by 1 of the following**	**At least 1 of the following associated risks**
• Chills, rigors, or fever. Fever (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]) must be observed and documented by a healthcare provider within 24 hours of Screening; • Suprapubic, pelvic, or lower abdominal pain; • Nausea or vomiting within 24 hours of Screening; • Dysuria, increased urinary frequency, or urinary urgency; or • Elevated WBC count (> 10,000/mm^3) or left shift (> 15% immature PMNs).	• Positive leukocyte esterase on urinalysis; • WBC count ≥ 10/mm^3 in unspun urine; or • WBC count ≥ 10/hpf in urine sediment.	• Implanted urinary tract instrumentation (eg, ureteric stents or other urinary tract prosthetic material), ongoing intermittent bladder catheterization, or presence of an indwelling bladder catheter (Note: Indwelling bladder catheters that have been in place prior to Screening must be removed or replaced prior to collection of the Screening urine for urinalysis and culture, unless removal or replacement is considered unsafe or contraindicated); • Current known functional or anatomical abnormality of the urogenital tract, including anatomic abnormalities of the urinary tract, neurogenic bladder, or post-void residual urine volume of ≥ 100 mL within the past 6 months; • Partial obstructive uropathy (eg, nephrolithiasis, fibrosis, urethral stricture) that is expected to be medically or surgically treated during study drug therapy (prior to EOT); • Urinary retention, including urinary retention in men due to previously diagnosed BPH; or • Azotemia, defined as blood urea nitrogen > 20 mg/dL (> 7.14 mmol/L) (or blood urea > 42.8 mg/dL [> 7.13 mmol/L]), or serum creatinine > 1.4 mg/dL (>123.79 µmol/L), due to known prior intrinsic renal disease.
BPH = benign prostatic hyperplasia; cUTI = complicated urinary tract infection; EOT = End of Treatment; hpf = high-power field; PMN = polymorphonuclear leukocyte; WBC = white blood cell.		

AP		
Signs or symptoms evidenced by at least 2 of the following	**Pyuria evidenced by 1 of the following**	**At least 1 of the following associated risks**
• Chills, rigors, or fever. Fever (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]) must be observed and documented by a healthcare provider within 24 hours of Screening; • Flank pain (onset within 7 days prior to randomization); • Costo-vertebral angle tenderness on physical examination; • Nausea or vomiting within 24 hours of Screening; • Dysuria, increased urinary frequency, or urinary urgency; or • Elevated WBC count (> 10,000/mm^3) or left shift (> 15% immature PMNs).	• Positive leukocyte esterase on urinalysis; • WBC count ≥ 10/mm^3 in unspun urine; or • WBC count ≥ 10/hpf in urine sediment.	Not applicable.
AP = acute uncomplicated pyelonephritis; hpf = high-power field; PMN = polymorphonuclear leukocyte; WBC = white blood cell.		

5. Patient has a baseline positive urine culture specimen obtained within 48 hours prior to the first dose of study drug;

   Note: Patients may be enrolled in this study and start IV study drug therapy before the Investigator knows the results of the baseline urine culture, if all other entry criteria are fulfilled. If known, the screening/baseline urine culture taken within 48 hours prior to the first dose of study drug contains ≥ 10^5 colony-forming units (CFU)/mL of a Gram-negative uropathogen susceptible to meropenem and imipenem, and the culture is not considered contaminated. If a patient grows ≥ 3 bacterial organisms ≥ 10^5 CFU/mL in the urine, the urine culture will be considered contaminated. An organism will not be considered a contaminant if the organism grows ≥ 10^5 CFU/mL in a urine culture and also grows in a concurrently obtained blood culture. If a patient's baseline urine culture is negative after randomization, the Investigator decides whether the patient should continue to receive the study drug or should discontinue the study drug and initiate non-study antibiotics.

   Note: Imipenem and meropenem susceptible pathogen is defined as a Gram-negative pathogen by susceptibility data of minimum inhibitory concentration (MIC) less than 2 µg/mL to imipenem and meropenem OR imipenem and meropenem disk diffusion (zone diameter ≥ 22 mm). If MIC or disk diffusion data are not available in the local laboratory or before the availability of MIC or disk diffusion results, each site can use other susceptibility testings and criteria in the institution as the initial evidence of imipenem and meropenem susceptible pathogen for enrollment. In any case, pathogen identification and susceptibility testing performed at the central laboratory will be used to determine imipenem and meropenem susceptible pathogen in the final study analysis.

6. Female patients who are no longer of childbearing potential must meet 1 of the following criteria:
    a. Women ≥ 50 years of age who are considered postmenopausal as they have been amenorrhoeic for ≥ 12 months;
    b. Women < 50 years of age who are considered postmenopausal as they have been amenorrhoeic for ≥ 12 months and if the follicle-stimulating hormone (FSH) level is in the postmenopausal range. If the FSH level is not available at the time of randomization, the patient must have a negative urine and/or serum pregnancy test and agree to use contraception methods until the FSH result is available; or
    c. Documented permanent sterilization, defined as hysterectomy, bilateral oophorectomy, or bilateral salpingectomy.
7. Female patients of childbearing potential must have a negative urine and/or serum pregnancy test (serum β-human chorionic gonadotropin) at Screening;

    Note: Females of childbearing potential include female patients who have experienced menarche (or begin menarche over the course of the study), and who are not postmenopausal or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy).
8. Patients must agree to use contraception methods as defined below:
    a. Female patients of childbearing potential will be included if they are either sexually inactive (abstinent) for 90 days prior to the first dose of study drug, or are using one of the following highly effective birth control methods (ie, results in < 1% failure rate when used consistently and correctly):
        i. Intrauterine device in place for at least 3 months prior to the first dose of study drug and throughout the study;
        ii. Surgical sterilization of the partner (provided they are the sole sexual partner), defined as vasectomy for 6 months minimum and assessed as surgical success;
        iii. Combined (estrogen or progestogen containing) hormonal contraception associated with the inhibition of ovulation (either oral, intravaginal, or transdermal);
        iv. Progestogen only hormonal contraception associated with the inhibition of ovulation (either oral, injectable, or implantable);
        v. Intrauterine hormone releasing system; or
        vi. Bilateral tubal occlusion.

    Note: Sexual abstinence or use of contraceptive measures must continue throughout the study and for 12 weeks after the last dose of study drug.

    Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. In this study, abstinence is only acceptable if in line with the patient's preferred and usual lifestyle. Periodic abstinence (calendar, symptothermal, post-ovulation methods),

withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea methods are not acceptable methods of contraception.

b. Male patients with female partners of childbearing potential must use highly effective methods of birth control during their participation in the study and for 12 weeks after the last dose of study drug. In addition, male patients with female partners of childbearing potential must also use a condom during their participation in the study and for 12 weeks after the last dose of study drug.

Note: Highly effective methods of birth control for male patients enrolled in the study include the following: surgical sterilization (vasectomy assessed as surgical success) of patient at least 6 months before Screening or a female partner of childbearing potential (provided they are the sole female sexual partner) using highly effective contraception as described in Inclusion Criterion #8a).

9. Female patients must agree to not donate eggs, or retrieve eggs for her own use from the time of informed consent until 12 weeks after the last dose, or male patients must agree to not freeze or donate sperm starting from the time of informed consent until 12 weeks after the last dose;
10. Willing to comply with all study activities and procedures, whether in the hospital or after discharge, for the duration of the study; and
11. Able to provide signed, written informed consent prior to any study-related procedures being performed.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Has a known imipenem- and/or meropenem-resistant Gram-negative uropathogen ($\geq 10^5$ CFU/mL), isolated from study-qualifying urine culture;

   Note: If after randomization the susceptibility testing indicates resistance to imipenem and/or meropenem, the patient may remain on the study at the Investigator's discretion.

2. Has known or suspected single or concurrent infection with *Acinetobacter* species or other organisms that are not adequately covered by the study drug (eg, concurrent viral, mycobacterial, or fungal infection) and needs to be managed with other anti-infectives;

   Note: Patients with qualifying pathogen coinfected (or suspected to be coinfected) with a Gram-positive pathogen may be administered narrow spectrum, open-label glycopeptide (eg, vancomycin), oxazolidinone (eg, linezolid), or daptomycin concomitantly with the study drug at the Investigator's discretion.

3. Has only a known Gram-positive primary uropathogen ($\geq 10^5$ CFU/mL), isolated from study-qualifying urine culture;

4. Has a known study-qualifying urine culture with ≥ 3 bacterial organisms ≥ 10^5 CFU/mL;

   Note: A Gram-negative organism will not be considered a contaminant if the organism grows ≥ 10^5 CFU/mL in a urine culture and also grows in a concurrently obtained blood culture.

5. Has a complete obstruction of any portion of the urinary tract that is not anticipated to be medically or surgically relieved during this study therapy and before End of Treatment (EOT);
6. Has a previous or planned cystectomy or permanent urinary diversion (eg, ileal loop, cutaneous ureterostomy);
7. Has a refractory vesicoureteral reflux (Grade 4 or 5);
8. Has a suspected or confirmed perinephric or renal corticomedullary abscess or polycystic kidney disease;
9. Has suspected or confirmed prostatitis, orchitis, epididymitis, urethritis, or sexually transmitted disease;
10. Has a non-renal source of infection concurrently that could interfere with the evaluation of response to the study drug;
11. Has any recent history of accidental trauma to the pelvis (in the pelvic cavity) or urinary tract;
12. Requires bladder irrigation with antibiotics or requires antibiotics to be administered directly via urinary catheter;
13. Has received a potentially effective systemic antibacterial therapy within 48 hours prior to the first dose of study drug, with the exception of any of the following:
    a. Receipt of a single dose of a short-acting antibacterial agent (APPENDIX C) (no more than 15% of patients will be enrolled with this exception);
    b. Receipt of > 48 hours of prior antibiotic therapy and, in the Investigator's opinion, failed that prior antibiotic therapy (ie, worsening signs and symptoms); or
    c. Documented to have cUTI or AP caused by a pathogen that is not susceptible to the prior antibiotic therapy.
14. Has a history of serious allergy, hypersensitivity (eg, anaphylaxis), or any serious allergic reaction to carbapenems, cephems, penicillins, other β-lactam antibiotics, or any β-lactamase inhibitors (eg, tazobactam, sulbactam, or clavulanic acid);
15. Has a history of epilepsy or known seizure disorder (excluding a history of childhood febrile seizures);
16. Is considered unlikely to survive the study period or has a rapidly progressive or terminal illness;
17. Is a female patient who is pregnant or breastfeeding;
18. Is a female patient who expects to be pregnant or a male patient who expects their partner to be pregnant from the time of informed consent until 12 weeks after the last dose;
19. Has current or anticipated neutropenia (< 500 polymorphonuclear neutrophils/mm^3, obtained from the local laboratory at Screening);

20. Has platelet count < 50,000 per microliter;
21. Has renal transplantation and received antibacterial drug prophylaxis within 48 hours before screening and/or likely to receive antibacterial drug prophylaxis during the study period;
22. Has participated in other clinical study within 90 days before this clinical study, or plans to participate in any other clinical study during the course of the study;
23. Has an estimated creatinine clearance (CrCl) < 30 mL/min or > 240 mL/min based on the Cockcroft-Gault formula or is receiving hemodialysis or peritoneal dialysis;
24. Has prior exposure to nacubactam alone or in combination with another product;
25. Has gross hematuria that is not caused by infectious diseases;
26. Meets Hy's criteria of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN) and total bilirubin > 2 × ULN;

    Note: Patients with AST and/or ALT up to 5 × ULN are eligible if these elevations are acute and are documented as being directly related to the infectious process being treated.
27. Has evidence of significant hepatic disease or dysfunction, including known acute viral hepatitis or hepatic encephalopathy;
28. Has manifestations of end-stage liver disease, such as ascites or hepatic encephalopathy;
29. Has a known history of HIV with either a cluster of differentiation 4 count < 200 cells/mm^3 at the last measurement or current diagnosis of another acquired immunodeficiency syndrome-defining illness;
30. Has an uncomplicated urinary tract infection (UTI) except AP (acute uncomplicated cystitis that does not meet the cUTI disease definition [see Inclusion Criterion #4]);
31. Has any condition that, in the opinion of the Investigator, would compromise the safety of the patient or the quality of the data (eg, due to underlying disease, comorbidity, clinically meaningful laboratory abnormality), including a potential concern about a history of a disease that may compromise the safety of the patient during the course of the study (eg, history of clinically significant QT interval prolongation, clinically important congenital syndromes, etc);

    Note: Patients with electrolytes that are above or below the normal value range and deemed by the PI to be clinically significant may be excluded.
32. Is anticipated to begin a new drug that is classified as high risk of prolonging the QT interval (listed in APPENDIX D) during the treatment period;

    Note: If patients have been using the drugs listed in APPENDIX D prior to the enrollment and need to continue using them and patient meets all entry criteria, the patient can be enrolled and continue using them during the study period.
33. Heart-rate-corrected QT interval by the Fridericia formula (QTcF) > 470 msec at Screening;

    Note: If QTcF exceeds 470 msec, the electrocardiogram (ECG) may be repeated 2 more times after rest and the mean of the 3 values will be used to determine the subject's eligibility.

34. Clinically significant bradycardia with a heart rate < 50 bpm;

    Note: Patients with such a low heart may have their heart rate repeated up to 2 additional times to determine eligibility.

35. Diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); and

    Note: A SARS-CoV-2 test (genetic testing will be suggested but other antigen testing is allowed) should be conducted at Screening for highly suspected Coronavirus Disease 2019 (COVID-19) patients at the Investigator's discretion. Patients who are tested for SARS-CoV-2 will be started on study drug only after a negative result is confirmed.

    Note: Patients eligible for the study with the exception of meeting COVID-19 criteria will be allowed to rescreen more than 2 weeks after testing positive and must have a negative test result for eligibility.

36. Is using or planning to use any of the excluded medications and/or procedures except opioids and urinary anesthetics listed in Section 5.6.1 within the time period specified.

WITHDRAWAL CRITERIA:

Patients may be discontinued from study drug for any of the following reasons but will still be followed for safety assessments approximately 7 to 14 days after Early Termination (ET):

1. Occurrence of a treatment-emergent adverse event (TEAE) that warrants study drug discontinuation in the judgment of the Investigator;
2. Occurrence of exacerbation of underlying disease that warrants study drug discontinuation in the judgment of the Investigator;
3. Patient ineligibility after the start of the study in the judgment of the Investigator;
4. Required use of prohibited concomitant medications except urinary anesthetics and opioid drugs;
5. Significant prolongation of the QT/QTc interval (QTcF > 500 msec or increase from baseline > 60 msec) as measured by the mean of 3 values after study drug administration; or
6. Occurrence of an event that warrants discontinuation in the judgment of the Investigator.

Participation of a patient in this clinical study may be discontinued for any of the following reasons:

1. The patient withdraws consent or requests discontinuation from the study for any reason;
2. Pregnancy;
3. Termination of the study by the Sponsor or the regulatory authority; or
4. The patient is suspected/diagnosed with SARS-CoV-2 infection and warrants discontinuation in the judgment of the Investigator.
5. Insufficient therapeutic effect of the study drug that could lead to clinical worsening, or lack of clinical progress in the judgement of investigators;

STUDY DESIGN AND DURATION:

This is a multi-center, randomized, double-blind study to evaluate the efficacy and safety of cefepime/nacubactam or aztreonam/nacubactam compared to imipenem/cilastatin for the treatment of cUTI or AP, in adults.

In this study, the efficacy and safety of cefepime/nacubactam is primarily evaluated because cefepime has a broader antibacterial spectrum (Gram-positive and Gram-negative bacteria) and cefepime/nacubactam is expected to be frequently used for infections caused by Class A and/or D carbapenemase-producing Enterobacterales while aztreonam has an indication only for Gram-negative bacteria and aztreonam/nacubactam is positioned to be used only for infections caused by Class B carbapenemase-producing Enterobacterales in principle.

Approximately 600 patients will be randomized in a 2:1:1 ratio to receive either 2 g cefepime/1 g nacubactam, 2 g aztreonam/1 g nacubactam, or 1 g imipenem/1 g cilastatin.

Dosage of cefepime, aztreonam, nacubactam, and imipenem/cilastatin according to renal function is shown in Table S1.

Randomization will be stratified by entry diagnosis (cUTI or AP) and by geographic region (Japan, China, or Other). At least 30% of patients will have a diagnosis of AP and at least 60% will have a diagnosis of cUTI.

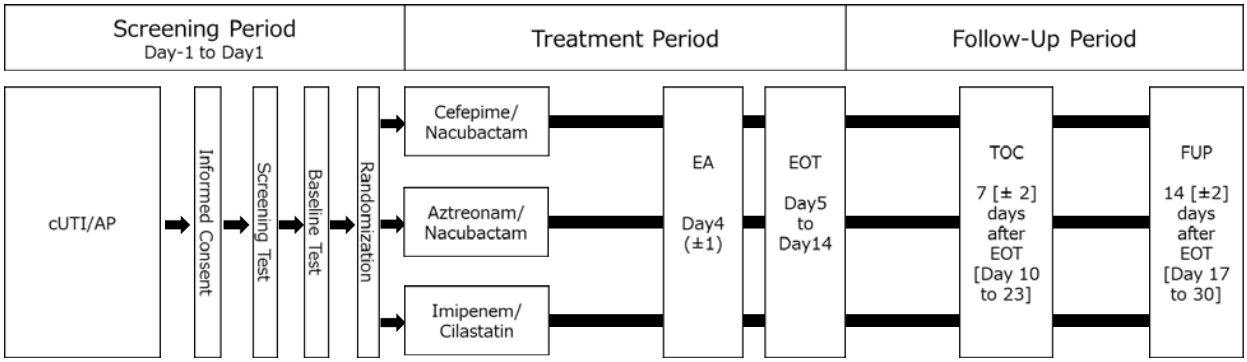
Patients with secondary bacteremia (defined as an organism[s] isolated from a non-contaminated blood culture that is the same as the cUTI/AP-qualifying organism[s] isolated from a urine culture or genitourinary tissue culture) will be included in the study, but categorized by the primary indication and recorded as having secondary bacteremia.

Study drug will be administered every 8 hours (± 1 hour) via an IV infusion over a period of 60 minutes (± 15 minutes). All patients will be treated for a minimum of 5 days (ie, 15 IV infusions) to 10 days. Duration may continue for up to 14 days in selected situations (eg, baseline bacteremia), after discussion with the Medical Monitor. Patients will return for 2 follow-up visits: a Test of Cure visit (TOC) (7 [± 2] days after EOT [Day 10 to 23]) and a Follow-Up visit (FUP) (14 [±2] days after EOT [Day 17 to 30]). Patients who withdraw from the study early will undergo an Early Termination (ET) visit. Study drug administration should be discontinued in patients whose baseline urine culture does not meet the requirements for a baseline qualifying pathogen and, in the opinion of the Investigator, the patient does not have a UTI and the patient is not improving.

For instances when a patient grows only a Gram-negative organism resistant to imipenem and/or meropenem, the patient should discontinue study drug but may remain in the study to complete all study assessments.

Figure S1 presents a schematic of the study design.

Figure S1. Study Design



AP = acute uncomplicated pyelonephritis; cUTI = complicated urinary tract infection; EA = Early Assessment; EOT = End of Treatment; FUP = Follow-Up visit; TOC = Test of Cure visit.

Patients with a qualifying Gram-negative uropathogen coinfected (or suspected to be coinfected) with a Gram-positive uropathogen detected after randomization may be administered narrow spectrum, open-label glycopeptide (eg, vancomycin), oxazolidinone (eg, linezolid), or daptomycin concomitantly with the blinded study drug at the Investigator's discretion. Investigators should discuss such cases with the Medical Monitor.

Patients will be monitored for safety throughout the duration of the study. Safety assessments will include vital signs, physical examinations, clinical laboratory assessments, adverse event (AE) assessments, and 12-lead ECGs. A urine and/or serum pregnancy test will be performed at Screening and FUP/ET for female patients of childbearing potential only and postmenopausal women < 50 years of age, if the follicle-stimulating hormone (FSH) level is not available at the time of randomization.

An independent Data Safety Monitoring Board (DSMB) will review accumulated safety data and will also review serious AEs on an ongoing basis. The DSMB will make recommendations based on the safety data. Further details regarding the data safety monitoring guidelines will be included in the DSMB Charter.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Patients will receive either 2 g cefepime/1 g nacubactam, 2 g aztreonam/1 g nacubactam, or 1 g imipenem/1 g cilastatin every 8 hours (± 1 hour) for at least 5 days and up to 14 days. Study drug will be administered via IV infusion over a period of 60 minutes (± 15 minutes).

If CrCl is ≥ 30 and < 60 mL/min, patients will receive 1 g cefepime/0.5 g nacubactam or 1 g aztreonam/0.5 g nacubactam or 0.5 g imipenem/0.5 g cilastatin every 8 hours. If CrCl is ≥ 60 and < 90 mL/min, patients will receive 2 g cefepime/1 g nacubactam or 2 g aztreonam/1 g nacubactam or 0.75 g imipenem/0.75 g cilastatin every 8 hours. If CrCl is ≥ 90 and ≤ 240 mL/min, patients will receive 2 g cefepime/1 g nacubactam or 2 g aztreonam/1 g nacubactam or 1 g imipenem/1 g cilastatin every 8 hours. Dosage of nacubactam, cefepime, and aztreonam, and imipenem/cilastatin according to renal function are shown in Table S1.

Table S1. Study Drug Dosage According to Renal Function

CrCl (mL/minute)	Cefepime or Aztreonam (g)	Nacubactam (g)	Imipenem/Cilastatin (g)	Interval (hour)
≥ 90 and ≤ 240	2	1	1/1	8
≥ 60 and < 90	2	1	0.75/0.75	8
≥ 30 and < 60	1	0.5	0.5/0.5	8
CrCl = creatinine clearance.				

For patients with moderate renal impairment at baseline whose CrCl drops below 30 mL/min after baseline, serum creatinine should be repeated to confirm the initial result and estimate CrCl. Patients may need to be discontinued from the study, according to the Investigator's judgment or when the patient's safety is at risk.

CrCl will be calculated based on the Cockcroft-Gault formula:

- Male: Creatinine clearance mL/min = (140 – age) × weight (kg) / (72 × serum creatinine [mg/dL]); and
- Female: Creatinine clearance mL/min = 0.85 × ([140 – age] × weight [kg] / [72 × serum creatinine (mg/dL)]).

EFFICACY ENDPOINTS:

The primary efficacy endpoint is the proportion of patients who achieve composite clinical and microbiological success at TOC in the Microbiological Modified Intent-to-Treat (m-MITT) Population. Composite clinical and microbiological success is defined as the composite clinical outcome of cure and the microbiological outcome of eradication.

Secondary efficacy endpoints for cUTI and AP

The secondary efficacy endpoints for cUTI and AP include the following:

- The proportion of patients with composite clinical and microbiological success at TOC in the Clinically Evaluable (CE) and Microbiologically Evaluable (ME) Populations;
- The proportion of patients with composite clinical and microbiological success at Early Assessment (EA), EOT, and FUP in the m-MITT Population;
- The proportion of patients with a microbiological outcome of eradication at EA, EOT, TOC, and FUP in the m-MITT Population and at TOC in the ME Population;
- The proportion of patients with a clinical outcome of cure at EA, EOT, TOC, and FUP in the m-MITT Population and at TOC in the CE and ME Populations;
- The proportion of patients with a clinical outcome of cure at EA, EOT, TOC, and FUP in the m-MITT Population and at TOC in the CE and ME Populations and microbiological outcome of eradication at EA, EOT, TOC, and FUP in the m-MITT Population and at TOC in the ME Population per type of pathogen, type of resistance, and antimicrobial susceptibility; and
- The proportion of patients with composite clinical outcome of recurrence and/or microbiological outcome of recurrence at the FUP in the m-MITT, CE, and ME population.

Secondary efficacy endpoints for secondary bacteremia

Patients with cUTI/AP who meet the following conditions will be determined programmatically as secondary bacteremia:

- Isolation of a Gram-negative bacteria from at least 1 blood culture at baseline AND this isolated pathogen is also identified from the site of infection; AND
- At least 1 of the following within 24 hours prior to the first dose of study drug:
  a. Fever (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]) OR hypothermia (rectal/core temperature < 35°C [< 95°F]);
  b. Elevated peripheral white blood cell (WBC) count (> 10,000/mm^3);
  c. > 15% immature polymorphonuclear neutrophils (bands) regardless of peripheral WBC count;
  d. Leukopenia (WBC < 4,500/mm^3);
  e. Tachycardia > 100 bpm;
  f. Tachypnea > 20 breaths/min;
  g. Hypotension, systolic < 90 mmHg; or
  h. C-reactive protein > 20 mg/dL.

Clinical outcome of cure from secondary bacteremia is defined as complete resolution or significant improvement of the baseline signs and symptoms of secondary bacteremia.

The secondary efficacy endpoints for secondary bacteremia include the following:

- The proportion of patients with composite clinical and microbiological success of cUTI or AP at TOC in the m-MITT, CE, and ME Populations;
- The proportion of patients with a clinical outcome of cure from cUTI or AP at TOC in the m-MITT, CE, and ME Populations;
- The proportion of patients with a microbiological outcome of eradication from cUTI or AP at TOC in the m-MITT and ME Populations;
- The proportion of patients with a clinical outcome of cure from secondary bacteremia at TOC in the m-MITT, CE, and ME Populations;
- The proportion of patients with a microbiological outcome of eradication from secondary bacteremia at TOC in the m-MITT and ME Populations;
- The proportion of patients in the m-MITT and ME Populations free from the definition of secondary bacteremia AND a clinical outcome of cure from cUTI or AP AND a microbiological outcome of eradication from cUTI or AP at TOC; and
- The proportion of patients who are free from secondary bacteremia at TOC in the m-MITT and ME Populations.

The exploratory efficacy endpoints include the following:

- Clinical response at EA, EOT, TOC, and FUP, as defined by the following parameters:
  a. Signs and symptoms of cUTI; and
  b. Proportion of patients in cure, improvement, failure, recurrence, or indeterminate categories for clinical response.
- Microbiological response at EA, EOT, TOC, and FUP, as defined by the following parameters:
  a. Bacterial load in CFU/mL for cUTI causative pathogens in urine; and
  b. Proportion of patients in eradication, persistence, recurrence, or indeterminate categories for microbiological response.

CLINICAL OUTCOME:

cUTI/AP

Assessment of clinical outcome will be completed at EA, EOT, TOC, FUP, and ET. The Investigator will assign a clinical outcome as defined in Table S2.

Table S2. Clinical Outcome Criteria

Category	Criteria
Cure	The complete resolution (or return to premorbid state) of the baseline signs and symptoms of cUTI or AP that were present at Screening (and no new urinary symptoms or worsening of symptoms consistent with the specific baseline condition), such that no further antimicrobial therapy is warranted. Symptom resolution does not necessarily include pre-infection baseline symptoms associated with the patient's pre-study condition (eg, anatomic abnormalities that predispose to cUTI, such as symptoms associated with the presence of an indwelling urinary catheter). **This outcome category can be used at EA, EOT, TOC, FUP, and ET.**
Improvement	Lessening, incomplete resolution, or no worsening of baseline clinical signs and symptoms, but continued IV therapy for management is warranted. **This outcome category can only be used at EA.**
Failure	Patients who experience any 1 of the following: • At EA and EOT, worsening of baseline clinical signs and symptoms or the development of new clinical signs and symptoms of infection, sufficient to stop study drug and initiate non-study antimicrobial; • At TOC and FUP, persistence or incomplete resolution of baseline clinical signs and symptoms of infection, requiring additional antibiotic therapy; • At any visit until TOC, a change in the patient's baseline Gram-negative antimicrobial therapy to treat the baseline infection (other than dose adjustment) after randomization; • Withdrawal from the study due to an AE or due to lack of clinical improvement; or • Death of the patient during the study. **This outcome category can be used at EA, EOT, TOC, FUP, and ET.**
Recurrence	Baseline signs and symptoms were present at FUP after a response of cure. **This outcome category can only be used at FUP.**
Indeterminate	Clinical outcome cannot be determined. This outcome category can be used at EA, EOT, TOC, FUP, and ET.
AE = adverse event; AP = acute uncomplicated pyelonephritis; cUTI = complicated urinary tract infection; EA = Early Assessment; EOT = End of Treatment; ET = Early Termination; FUP = Follow-Up visit; IV = intravenous(ly); TOC = Test of Cure visit.	

MICROBIOLOGICAL OUTCOME:

The criteria for microbiological outcome are defined in Table S3 and Table S4. Microbiological outcome will be determined programmatically based on the results from the site of infection.

Table S3. Microbiological Outcome Criteria for cUTI or AP

Category	Criteria
Eradication	The baseline qualifying Gram-negative pathogen(s) is reduced to $< 10^3$ CFU/mL in urine culture.
Persistence	Demonstration that 1 or more of the baseline Gram-negative pathogen(s) remains continuously present in urine culture at $\geq 10^3$ CFU/mL.
Recurrence	Isolation of the same baseline Gram-negative pathogen(s) $\geq 10^3$ CFU/mL from urine culture after a response of eradication.
Indeterminate	No urine culture is available, or the culture cannot be interpreted for any reason.
Microbiological outcome will not be evaluated in the following cases: • New pathogen infection – the post-baseline organism is different from the baseline Gram-negative organism but is thought to be a pathogen based on a number of reasons that will be delineated in the protocol (eg, Gram-negative, obtained in multiple cultures); or • Contaminant – the post-baseline organism is different from the baseline Gram-negative organism but is identified as a common skin flora organism and has not been cultured from another site. Note: The qualifying pathogen is defined as a single Gram-negative organism at a concentration $\geq 10^5$ CFU/mL in a non-contaminated urine culture. Note: Presumed eradication is assessed at FUP and categorized as eradication only if the baseline qualifying Gram-negative pathogen(s) is eradicated (reduced to $< 10^3$ CFU/mL) at TOC, and a urine sample cannot be collected but there is a clinical outcome of cure at FUP. Therefore, a urine sample should also be collected at FUP, unless the baseline qualifying Gram-negative pathogen(s) is eradicated (reduced to $< 10^3$ CFU/mL) at TOC. AP = acute uncomplicated pyelonephritis; CFU = colony-forming unit(s); cUTI = complicated urinary tract infection; FUP = Follow-Up visit; TOC = Test of Cure visit.	

Table S4. Microbiological Outcome Criteria for Secondary Bacteremia

Category	Criteria
Eradication	The baseline qualifying Gram-negative pathogen(s) is negative in blood culture. Presumed eradication is defined as eradication.
Persistence	The baseline qualifying Gram-negative pathogen(s) is positive in blood culture.
Recurrence	Isolation of the same Gram-negative pathogen(s) from blood culture after a response of eradication.
Indeterminate	No blood culture is available or the culture cannot be interpreted for any reason.
Microbiological outcome will not be evaluated in the following cases: • New pathogen infection – the post-baseline organism is different from the baseline Gram-negative organism but is thought to be a pathogen based on a number of reasons that will be delineated in the protocol (eg, Gram-negative, obtained in multiple cultures); or • Contaminant – the post-baseline organism is different from the baseline Gram-negative organism but is identified as a common skin flora organism and has not been cultured from another site. Note: Presumed eradication is assessed at TOC when the baseline qualifying Gram-negative pathogen(s) is negative for at least 48 hours in subsequent blood cultures taken during the treatment period and there is a clinical outcome of cure at TOC. TOC = Test of Cure visit.	

COMPOSITE CLINICAL AND MICROBIOLOGICAL SUCCESS

The algorithm for composite clinical and microbiological success at EA, EOT, TOC, FUP, and ET is summarized in Table S5.

Table S5. Composite Clinical and Microbiological Success

Clinical Outcome	Microbiological Outcome			
	Eradication	**Persistence**	**Recurrence[1]**	**Indeterminate**
Cure	Success	Failure	Failure	Failure
Failure[2]	Failure	Failure	Failure	Failure
Indeterminate	Clinical outcome for the last visit before EA, EOT, TOC, FUP, or ET = failure; otherwise = indeterminate	Failure	Failure	Clinical outcome for the last visit before EA, EOT, TOC, FUP, or ET = failure; otherwise = indeterminate

1. For an outcome of recurrence, patients must have documented prior eradication at any prior time point.
2. In the assessment of clinical outcome at EA, category of "improvement" is included. In the assessment of clinical outcome at FUP, category of "recurrence" is included.

EA = Early Assessment; EOT = End of Treatment; ET = Early Termination; FUP = Follow-Up visit; TOC = Test of Cure visit.

PHARMACOKINETIC ASSESSMENTS:

Blood samples for PK analysis will be collected from all patients. All patients will be assigned to either a multiple PK sampling or a sparse PK sampling group at the discretion of the Investigator.

Infusion start and end times, as well as PK sampling times, will be recorded in the source documents. The method of PK sample handling is detailed in the Laboratory Manual provided by the Sponsor.

In the case of multiple sampling, the PK plasma samples will be used to estimate PK parameters of nacubactam, cefepime, and aztreonam such as area under the plasma concentration-time curve, maximum observed plasma concentration, time to reach maximum observed plasma concentration, total drug clearance, terminal elimination half-life, minimum observed plasma concentration, and predicted steady-state volume of distribution using a non-compartmental model. PK parameters will be summarized using appropriate descriptive statistics.

Scatter plots of plasma concentrations of nacubactam, cefepime, and aztreonam from multiple sampling and sparse sampling will be drawn, respectively.

PK characterization and evaluation of plasma exposures of nacubactam, cefepime, and aztreonam will be performed using plasma concentrations from all patients in the cefepime/nacubactam and aztreonam/nacubactam treatment groups by means of population PK (PPK) modeling methods. PK/pharmacodynamic (PD) analysis will be performed by analyzing the relationship between individual PK/PD parameters and individual clinical/biological efficacy data, and PPK analysis and PK/PD analysis will be conducted independently of this protocol and the results of both analyses will be reported independently of the Clinical Study Report for this study.

The PK samples will be collected from all treatment groups to maintain the blind. Only PK samples obtained from the cefepime/nacubactam and aztreonam/nacubactam groups will be analyzed (using a validated assay) by the bioanalytical laboratory. While the PK analyses will be ongoing during the study, the Sponsor and all study personnel will remain blinded to the results (see Section 5.3.2).

Multiple PK sampling

In the case the patient is assigned to multiple sampling, samples will be collected on Day 1 after the first infusion of the day:

- At the end of the infusion (± 5 minutes); and
- At 2, 4, 6, and 8 hours (± 10 minutes) after the start of the study drug infusion. The sample will be collected prior to the start of the next infusion.

Note: At least 4 time points, including 1 hour after the start of the study drug infusion (first infusion on that day) on Day 1, are needed.

If multiple PK sampling cannot be conducted on Day 1, it should be conducted on Day 3 or Day 5 instead. If sampling occurs on Day 3 or Day 5, samples can be collected after any of the 3 infusions on that day.

Table S6 provides the sampling times for multiple PK assessments.

Table S6. Sampling Times for Multiple PK Assessments

Multiple PK Sampling Time (Time Allowance)	Day 1 (Post-Randomization)[1]	Day 3	Day 5
End of infusion (± 5 minutes)	X	(X)	(X)
2 hours (± 10 minutes) after the start of infusion	X	(X)	(X)
4 hours (± 10 minutes) after the start of infusion	X	(X)	(X)
6 hours (± 10 minutes) after the start of infusion	X	(X)	(X)
8 hours (± 10 minutes) after the start of infusion[2]	X	(X)	(X)
(X) denotes samples that are only to be performed on Day 3 or Day 5 if multiple sampling could not be conducted on Day 1. If sampling occurs on Day 3 or Day 5, samples can be collected after any of the 3 infusions on that day. 1. The PK sample should be taken after the first infusion of that day. 2. Sample should be collected prior to the start of the next infusion. Note: At least 4 time points, including 1 hour after the start of the study drug infusion (first infusion on that day) on Day 1, are needed. PK = pharmacokinetic(s).			

Sparse PK sampling

In the case the patient is assigned to sparse sampling, samples will be collected on Day 1, Day 3, or Day 5, after any of the 3 infusions on that day:

- Around the end of the infusion;
- Around 2 to 4 hours after the start of the study drug infusion; and
- Around 4 to 8 hours after the start of the study drug infusion. The sample will be collected prior to the start of the next infusion.

Note: At least 2 time points after the start of the study drug infusion (for any of the 3 infusions on that day) on Day 1, Day 3, or Day 5 are needed.

Table S7 provides the sampling times for sparse PK assessments.

Table S7. Sampling Times for Sparse PK Assessments

Sparse PK Sampling Time	Day 1 (Post-Randomization)[1]	Day 3[1]	Day 5[1]
Around the end of infusion	X	(X)	(X)
Around 2 to 4 hours after the start of infusion	X	(X)	(X)
Around 4 to 8 hours after the start of infusion[2]	X	(X)	(X)

(X) denotes samples that are only to be performed on Day 3 or Day 5 if sparse sampling could not be conducted on Day 1.
1. The PK sample should be taken after any of the 3 infusions of that day.
2. Sample should be collected prior to the start of the next infusion.
Note: At least 2 time points after the start of the study drug infusion (for any of the 3 infusions on that day) on Day 1, Day 3, or Day 5 are needed.
PK = pharmacokinetic(s).

OTHER ASSESSMENTS:

The exploratory variables for this study are the minimum inhibitory concentrations (MIC) for cefepime/nacubactam, aztreonam/nacubactam, and nacubactam for causative uropathogens.

Bacterial whole genome sequencing analysis, or other appropriate methods, may be conducted from purified cultures of bacterial isolates to explore type of resistance.

MICROBIOLOGY ASSESSMENTS:

Urine culture

Urine samples will be obtained at Screening, prior to the first dose of study drug on Day 1, EA, EOT, TOC, FUP (if clinically indicated), and ET.

Urine samples for microbiological testing will be collected by clean-catch midstream, intermittent urethral catheter (straight catheterization using sterile technique), a newly inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, suprapubic catheter, nephrostomy tube, or ureter aspiration.

A urine sample taken within 48 hours prior to the first dose of study drug can be used for screening and baseline microbiologic assessments if the organism(s) isolated from cultures is available to be sent to the central laboratory for analysis. However, all patients who had a urine sample not taken by the method specified in the protocol must have a repeat urine sample culture obtained prior to the start of study drug administration. This sample should be taken as close to randomization as possible (within 2 hours prior to the first dose of study drug, if possible). A repeat urine sample must be obtained prior to the start of study drug for any patients enrolled after receiving a single dose of a short-acting antibiotic or patients who failed preceding antimicrobial therapy. The sample should be collected as close to randomization as possible (within 2 hours prior to the first dose of study drug, if possible).

Up to 2 Gram-negative bacterial isolates per urine culture (at concentrations of $\geq 10^5$ CFU/mL of urine) will be considered as qualifying pathogens. If a patient grows ≥ 3 bacterial organisms $\geq 10^5$ CFU/mL in the urine, the urine culture will be considered contaminated. An organism will not be considered a contaminant if the organism grows $\geq 10^5$ CFU/mL in a urine culture and also grows in a concurrently obtained blood culture.

Prior to the first dose of study drug, urine samples submitted for culture must have a urinalysis/dipstick and microscopic analysis performed at the local laboratory. Gram staining (or other possible testings) should be performed if available.

At each sampling point, the local laboratory will culture each urine sample for organism identification, quantification, and susceptibility testing (only at Screening).

Imipenem and meropenem susceptible pathogen is defined as a Gram-negative pathogen by susceptibility data of minimum inhibitory concentration (MIC) less than 2 μg/mL to imipenem and meropenem OR imipenem and meropenem disk diffusion (zone diameter ≥ 22 mm). If MIC

or disk diffusion data are not available in the local laboratory or before the availability of MIC or disk diffusion results, each site can use other susceptibility testings and criteria in the institution as the initial evidence of imipenem and meropenem susceptible pathogen for enrollment. In any case, pathogen identification and susceptibility testing performed at the central laboratory will be used to determine imipenem and meropenem susceptible pathogen in the final study analysis.

Prior to the first dose of study drug, only organisms at concentrations of $\geq 10^5$ CFU/mL of urine and not deemed to be a contaminant as detailed in the Microbiology Laboratory Manual will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing; if the same organism grows in urine (at concentrations of $\geq 10^5$ CFU/mL) and blood, these organisms should be sent to the central laboratory.

For all post-baseline urine cultures, only organisms at concentrations of $\geq 10^3$ CFU/mL of urine and not deemed to be a contaminant as detailed in the Microbiology Laboratory Manual will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing.

If a patient's baseline urine culture is negative at the time a negative culture is confirmed but the patient is improving, the Investigator can keep the patient on treatment. If the baseline urine culture is negative at the time a negative culture is confirmed and the patient is not improving, study treatment will be stopped, and the patient will be followed for safety assessments approximately 7 to 14 days after ET.

Qualifying pathogen

A qualifying pathogen is defined as a single Gram-negative organism at a concentration $\geq 10^5$ CFU/mL in a non-contaminated urine culture. If a culture grows ≥ 3 bacterial organisms $\geq 10^5$ CFU/mL in the urine, the urine culture will be considered contaminated. A Gram-negative organism will not be considered a contaminant if the organism grows $\geq 10^5$ CFU/mL in a urine culture and also grows in a concurrently obtained blood culture.

The list of Gram-negative uropathogens that may be considered causative in cUTI or AP is included in Table S8. Organisms identified during the study that are not listed in Table S8 as uropathogens or as contaminants in the Microbiology Laboratory Manual will be assessed on a case-by-case basis.

Table S8. Potential Uropathogens

Potential Gram-Negative Uropathogens	
Citrobacter freundii	*Citrobacter koseri*
Enterobacter cloacae	*Escherichia coli*
Klebsiella aerogenes	*Klebsiella oxytoca*
Klebsiella pneumoniae	*Morganella morganii*
Proteus mirabilis	*Proteus vulgaris*
Providencia rettgeri	*Providencia stuartii*
Pseudomonas aeruginosa	*Serratia marcescens*

Blood culture

Two sets of blood culture samples from 2 separate venipuncture sites will be obtained at Screening and prior to the first dose of study drug on Day 1 for baseline blood cultures (duplicate assessments do not need to be performed if Screening and Day 1 occur on the same day or within 24 hours). The blood culture should be obtained within the allowed Screening Period and within 48 hours

prior to the first dose of study drug to align with the requirement to have a urine sample taken within 48 hours.

Each set of blood culture samples will include 1 aerobic and 1 anaerobic bottle (an additional aerobic bottle is allowed if anaerobic culture is not standard practice at the site). However, for cUTI and AP, a single aerobic blood culture is sufficient if it is not the institution's standard of care to obtain an anerobic culture. If a blood culture is positive at baseline for an organism obtained in a concurrently collected urine sample, blood cultures will be collected until the baseline qualifying Gram-negative pathogen(s) is negative for at least 48 hours in subsequent blood cultures. Additional blood cultures will be collected at the Investigator's discretion. In that case, 2 sets of blood culture samples from 2 separate venipuncture sites will be obtained. The frequency of repeating those blood cultures should be at the discretion of the Investigator, but there must be documentation of a negative blood culture 48 hours after any baseline blood culture or after any subsequent blood culture is found to be positive. For patients with fever spikes (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]) during the study, additional blood samples may be obtained at the time of the fever spike. Specimens will be sent to the local laboratory for culture identification and susceptibility testing (only at Screening). All isolates from blood culture will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing as outlined in the Microbiology Laboratory Manual.

SAFETY ASSESSMENTS:

The safety parameters include the incidence, severity, causality, and seriousness of TEAEs and the evaluation of changes from baseline in safety laboratory test results, 12-lead ECGs, vital signs, and physical examinations.

STATISTICAL ANALYSES:

Intent-to-Treat (ITT) Population: All patients who are randomized.

Modified Intent-to-Treat (MITT) Population: All patients who meet ITT criteria and receive any amount of study drug.

m-MITT Population: All randomized patients who meet MITT criteria and who have a baseline qualifying pathogen that susceptible to imipenem and meropenem (see Section 7.1.3.1 for the definition of a qualifying pathogen). The definition of imipenem and meropenem susceptible pathogen is described in Inclusion Criterion #5.

CE Population: All patients who meet the definition for the MITT Population and who meet the following important components of the study as specified in the protocol:

- Receive at least 80% of the intended doses of randomized study drug treatment;
- Have a clinical assessment at TOC, unless criteria for clinical failure were met at an earlier timepoint;

- Did not receive concomitant antibacterial treatment with a non-study antibacterial drug to which the uropathogen was susceptible between the time of the baseline culture and the TOC culture, unless criteria for clinical failure were met; and
- Do not have any other major protocol violations that would affect assessment of efficacy.

ME Population: Patients who meet the definition for both the m-MITT and CE Populations. In addition, to be included in the ME Population, patients must not have a microbiological outcome at TOC of Indeterminate. However, any interpretable positive urine culture obtained from EOT through TOC will be carried forward to TOC.

Safety Population: All patients who receive at least 1 dose of study drug during the study.

PK Population: All patients in the Safety Population who have at least 1 analyzable PK sample.

Analysis of Efficacy

The statistical and analytical plans presented below are an overview of key analysis methods. Details of the analysis will be specified in the Statistical Analysis Plan (SAP).

The primary efficacy endpoint is the proportion of patients who achieve complete composite clinical and microbiological success at TOC in the m-MITT Population. The non-inferiority hypothesis test is a 1-sided hypothesis test performed at the 2.5% level of significance. This is based on the lower limit of the 2-sided 95% confidence intervals (CIs) for the observed difference in the proportion of patients with composite clinical and microbiological success (cefepime/nacubactam group minus imipenem/cilastatin group) at the TOC. Patients with missing data will be included in the denominator for the calculation of success rate. Thus, patients with missing data will be considered as failures for the analysis. The primary analysis is based on a CI computed using the Miettinen and Nurminen method. If the lower limit of the 2-sided 95% CI for the difference between treatment groups at TOC in the m-MITT Population is > -15.0%, the null hypotheses will be rejected and non-inferiority will be concluded based on the primary efficacy endpoint.

If non-inferiority is declared for the primary efficacy endpoint, a test for superiority will be performed using a hierarchical gatekeeping approach for overall control of the Type 1 error. For this analysis, if the lower bound of the 95% CI for the treatment difference in treatment success at TOC in the m-MITT Population is > 0.0%, superiority will be declared.

Furthermore, if non-inferiority of the cefepime/nacubactam group is declared for the primary efficacy endpoint, the non-inferiority hypothesis test for the aztreonam/nacubactam group will be performed using a hierarchical gatekeeping approach for overall control of the Type 1 error. For this analysis, and for the treatment difference (aztreonam/nacubactam group minus imipenem/cilastatin group) in treatment success at TOC, the same approach as in the cefepime/nacubactam group will be used.

For the secondary efficacy endpoints, the number and percentage of patients with each response will be summarized by treatment group. The 2-sided 95% CI for the difference between treatment groups in the proportion of patients with favorable response will be presented using the same approach as for the primary analyses.

Plasma nacubactam, cefepime, and aztreonam concentrations and PK parameters obtained by analyzing plasma concentrations of nacubactam, cefepime, and aztreonam from multiple sampling

groups using non-compartmental analysis methods will be summarized using the appropriate descriptive statistics, which will be fully outlined in the SAP.

PPK analyses will be performed using nacubactam, cefepime, and aztreonam plasma concentrations from all patients in the cefepime/nacubactam and aztreonam/nacubactam treatment groups. PK/PD analyses will be performed by analyzing the relationship between individual estimated PK/PD parameters and individual efficacy data. The results of both analyses will be reported independently of the Clinical Study Report for this study.

Analysis of Safety

Safety analyses will be performed on all patients in the Safety Population. Analyses will be based on TEAEs, vital signs, clinical laboratory assessments, physical examination findings, and 12-lead ECGs. Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

SAMPLE SIZE DETERMINATION:

Using a 15% non-inferiority margin, 1-sided alpha of 0.025, 80% power, a composite clinical and microbiological success rate of 70% in each treatment group (cefepime/nacubactam, imipenem/cilastatin) at TOC, and a 2:1 allocation ratio, a total of 330 patients are required in the m-MITT Population. In addition, 110 patients will be required in the m-MITT Population for the aztreonam/nacubactam group, the same as the imipenem/cilastatin group, in order to evaluate efficacy and safety of the aztreonam/nacubactam group. Assuming 75% of patients will be evaluable for the m-MITT Population, a total of approximately 600 patients will be randomized using a 2:1:1 allocation ratio (300 patients in the cefepime/nacubactam group, 150 patients in the aztreonam/nacubactam group, and 150 patients in the imipenem/cilastatin group). A review of the overall percentage of patients in the m-MITT Population will be conducted after approximately 60% of patients are randomized. Based on this assessment, the sample size may be adjusted to ensure the study remains sufficiently powered.

SITES: Approximately 90 sites in Europe and Asia Pacific

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AP	Acute uncomplicated pyelonephritis
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time 0 to infinity
AUC_{0-8}	Area under the plasma concentration-time curve from time 0 to 8 hours
BLI	β-lactamase inhibitor
CE	Clinically Evaluable
CFR	Code of Federal Regulations
CFU	Colony-forming unit(s)
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration
COVID-19	Coronavirus Disease 2019
CRA	Clinical research associate
CrCl	Creatinine clearance
CTA	Clinical trial authorisation
cUTI	Complicated urinary tract infection
DSMB	Data Safety Monitoring Board
EA	Early Assessment
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure In Utero
ELF	Epithelial lining fluid
EOT	End of Treatment
ESBL	Extended-spectrum β-lactamase
ET	Early Termination
EU	European Union
FSH	Follicle-stimulating hormone
FUP	Follow-Up visit
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GLP	Good Laboratory Practice

Abbreviation	Definition
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	Intravenous(ly)
KPC	*Klebsiella pneumoniae* carbapenemase
LPLO	Last patient last observation
MBL	Metallo-β-lactamase
ME	Microbiologically Evaluable
MIC	Minimum inhibitory concentration
MIC_{50}	Minimum inhibitory concentration required to inhibit growth of 50% of organisms
MIC_{90}	Minimum inhibitory concentration required to inhibit growth of 90% of organisms
MITT	Modified Intent-to-Treat
m-MITT	Microbiological Modified Intent-to-Treat
NIMP	Non-investigational medicinal product
OXA	Oxacillinase
PBP2	Penicillin-binding protein 2
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PPK	Population pharmacokinetics
PTA	Probability of target attainment
QTc	Heart-rate-corrected QT interval
QTcF	Heart-rate-corrected QT interval by the Fridericia formula
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
spp.	Species
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
TID	Three times a day
TOC	Test of Cure visit
ULN	Upper limit of normal

Abbreviation	Definition
UTI	Urinary tract infection
WBC	White blood cell

1 INTRODUCTION AND BACKGROUND INFORMATION

Urinary tract infections (UTIs) are a major cause of hospital admissions and are associated with significant morbidity and mortality, as well as a high economic burden. The majority of UTIs are those acquired in the community setting (57.4%), whereas 35.6% are healthcare associated and 7% are nosocomial. UTIs can be classified according to the anatomic site of infection, such as cystitis or pyelonephritis, and are further classified into complicated or uncomplicated, irrespective of the site and severity of the infection. Complicated UTIs (cUTIs) occur in subjects with anatomic or functional abnormalities of the urinary tract or in those with significant medical or surgical comorbidities. The microbiology of cUTI is characterized by greater variety of organisms and an increased likelihood of antimicrobial resistance as compared with uncomplicated UTIs.

The most common causative bacteria in cUTI are Gram-negative bacteria including *Escherichia coli*, *Klebsiella* species (spp.), *Proteus* spp., *Enterobacter cloacae*, *Serratia marcescens,* and *Pseudomonas aeruginosa*. A variety of therapeutic drugs for bacterial infections are available, but β-lactam antibiotics such as penicillins are the most important group among therapeutic drugs in terms of efficacy and safety. In particular, carbapenems could be important as they can also be indicated for intractable infections, and the emergence of resistant bacteria to them is a very serious problem. The mechanisms by which pathogenic bacteria acquire resistance to β-lactam antibiotics vary, but the most important and general one is the inactivation (degradation) of the drug by the production of β-lactamase. Currently, it is said there are over 2,000 species of β-lactamases, which are classified into Class A to D. Extended-spectrum β-lactamase (ESBL) and AmpC enzyme, which degrade third-generation cephalosporins of therapeutic importance, and carbapenemase, which degrades carbapenems, have also been reported. Carbapenemase can be classified in several types, including Class A *Klebsiella pneumoniae* carbapenemase (KPC) type enzyme, Class D oxacillinase (OXA) -48 like enzyme, Class B New Delhi metallo-β-lactamase (MBL) type enzyme, imipenemase type enzyme, and Verona integron-encoded MBL type enzyme as representative enzymes, and resistant bacteria with different enzymatic types have been isolated from region to region.

1.1 Nacubactam

Nacubactam is a novel diazabicyclooctane-type β-lactamase inhibitor (BLI) that was discovered by Meiji Seika Pharma Co., Ltd., and is in clinical development in support of the intended coadministration with either cefepime or aztreonam. Nacubactam, when paired with β-lactams, has been shown to restore or potentiate the efficacy against Ambler Class A, B, C, and D β-lactamase-producing Gram-negative bacteria in a nonclinical setting. Nacubactam has been shown to have a dual mode of action: (i) as an inhibitor of serine β-lactamases (Classes A and C and some Class D), resulting in protection of the partner β-lactam, and (ii) as an inhibitor of penicillin-binding protein 2 (PBP2) of Enterobacterales, resulting in antibacterial activity and ‘enhancing’ the activity of β-lactam agents. When administered in combination with a β-lactam (cefepime or aztreonam), nacubactam therefore has the potential to treat infections caused by carbapenem-resistant Enterobacterales, including MBL -producing bacteria, which represents an area of significant unmet medical need.

1.2 Nonclinical Studies

Please refer to the current Investigator’s Brochure (IB) for detailed information regarding nonclinical studies.

1.2.1 Microbiology

β-lactams (cefepime or aztreonam) in combination with nacubactam showed potent activity against Enterobacterales, including β-lactamase-producing isolates. Nacubactam potentiated cefepime or aztreonam activity against *Pseudomonas aeruginosa* with depressed AmpC or acquired ESBL, but not against isolates producing MBL. In case of *Acinetobacter baumannii*, nacubactam achieved no significant potentiation of aztreonam or cefepime against OXA or MBL positive isolates. In addition, nacubactam did not show the combination effect with cefepime or aztreonam against Gram-positive pathogens.

Antimicrobial activities of β-lactam alone and in combination with nacubactam were investigated against 1,722 Enterobacterales, 203 *P. aeruginosa*, and 102 *Acinetobacter* spp. (Table 1). These randomly selected isolates were collected globally and mainly in 2018 (94.1%). Against all the Enterobacterales tested, the minimum inhibitory concentration (MIC) required to inhibit growth of 50% of organisms (MIC_{50}) of β-lactam/nacubactam (1:1) was generally similar to that of β-lactam alone but the MIC required to inhibit growth of 90% of organisms (MIC_{90}) of the combination was greatly improved compared with β-lactam alone against Enterobacterales, reflecting the likelihood that many of these organisms produce various β-lactamases. Against the non-fermenter bacteria, the β-lactam/nacubactam (1:1) combination lowered the MIC_{50} and MIC_{90} by 2-fold at most, compared with β-lactam alone.

Table 1. Antimicrobial Activity of Cefepime/Nacubactam and Aztreonam/Nacubactam in a 1:1 Ratio Against 2027 Randomly Selected Enterobacterales and Non-Fermenting Species

Organism	Number of Isolates	MIC (mg/L)									
		Cefepime		Cefepime/Nacubactam[1]		Aztreonam		Aztreonam/Nacubactam[1]		Imipenem	
		MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Enterobacterales	1722	0.06	32	0.06	0.5	0.12	> 32	0.06	1	≤0.12	1
Asia-Pacific	686	0.06	16	0.03	0.25	0.06	32	0.06	0.5	≤0.12	1
Europe	690	0.06	> 32	0.06	0.5	0.12	> 32	0.06	1	≤0.12	1
Other regions[2]	346	0.06	32	0.06	0.5	0.12	> 32	0.06	1	≤0.12	1
Pseudomonas aeruginosa	203	2	16	2	8	8	32	8	16	1	>8
Acinetobacter spp.	102	32	> 64	16	64	64	> 64	32	> 64	>8	>8

1. The combinatorial concentration of nacubactam in combination with β-lactam agent was a fixed ratio of 1:1.
2. North America and Latin America

MIC = minimum inhibitory concentration; MIC_{50} = minimum inhibitory concentration required to inhibit growth of 50% of organisms; MIC_{90} = minimum inhibitory concentration required to inhibit growth of 90% of organisms; spp. = species.

1.2.2 Toxicology and Safety Pharmacology

The pivotal toxicology and safety pharmacology studies intended to support safety claims were conducted in accordance with Organisation for Economic Co-operation and Development Principles of Good Laboratory Practice (GLP). Additional supportive toxicological studies were conducted as scientifically carefully conducted non-GLP studies.

Rats and cynomolgus monkeys were chosen for nonclinical in vivo safety studies; initial, exploratory safety studies were also conducted in dogs. Repeat-dose toxicity studies of up to 28 days in rats and cynomolgus monkeys have been completed. Nacubactam was well tolerated in single-dose and repeat-dose toxicity studies in rats and cynomolgus monkeys. There was no overt toxicity up to the maximum feasible doses tested with once daily intravenous (IV) administration up to 4 weeks. The no observed-adverse-effect-level was set at the maximum doses tested (1,000 mg/kg/day in rats and 500 mg/kg/day in cynomolgus monkeys). Nacubactam was also tested in combination with cefepime or aztreonam in 28 day-repeat IV dose combination studies in rats. There was no exacerbation of toxicity derived from each test substance or new toxicity observed.

The genotoxicity, reproductive and developmental toxicity (fertility and early embryonic development to implantation and embryo-fetal development), antigenicity, and phototoxicity were investigated, and none identified findings of concern.

1.3 Clinical Pharmacology Studies

Table 2 provides an overview of completed clinical pharmacology studies.

Table 2. Overview of Clinical Pharmacology Studies

Study No. (Country)	Objectives	No. of Subjects	Dose of Nacubactam	Concomitant Drug	Administration	Population
OP0595-1 (Australia)	Safety, tolerability, and PK	40	0.05, 0.15, 0.5, 1, and 2 g and placebo	-	Single dose	Healthy male volunteers
OP0595-2 (Japan)	Safety, tolerability, and PK	20	1 and 2 g and placebo	-	Single dose and repeated administration	Healthy male volunteers
		8	4 g and placebo	-	Single dose	
OP0595-3 (Japan)	Safety, tolerability, and PK	8	2 g	Cefepime 2 g	Single dose	Healthy male volunteers
		8		Aztreonam 2 g		
		8		Meropenem 2 g		
		8		Piperacillin 4 g		
OP0595-4 (Japan)	Safety, tolerability, and PK	8	2 g and placebo	Cefepime 2 g	Repeated administration	Healthy male volunteers
		8		Aztreonam 2 g		
NP30052 (United States)	Safety, tolerability, and PK	16	1 and 2 g and placebo	-	Repeated administration	Healthy male and female volunteers
		15	4 g and placebo	-	Single dose and repeated administration	
			8 g and placebo		Single dose	
		15	2 g and placebo	Meropenem 2 g	Single dose and repeated administration	
NP39380 (United States)	PK parameters of nacubactam in patients with renal impairment and ESRD	29	1 g	-	Single dose	Patients with renal impairment
NP39596 (Latvia, Serbia, Poland, and United States)	PK variability in patients with cUTI	20	2 g	Meropenem 2 g	Repeated administration	Patients with a cUTI
NP39750 (United States)	Characterization of intrapulmonary penetration	21	2 g	Meropenem 2 g	Single dose	Healthy male and female volunteers

cUTI = complicated urinary tract infection; No. = number; PK = pharmacokinetic(s); ESRD = end-stage renal disease.

1.3.1 Study OP0595-1 (Australia)

Following a 30-minute IV infusion, the nacubactam plasma profile peaked at 30 minutes post-infusion followed by a decrease in plasma levels. Apparent terminal elimination half-life ($t_{½}$) for nacubactam was 1.8 hours (nacubactam 0.15 g group) to 2.4 hours (nacubactam 2 g group). The maximum observed plasma concentration (C_{max}) ranged from 2.7 µg/mL (nacubactam 0.05 g group) to 112.2 µg/mL (nacubactam 2 g group). Area under the plasma concentration-time curve (AUC) from time 0 to infinity ($AUC_{0-\infty}$) ranged from 5.2 µg·hr/mL (nacubactam 0.05 g group) to 229.2 µg·hr/mL (nacubactam 2 g group). C_{max} and $AUC_{0-\infty}$ increased dose-dependently.

Treatment-emergent adverse events (TEAEs) were reported in 30% of subjects (12 of 40 subjects). The incidence of TEAEs was 33.3% (2 of 6 subjects) in the nacubactam 0.05, 0.5, and 1 g groups,

respectively, 16.7% (1 of 6 subjects) in the nacubactam 0.15 g and 2 g groups, respectively, and 40.0% (4 of 10 subjects) in the placebo group. All TEAEs recovered on or before Day 14.

The most frequently reported TEAE was headache. Events considered possibly related to the investigational product were headache reported in 3 subjects. All other TEAEs were considered to be not related or unlikely related to the investigational product.

There were no serious adverse events (SAEs) or deaths reported and no subjects were withdrawn from the study due to a TEAE. No clinically important abnormal findings or changes were reported in vital signs, electrocardiograms (ECGs), physical findings, or laboratory parameters, such as blood chemistry and urinalysis, including items affected by renal function such as N-acetyl-β-d-glucosaminidase and β2-microglobulin.

1.3.2 Study OP0595-2 (Japan)

The C_{max} and $AUC_{0-\infty}$ of plasma nacubactam increased with increasing dosage after single IV administration (90-minute IV infusion) of nacubactam 1, 2, or 4 g, and dose proportionality was confirmed. The C_{max} and $AUC_{0-\infty}$ of plasma nacubactam also increased with increasing dosage after multiple IV administrations (over 90-minute IV infusion) of nacubactam 1 or 2 g three times a day (TID) for 7 days. The minimum observed plasma concentration (C_{min}) values on Day 4 (the second day of multiple administrations) and later were almost constant, and values of C_{max} and $AUC_{0-\infty}$ on Day 9 (the seventh day of multiple administration) were almost the same as those in the single administration, and it was considered that nacubactam reached its steady state promptly after the start of administration with little accumulation.

In addition, almost all of nacubactam was excreted in the urine in the unchanged form by 24 hours after the single administration of nacubactam (Day 1) and on the seventh day of multiple administrations (Day 9), and nacubactam was considered to be a type of drug with renal excretion.

Regarding the safety of nacubactam after single and multiple administrations, no safety issue was reported, as there were no SAEs, and the grade of adverse events (AEs) developed were mild, recovered without treatment, or the causal relationship with the investigational drug was judged to be not related.

The effect of nacubactam administration on the QT/QTc interval was investigated, and prolongation of the QT/QTc interval associated with the increase in the plasma nacubactam concentration was not reported.

1.3.3 Study OP0595-3 (Japan)

When a single dose of nacubactam 2 g with concomitant administration of each concomitant drug (cefepime 2 g, aztreonam 2 g, meropenem 2 g, and piperacillin 4 g) was administered IV over a period of 60 minutes to Japanese healthy adult males, the plasma concentrations of nacubactam were similar to those after administration of nacubactam alone. The urinary excretion rate of nacubactam did not change with concomitant drug administration. Based on these findings, it was confirmed that administration of nacubactam with concomitant administration of cefepime, aztreonam, meropenem, or piperacillin did not affect the pharmacokinetics (PK) of nacubactam.

When nacubactam was concomitantly administered, plasma concentrations of cefepime, aztreonam, meropenem, or piperacillin were similar to those of administration of each concomitant drug alone. The urinary excretion rate of each concomitant drug did not change with the

administration of nacubactam. Based on these findings, it was confirmed that administration of each concomitant drug with concomitant administration of nacubactam did not affect the PK of cefepime, aztreonam, meropenem, and piperacillin.

As a result of investigating the safety of nacubactam and each concomitant drug as single administration, and nacubactam with each concomitant drug as combination administration, no SAEs or TEAEs leading to discontinuation of the investigational product were reported in any treatment conditions. All TEAEs reported were mild in severity, and the subjects recovered without treatment. The causality with the investigational product was judged to be not related. Based on these findings, the safety and tolerability after administration of nacubactam with concomitant administration of cefepime, aztreonam, meropenem, or piperacillin were confirmed.

1.3.4 Study OP0595-4 (Japan)

Multiple IV administration of nacubactam 2 g with cefepime 2 g or aztreonam 2 g TID every 8 hours for 7 days (60-minute IV infusion) in Japanese healthy adult males was conducted to investigate the safety, tolerability, and PK.

Following multiple IV administration of nacubactam with cefepime TID for 7 days (60-minute IV infusion), the geometric mean ratios (Day 7/Day 1) of C_{max}, AUC from time 0 to 8 hours (AUC_{0-8}), and $AUC_{0-\infty}$ for nacubactam and cefepime were all approximately 1.0 (1.0101 to 1.0956), and the changes in exposure of both drugs with multiple concomitant administrations were little.

Following multiple IV administration of nacubactam with aztreonam TID for 7 days (60-minute IV infusion), the geometric mean ratios (Day 7/Day 1) of C_{max}, AUC_{0-8}, and $AUC_{0-\infty}$ for nacubactam and aztreonam were all approximately 1.0 (0.9102 to 1.0250), and the changes in exposure of both drugs with multiple concomitant administration were little.

Plasma concentrations of nacubactam, cefepime, and aztreonam reached the steady-state up to Day 4, and the mean accumulation ratios based on C_{max} and AUC_{0-8} were in the range of 0.9115 to 1.0985.

There were no SAEs in this study. There was 1 TEAE (seborrhoeic dermatitis) leading to the discontinuation of study in 1 subject in the “nacubactam with cefepime” group of cohort 1. All of the 3 TEAEs reported in the “nacubactam with cefepime” group of cohort 1 were mild. One subject with transaminases increased was reported as recovering without treatment, and one subject with haematuria recovered without treatment. One subject with seborrhoeic dermatitis recovered following the treatment provided. For all these TEAEs, the causality with the investigational product or concomitant drug was judged to be “not related.”

1.3.5 Study NP30052 (United States)

Safety, tolerability, and PK were assessed following multiple IV administrations of nacubactam in non-Japanese healthy adult males and females.

Tolerability of nacubactam after single IV administration from 1 to 8 g, or after multiple administrations from 1 to 4 g TID for 7 days by IV infusions over 1.5 hours or longer per administration were similar to placebo and no safety concern of clinical importance was reported. Tolerability was confirmed following a concomitant IV administration of nacubactam 2 g and meropenem 2 g administered as IV infusion over 1.5 hours via a double lumen catheter TID for

7 days. The safety profile of the concomitant IV administration was similar compared with that of meropenem alone.

The PK of nacubactam was linear up to 4 g TID of multiple administrations or 8 g of single administration. No clinically important drug-drug interaction between nacubactam and meropenem was found.

1.3.6 Study NP39380 (United States)

PK was examined following single IV administration of nacubactam 1 g over 0.5 hours in patients with decreased kidney function and with end stage renal failure.

It was confirmed that renal impairment had a great effect on the PK of nacubactam. A good linearity was observed between renal function and clearance of nacubactam or renal clearance. Similar relationships were also obtained by multiple methods for measurement and estimation of renal function. No clear correlation was obtained between the distribution volume of nacubactam and renal function. The total exposure of nacubactam was higher in patients with decreased renal function than in subjects with normal renal function. Nacubactam was easily removed by hemodialysis, and was removed over 60% on average with 4 hours of hemodialysis. The clearance of nacubactam with dialysis was estimated to be approximately 10 L/hr.

Nacubactam was well tolerated in all subjects receiving a single dose of nacubactam 1 g, and no apparent effect on renal impairment was reported for the safety profile.

1.3.7 Study NP39596 (Latvia, Serbia, Poland, and United States)

The PK was examined following multiple IV administrations (the maximum period of administration was 14 days) of nacubactam 2 g and meropenem 2 g TID over at least 1.5 hours in cUTI patients.

No apparent changes were observed in apparent total body clearance, renal clearance, or apparent volume of distribution at steady state after multiple administration of nacubactam. Accumulation of plasma concentrations was limited after multiple TID doses, even in patients with decreased renal function. Inter-individual recovery of nacubactam in urine varied largely, but differences in plasma PK parameters were not large.

The PK characteristics of meropenem in cUTI patients were confirmed, and they were consistent with the data obtained in other studies.

The tolerability was confirmed after IV administration of nacubactam 2 g and meropenem 2 g TID for up to 14 days. No apparent issue on the safety was reported, and reported events were consistent with known safety profiles of meropenem.

1.3.8 Study NP39750 (United States)

Intra-pulmonary transferability was examined following single IV administration of nacubactam 2 g and meropenem 2 g over 1.5 hours via a double lumen catheter in non-Japanese healthy adult males and females.

The concentration of nacubactam in the epithelial lining fluid (ELF) was about one-third of the corresponding plasma concentration at each time point, and the average ratio of the concentration in the ELF to the plasma concentration was 39%.

Since the ratio of ELF to plasma concentration was almost constant over the observation period and the estimated half-lives in ELF and plasma were comparable (1.82 and 1.71 hours, respectively), rapid equilibrium between ELF concentration and plasma concentration was considered.

1.4 Rationale for Dose Selection

In setting the dose regimen for cefepime/nacubactam or aztreonam/nacubactam, a population PK (PPK) model has been developed using PK data from administration of nacubactam to healthy volunteers and volunteers with impaired renal function, and published PPK models were used for cefepime or aztreonam. The PK/pharmacodynamics (PD) target values for nacubactam in combination with cefepime or aztreonam were determined based on mainly in vitro one-compartment infection model and those for cefepime and aztreonam were identified from published literature. Monte Carlo simulation using the PPK models of the three drugs and MIC distributions of cefepime or aztreonam in combination with nacubactam was conducted to evaluate probability of target attainment (PTA).

Dose levels of 2 g cefepime/1 g nacubactam or 2 g aztreonam/1 g nacubactam every 8 hours were selected for this study based principally on PTA analyses described above.

When dose regimens of 2 g cefepime/1 g nacubactam or 2 g aztreonam/1 g nacubactam were assumed, maximum MIC at which probability of PK/PD targets exceeding 90% were 8 mg/L (European Committee on Antimicrobial Susceptibility Testing breakpoint for cefepime and aztreonam resistance) using net bacterial stasis in vitro PK/PD target, 4 mg/L using 1-log10 colony-forming unit (CFU) reduction from baseline in vitro PK/PD target, and 2 mg/L using 2-log10 CFU reduction from baseline in vitro PK/PD target, respectively.

Namely, 2 g cefepime/1 g nacubactam or 2 g aztreonam/1 g nacubactam every 8 hours showed greater than 90% PTA at MIC_{90} value (2 mg/L) against target organisms.

In addition, 1 g cefepime/1 g nacubactam or 1 g aztreonam/1 g nacubactam every 8 hours was able to reduce the bacterial burden and prevent the amplification of resistance sub-populations within the hollow fiber infection model using β-lactamase positive Enterobacterales, including carbapenemase-producing isolates, over the 10-day period.

Therefore, 2 g cefepime/1 g nacubactam or 2 g aztreonam/1 g nacubactam every 8 hours were assumed to be more effective than 1 g cefepime/1 g nacubactam or 1 g aztreonam/1 g nacubactam every 8 hours.

Furthermore, the cefepime/nacubactam and aztreonam/nacubactam dosing regimens by creatinine clearance (CrCl)-based dosing group were determined considering the consistency of Day 1 AUC values among simulated patients over the range of CrCl values evaluated relative to those for simulated patients with normal renal function after administration of 2 g cefepime/1 g nacubactam or 2 g aztreonam/1 g nacubactam every 8 hours.

In previous clinical pharmacology studies, the safety and tolerability of nacubactam following a single IV infusion of nacubactam up to 8 g were confirmed in healthy Caucasian adult male subjects, and the safety and tolerability of a single IV infusion of nacubactam up to 4 g were also confirmed in healthy Japanese adult male subjects. Studies using a single dose of 2 g of nacubactam in combination with 2 g of β-lactams (meropenem, cefepime, or aztreonam) and multiple doses of 2 g of nacubactam in combination with 2 g of β-lactams (meropenem, cefepime,

or aztreonam) TID for 7 days were conducted and no severe AEs were observed. In addition, co-administration of 1 g of nacubactam and 1 g of β-lactams (cefepime or aztreonam) showed promising potency against causative pathogens in nonclinical PK/PD studies. And the selected dose and dosage regimen also considered to be safe based on the non-clinical studies.

Overall, based on these results from clinical pharmacology studies (the PK and safety data) and non-clinical PK/PD studies, the dose of 2 g cefepime or 2 g aztreonam in combination with 1 g nacubactam every 8 hours was chosen for this study.

1.5 Risk/Benefit Assessment

Summaries of findings from both clinical and nonclinical studies conducted with nacubactam can be found in the IB. The following sections outline the risk assessment for this protocol.

1.5.1 Risk Assessment

There are no important identified risks associated with the use of nacubactam.

1.5.2 Benefit Assessment

Nacubactam is a novel BLI in development for the treatment of serious Gram-negative bacterial infections. It has inhibitory activities encompassing Class A (ESBL and KPC) and Class C (AmpC) β-lactamases; it also acts as an antibiotic by inhibiting PBP2 of Enterobacterales and enhancing the activity of β-lactam agents, which mainly binds to penicillin-binding protein 3.

When used with β-lactam antibiotics, nacubactam has been shown to be active against carbapenemase-producing Enterobacterales (including KPC and Class B [metallo-] and Class D [oxacillinase] carbapenemases) in in vitro and in vivo studies.

1.5.3 Overall Risk/Benefit Conclusion

Nacubactam exhibited good safety and tolerability in repeat-dose nonclinical toxicology studies.

Overall, no significant safety concerns have been prospectively identified about the use of the repeat-dose combination of nacubactam with cefepime or nacubactam with aztreonam in healthy volunteers.

There were no serious adverse reactions or deaths identified in all clinical studies; one SAE of moderate musculoskeletal chest pain, considered unrelated to nacubactam and that resulted in interruption of study treatment, was reported in Study NP39596. The same patient in Study NP39596 later withdrew from study treatment because of diarrhea and nausea. One SAE of severe atrial fibrillation associated with hypertension, considered unrelated to nacubactam, was reported in Study NP39380. One AE leading to withdrawal from study treatment was mild seborrhoeic dermatitis that occurred in Study OP0595-4. No subjects were withdrawn because of an AE in any other company-sponsored interventional studies.

The overall clinical safety profile is favorable to the risk/benefit assessment of nacubactam.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the efficacy and safety of cefepime/nacubactam and to assess the safety of aztreonam/nacubactam administered by IV infusion compared to imipenem/cilastatin in patients with cUTI or acute uncomplicated pyelonephritis (AP).

2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To assess the efficacy of aztreonam/nacubactam administered by IV infusion in patients with cUTI or AP;
- To assess the efficacy of cefepime/nacubactam and aztreonam/nacubactam administered by IV infusion in patients with secondary bacteremia due to cUTI or AP;
- To assess the PK of cefepime/nacubactam and aztreonam/nacubactam administered by IV infusion in patients with cUTI or AP; and
- To assess clinical and microbiological response of cefepime/nacubactam and aztreonam/nacubactam administered by IV infusion per type of pathogen, type of resistance, and antimicrobial susceptibility.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a multi-center, randomized, double-blind study to evaluate the efficacy and safety of cefepime/nacubactam or aztreonam/nacubactam compared to imipenem/cilastatin for the treatment of cUTI or AP, in adults.

In this study, the efficacy and safety of cefepime/nacubactam is primarily evaluated because cefepime has a broader antibacterial spectrum (Gram-positive and Gram-negative bacteria) and cefepime/nacubactam is expected to be frequently used for infections caused by Class A and/or D carbapenemase-producing Enterobacterales while aztreonam has an indication only for Gram-negative bacteria and aztreonam/nacubactam is positioned to be used only for infections caused by Class B carbapenemase-producing Enterobacterales in principle.

Approximately 600 patients will be randomized in a 2:1:1 ratio to receive either 2 g cefepime/1 g nacubactam, 2 g aztreonam/1 g nacubactam, or 1 g imipenem/1 g cilastatin.

Dosage of cefepime, aztreonam, nacubactam, and imipenem/cilastatin according to renal function is shown in Table 4.

Randomization will be stratified by entry diagnosis (cUTI or AP) and by geographic region (Japan, China, or Other). At least 30% of patients will have a diagnosis of AP and at least 60% will have a diagnosis of cUTI.

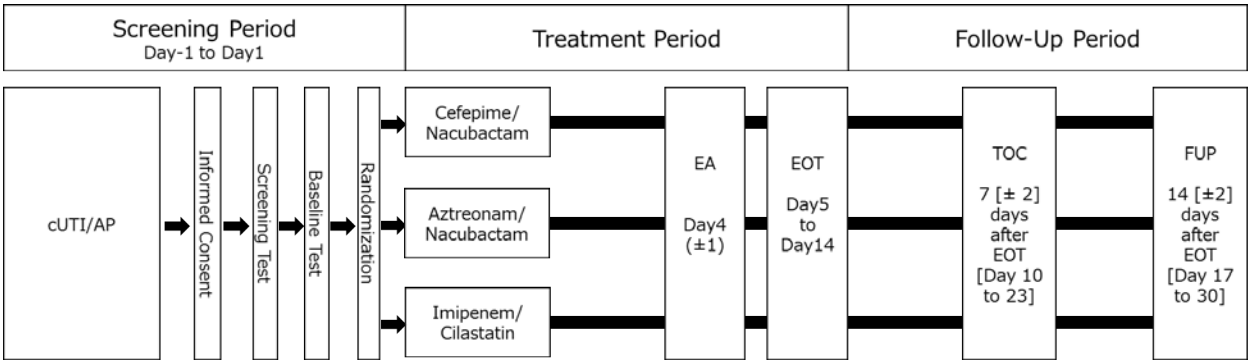
Patients with secondary bacteremia (defined as an organism[s] isolated from a non-contaminated blood culture that is the same as the cUTI/AP-qualifying organism[s] isolated from a urine culture or genitourinary tissue culture) will be included in the study, but categorized by the primary indication and recorded as having secondary bacteremia.

Study drug will be administered every 8 hours (± 1 hour) via an IV infusion over a period of 60 minutes (± 15 minutes). All patients will be treated for a minimum of 5 days (ie, 15 IV infusions) to 10 days. Duration may continue for up to 14 days in selected situations (eg, baseline bacteremia), after discussion with the Medical Monitor. Patients will return for 2 follow-up visits: a Test of Cure visit (TOC) (7 [± 2] days after End of Treatment (EOT) [Day 10 to 23]) and a Follow-Up visit (FUP) (14 [±2] days after EOT [Day 17 to 30]). Patients who withdraw from the study early will undergo an Early Termination (ET) visit. Study drug administration should be discontinued in patients whose baseline urine culture does not meet the requirements for a baseline qualifying pathogen and, in the opinion of the Investigator, the patient does not have a UTI and the patient is not improving.

For instances when a patient grows only a Gram-negative organism resistant to imipenem and/or meropenem, the patient should discontinue study drug but may remain in the study to complete all study assessments.

Figure 1 presents a schematic of the study design.

Figure 1. Study Design



AP = acute uncomplicated pyelonephritis; cUTI = complicated urinary tract infection; EA = Early Assessment; EOT = End of Treatment; FUP = Follow-Up visit; TOC = Test of Cure visit.

Patients with a qualifying Gram-negative uropathogen coinfected (or suspected to be coinfected) with a Gram-positive uropathogen detected after randomization may be administered narrow spectrum, open-label glycopeptide (eg, vancomycin), oxazolidinone (eg, linezolid), or daptomycin concomitantly with the blinded study drug at the Investigator's discretion. Investigators should discuss such cases with the Medical Monitor.

Patients will be monitored for safety throughout the duration of the study. Safety assessments will include vital signs, physical examinations, clinical laboratory assessments, AE assessments, and 12-lead ECGs. A urine and/or serum pregnancy test will be performed at Screening and FUP/ET for female patients of childbearing potential only and postmenopausal women < 50 years of age, if the follicle-stimulating hormone (FSH) level is not available at the time of randomization.

An independent Data Safety Monitoring Board (DSMB) will review accumulated safety data and will also review SAEs on an ongoing basis. The DSMB will make recommendations based on the safety data. Further details regarding the data safety monitoring guidelines will be included in the DSMB Charter.

3.2 Study Indication

The indication for this study is the treatment of cUTI and AP.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Male or female patients ≥ 18 years of age (or age of legal consent, whichever is older) at the time of obtaining informed consent and who can be hospitalized throughout the Treatment Period;
2. Weight ≤ 140 kg;
3. Expectation, in the opinion of the Investigator, that the patient's cUTI or AP will require treatment with at least 5 days of IV antibiotics;
4. Diagnosis of cUTI or AP as defined in the tables below:

   Note: If a patient meets the criteria for cUTI below and also has flank pain or costo-vertebral angle tenderness, the patient will be randomized as cUTI instead of AP.

cUTI		
Signs or symptoms evidenced by at least 2 of the following	**Pyuria evidenced by 1 of the following**	**At least 1 of the following associated risks**
• Chills, rigors, or fever. Fever (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]) must be observed and documented by a healthcare provider within 24 hours of Screening; • Suprapubic, pelvic, or lower abdominal pain; • Nausea or vomiting within 24 hours of Screening; • Dysuria, increased urinary frequency, or urinary urgency; or • Elevated WBC count (> 10,000/mm^3) or left shift (> 15% immature PMNs).	• Positive leukocyte esterase on urinalysis; • WBC count ≥ 10/mm^3 in unspun urine; or • WBC count ≥ 10/hpf in urine sediment.	• Implanted urinary tract instrumentation (eg, ureteric stents or other urinary tract prosthetic material), ongoing intermittent bladder catheterization, or presence of an indwelling bladder catheter (Note: Indwelling bladder catheters that have been in place prior to Screening must be removed or replaced prior to collection of the Screening urine for urinalysis and culture, unless removal or replacement is considered unsafe or contraindicated); • Current known functional or anatomical abnormality of the urogenital tract, including anatomic abnormalities of the urinary tract, neurogenic bladder, or post-void residual urine volume of ≥ 100 mL within the past 6 months; • Partial obstructive uropathy (eg, nephrolithiasis, fibrosis, urethral stricture) that is expected to be medically or surgically treated during study drug therapy (prior to EOT); • Urinary retention, including urinary retention in men due to previously diagnosed BPH; or • Azotemia, defined as blood urea nitrogen > 20 mg/dL (> 7.14 mmol/L) (or blood urea > 42.8 mg/dL [> 7.13 mmol/L]), or serum creatinine > 1.4 mg/dL (>123.79 µmol/L), due to known prior intrinsic renal disease.
BPH = benign prostatic hyperplasia; cUTI = complicated urinary tract infection; EOT = End of Treatment; hpf = high-power field; PMN = polymorphonuclear leukocyte; WBC = white blood cell.		

AP		
Signs or symptoms evidenced by at least 2 of the following	**Pyuria evidenced by 1 of the following**	**At least 1 of the following associated risks**
• Chills, rigors, or fever. Fever (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]) must be observed and documented by a healthcare provider within 24 hours of Screening; • Flank pain (onset within 7 days prior to randomization); • Costo-vertebral angle tenderness on physical examination; • Nausea or vomiting within 24 hours of Screening; • Dysuria, increased urinary frequency, or urinary urgency; or • Elevated WBC count (> 10,000/mm^3) or left shift (> 15% immature PMNs).	• Positive leukocyte esterase on urinalysis; • WBC count ≥ 10/mm^3 in unspun urine; or • WBC count ≥ 10/hpf in urine sediment.	Not applicable.
AP = acute uncomplicated pyelonephritis; hpf = high-power field; PMN = polymorphonuclear leukocyte; WBC = white blood cell.		

5. Patient has a baseline positive urine culture specimen obtained within 48 hours prior to the first dose of study drug;

   Note: Patients may be enrolled in this study and start IV study drug therapy before the Investigator knows the results of the baseline urine culture, if all other entry criteria are fulfilled. If known, the screening/baseline urine culture taken within 48 hours prior to the first dose of study drug contains ≥ 10^5 CFU/mL of a Gram-negative uropathogen susceptible to meropenem and imipenem, and the culture is not considered contaminated. If a patient grows ≥ 3 bacterial organisms ≥ 10^5 CFU/mL in the urine, the urine culture will be considered contaminated. An organism will not be considered a contaminant if the organism grows ≥ 10^5 CFU/mL in a urine culture and also grows in a concurrently obtained blood culture. If a patient's baseline urine culture is negative after randomization, the Investigator decides whether the patient should continue to receive the study drug or should discontinue the study drug and initiate non-study antibiotics.

   Note: Imipenem and meropenem susceptible pathogen is defined as a Gram-negative pathogen by susceptibility data of minimum inhibitory concentration (MIC) less than 2 µg/mL to imipenem and meropenem OR imipenem and meropenem disk diffusion (zone diameter ≥ 22 mm). If MIC or disk diffusion data are not available in the local laboratory or before the availability of MIC or disk diffusion results, each site can use other susceptibility testings and criteria in the institution as the initial evidence of imipenem and meropenem susceptible pathogen for enrollment. In any case, pathogen identification and susceptibility testing performed at the central laboratory will be used to determine imipenem and meropenem susceptible pathogen in the final study analysis.

6. Female patients who are no longer of childbearing potential must meet 1 of the following criteria:
    a. Women ≥ 50 years of age who are considered postmenopausal as they have been amenorrhoeic for ≥ 12 months;
    b. Women < 50 years of age who are considered postmenopausal as they have been amenorrhoeic for ≥ 12 months and if the FSH level is in the postmenopausal range. If the FSH level is not available at the time of randomization, the patient must have a negative urine and/or serum pregnancy test and agree to use contraception methods until the FSH result is available; or
    c. Documented permanent sterilization, defined as hysterectomy, bilateral oophorectomy, or bilateral salpingectomy.
7. Female patients of childbearing potential must have a negative urine and/or serum pregnancy test (serum β-human chorionic gonadotropin) at Screening;

    Note: Females of childbearing potential include female patients who have experienced menarche (or begin menarche over the course of the study), and who are not postmenopausal or permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, or bilateral salpingectomy).
8. Patients must agree to use contraception methods as defined below:
    a. Female patients of childbearing potential will be included if they are either sexually inactive (abstinent) for 90 days prior to the first dose of study drug, or are using one of the following highly effective birth control methods (ie, results in < 1% failure rate when used consistently and correctly):
        i. Intrauterine device in place for at least 3 months prior to the first dose of study drug and throughout the study;
        ii. Surgical sterilization of the partner (provided they are the sole sexual partner), defined as vasectomy for 6 months minimum and assessed as surgical success;
        iii. Combined (estrogen or progestogen containing) hormonal contraception associated with the inhibition of ovulation (either oral, intravaginal, or transdermal);
        iv. Progestogen only hormonal contraception associated with the inhibition of ovulation (either oral, injectable, or implantable);
        v. Intrauterine hormone releasing system; or
        vi. Bilateral tubal occlusion.

    Note: Sexual abstinence or use of contraceptive measures must continue throughout the study and for 12 weeks after the last dose of study drug.

    Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. In this study, abstinence is only acceptable if in line with the patient's preferred and usual lifestyle. Periodic abstinence (calendar, symptothermal, post-ovulation methods),

withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea methods are not acceptable methods of contraception.

b. Male patients with female partners of childbearing potential must use highly effective methods of birth control during their participation in the study and for 12 weeks after the last dose of study drug. In addition, male patients with female partners of childbearing potential must also use a condom during their participation in the study and for 12 weeks after the last dose of study drug.

Note: Highly effective methods of birth control for male patients enrolled in the study include the following: surgical sterilization (vasectomy assessed as surgical success) of patient at least 6 months before Screening or a female partner of childbearing potential (provided they are the sole female sexual partner) using highly effective contraception as described in Inclusion Criterion #8a).

9. Female patients must agree to not donate eggs, or retrieve eggs for her own use from the time of informed consent until 12 weeks after the last dose, or male patients must agree to not freeze or donate sperm starting from the time of informed consent until 12 weeks after the last dose;
10. Willing to comply with all study activities and procedures, whether in the hospital or after discharge, for the duration of the study; and
11. Able to provide signed, written informed consent prior to any study-related procedures being performed.

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Has a known imipenem- and/or meropenem-resistant Gram-negative uropathogen ($\geq 10^5$ CFU/mL), isolated from study-qualifying urine culture;

   Note: If after randomization the susceptibility testing indicates resistance to imipenem and/or meropenem, the patient may remain on the study at the Investigator's discretion.

2. Has known or suspected single or concurrent infection with *Acinetobacter* spp. or other organisms that are not adequately covered by the study drug (eg, concurrent viral, mycobacterial, or fungal infection) and needs to be managed with other anti-infectives;

   Note: Patients with qualifying pathogen coinfected (or suspected to be coinfected) with a Gram-positive pathogen may be administered narrow spectrum, open-label glycopeptide (eg, vancomycin), oxazolidinone (eg, linezolid), or daptomycin concomitantly with the study drug at the Investigator's discretion.

3. Has only a known Gram-positive primary uropathogen ($\geq 10^5$ CFU/mL), isolated from study-qualifying urine culture;
4. Has a known study-qualifying urine culture with ≥ 3 bacterial organisms $\geq 10^5$ CFU/mL;

   Note: A Gram-negative organism will not be considered a contaminant if the organism grows $\geq 10^5$ CFU/mL in a urine culture and also grows in a concurrently obtained blood culture.

5. Has a complete obstruction of any portion of the urinary tract that is not anticipated to be medically or surgically relieved during this study therapy and before EOT;

6. Has a previous or planned cystectomy or permanent urinary diversion (eg, ileal loop, cutaneous ureterostomy);
7. Has a refractory vesicoureteral reflux (Grade 4 or 5);
8. Has a suspected or confirmed perinephric or renal corticomedullary abscess or polycystic kidney disease;
9. Has suspected or confirmed prostatitis, orchitis, epididymitis, urethritis, or sexually transmitted disease;
10. Has a non-renal source of infection concurrently that could interfere with the evaluation of response to the study drug;
11. Has any recent history of accidental trauma to the pelvis (in the pelvic cavity) or urinary tract;
12. Requires bladder irrigation with antibiotics or requires antibiotics to be administered directly via urinary catheter;
13. Has received a potentially effective systemic antibacterial therapy within 48 hours prior to the first dose of study drug, with the exception of any of the following:
    a. Receipt of a single dose of a short-acting antibacterial agent (APPENDIX C) (no more than 15% of patients will be enrolled with this exception);
    b. Receipt of > 48 hours of prior antibiotic therapy and, in the Investigator's opinion, failed that prior antibiotic therapy (ie, worsening signs and symptoms); or
    c. Documented to have cUTI or AP caused by a pathogen that is not susceptible to the prior antibiotic therapy.
14. Has a history of serious allergy, hypersensitivity (eg, anaphylaxis), or any serious allergic reaction to carbapenems, cephems, penicillins, other β-lactam antibiotics, or any BLIs (eg, tazobactam, sulbactam, or clavulanic acid);
15. Has a history of epilepsy or known seizure disorder (excluding a history of childhood febrile seizures);
16. Is considered unlikely to survive the study period or has a rapidly progressive or terminal illness;
17. Is a female patient who is pregnant or breastfeeding;
18. Is a female patient who expects to be pregnant or a male patient who expects their partner to be pregnant from the time of informed consent until 12 weeks after the last dose;
19. Has current or anticipated neutropenia (< 500 polymorphonuclear neutrophils/mm^3, obtained from the local laboratory at Screening);
20. Has platelet count < 50,000 per microliter;
21. Has renal transplantation and received antibacterial drug prophylaxis within 48 hours before screening and/or likely to receive antibacterial drug prophylaxis during the study period;
22. Has participated in other clinical study within 90 days before this clinical study, or plans to participate in any other clinical study during the course of the study;

23. Has an estimated CrCl < 30 mL/min or > 240 mL/min based on the Cockcroft-Gault formula or is receiving hemodialysis or peritoneal dialysis;
24. Has prior exposure to nacubactam alone or in combination with another product;
25. Has gross hematuria that is not caused by infectious diseases;
26. Meets Hy's criteria of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN) and total bilirubin > 2 × ULN;

    Note: Patients with AST and/or ALT up to 5 × ULN are eligible if these elevations are acute and are documented as being directly related to the infectious process being treated.
27. Has evidence of significant hepatic disease or dysfunction, including known acute viral hepatitis or hepatic encephalopathy;
28. Has manifestations of end-stage liver disease, such as ascites or hepatic encephalopathy;
29. Has a known history of HIV with either a cluster of differentiation 4 count < 200 cells/mm^3 at the last measurement or current diagnosis of another acquired immunodeficiency syndrome-defining illness;
30. Has an uncomplicated UTI except AP (acute uncomplicated cystitis that does not meet the cUTI disease definition [see Inclusion Criterion #4]);
31. Has any condition that, in the opinion of the Investigator, would compromise the safety of the patient or the quality of the data (eg, due to underlying disease, comorbidity, clinically meaningful laboratory abnormality), including a potential concern about a history of a disease that may compromise the safety of the patient during the course of the study (eg, history of clinically significant QT interval prolongation, clinically important congenital syndromes, etc);

    Note: Patients with electrolytes that are above or below the normal value range and deemed by the PI to be clinically significant may be excluded.
32. Is anticipated to begin a new drug that is classified as high risk of prolonging the QT interval (listed in APPENDIX D) during the treatment period;

    Note: If patients have been using the drugs listed in APPENDIX D prior to the enrollment and need to continue using them and patient meets all entry criteria, the patient can be enrolled and continue using them during the study period.
33. Heart-rate-corrected QT interval by the Fridericia formula (QTcF) > 470 msec at Screening;

    Note: If QTcF exceeds 470 msec, the ECG may be repeated 2 more times after rest and the mean of the 3 values will be used to determine the subject's eligibility.
34. Clinically significant bradycardia with a heart rate <50 bpm;

    Note: Patients with such a low heart may have their heart rate repeated up to 2 additional times to determine eligibility.
35. Diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); and

    Note: A SARS-CoV-2 test (genetic testing will be suggested but other antigen testing is allowed) should be conducted at Screening for highly suspected Coronavirus Disease 2019

(COVID-19) patients at the Investigator's discretion. Patients who are tested for SARS-CoV-2 will be started on study drug only after a negative result is confirmed.

Note: Patients eligible for the study with the exception of meeting COVID-19 criteria will be allowed to rescreen more than 2 weeks after testing positive and must have a negative test result for eligibility.

36. Is using or planning to use any of the excluded medications and/or procedures except opioids and urinary anesthetics listed in Section 5.6.1 within the time period specified.

4.3 Withdrawal Criteria

Patients may be discontinued from study drug for any of the following reasons but will still be followed for safety assessments approximately 7 to 14 days after Early Termination (ET):

1. Occurrence of a TEAE that warrants study drug discontinuation in the judgment of the Investigator;
2. Occurrence of exacerbation of underlying disease that warrants study drug discontinuation in the judgment of the Investigator;
3. Patient ineligibility after the start of the study in the judgment of the Investigator;
4. Required use of prohibited concomitant medications except urinary anesthetics and opioid drugs;
5. Significant prolongation of the QT/QTc interval (QTcF > 500 msec or increase from baseline > 60 msec) as measured by the mean of 3 values after study drug administration; or
6. Occurrence of an event that warrants discontinuation in the judgment of the Investigator.

Participation of a patient in this clinical study may be discontinued for any of the following reasons:

1. The patient withdraws consent or requests discontinuation from the study for any reason;
2. Pregnancy;
3. Termination of the study by the Sponsor or the regulatory authority; or
4. The patient is suspected/diagnosed with SARS-CoV-2 infection and warrants discontinuation in the judgment of the Investigator.
5. Insufficient therapeutic effect of the study drug that could lead to clinical worsening, or lack of clinical progress in the judgement of investigators;

If a patient withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the ET visit. The reason for patient withdrawal must be documented in the electronic case report form (eCRF).

Patients who discontinue from study drug and complete the ET visit but are not discontinued from the study should continue to complete all safety assessments approximately 7 to 14 days after ET. AE assessment must be performed, but other assessments should be performed at the discretion of the Investigator, if clinically indicated.

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records.

Withdrawn patients will not be replaced.

5 STUDY TREATMENTS

5.1 Treatment Groups

Approximately 600 patients who have a diagnosis of cUTI or AP will be randomized in a 2:1:1 ratio to 1 of the following 3 treatment groups:

- 2 g cefepime/1 g nacubactam every 8 hours for at least 5 days and up to 14 days via IV infusion over a period of 60 minutes;
- 2 g aztreonam/1 g nacubactam every 8 hours for at least 5 days and up to 14 days via IV infusion over a period of 60 minutes; or
- 1 g imipenem/1 g cilastatin every 8 hours for at least 5 days and up to 14 days via IV infusion over a period of 60 minutes.

A summary of study drug information is provided in Table 3.

Table 3. Study Drug

Study Drug Name	Cefepime	Aztreonam	Nacubactam	Imipenem/Cilastatin
Dose/dosing schedule[1]	2 g/every 8 hours for at least 5 days and up to 14 days over a period of 60 minutes		1 g/every 8 hours for at least 5 days and up to 14 days over a period of 60 minutes	
Route of administration	IV			
Dose stopping criteria	If the discontinuation criteria are met.			
Treatment Period	5 to 14 days			
Follow-up Periods	14 (± 2) days after EOT			
Commercially or locally supplied	Centrally	Centrally[2]	Centrally	Centrally

1. Dosage of cefepime, aztreonam, nacubactam, and imipenem/cilastatin according to renal function are shown in Table 4.
2. Aztreonam in China will be distributed by Fobeni.

EOT = End of Treatment; IV = intravenous.

Dosage of cefepime, aztreonam, nacubactam, and imipenem/cilastatin according to renal function is shown in Table 4.

5.2 Rationale for Dosing

Dose levels of 2 g cefepime/1 g nacubactam or 2 g aztreonam/1 g nacubactam every 8 hours were selected for this study based principally on percent probabilities of PK/PD target attainment using PPK models for cefepime, aztreonam, and nacubactam, nonclinical PK/PD targets for efficacy, in vitro surveillance data, and Monte Carlo simulation.

In previous clinical pharmacology studies, the safety and tolerability of nacubactam following a single IV infusion of nacubactam up to 8 g were confirmed in healthy Caucasian adult male subjects, and the safety and tolerability of a single IV infusion of nacubactam up to 4 g were also confirmed in healthy Japanese adult male subjects. Studies using a single dose of 2 g of nacubactam in combination with 2 g of β-lactams (meropenem, cefepime, or aztreonam) and multiple doses of 2 g of nacubactam in combination with 2 g of β-lactams (meropenem, cefepime, or aztreonam) TID for 7 days were conducted and no severe AEs were observed. In addition, co-administration of 1 g of nacubactam and 1 g of β-lactams (cefepime or aztreonam) showed

promising potency against causative pathogens in nonclinical PK/PD studies. And the selected dose and dosage regimen also considered to be safe based on the non-clinical studies.

Given these results, the proposed dose regimen for this study (2 g of cefepime/1 g of nacubactam or 2 g aztreonam/1 g nacubactam, every 8 hours) was deemed to be safe and potent against pathogens from target indications (cUTI/AP) (see Section 1.4).

Dose adjustments will be made for patients with renal insufficiency (see Section 5.5.3.1).

5.3 Randomization and Blinding

5.3.1 Randomization

Patients will be randomized to receive either cefepime/nacubactam, aztreonam/nacubactam, or imipenem/cilastatin through a centralized Interactive Response Technology (IRT). The patient will be randomized after the inclusion and exclusion criteria are verified. A manual will be provided that describes the IRT and includes complete user instructions.

To ensure balance among treatment arms, the randomization will be stratified by type of infection (AP or cUTI) and geographic region (Japan, China, or Other).

Enrollment of patients who have received a single dose of a short-acting oral or IV antibacterial agent for cUTI within 48 hours prior to the first dose of study drug will be limited to 15% of patients.

In order to enroll at least 30% of patients with a diagnosis of AP, enrollment for cUTI should be no more than 70% but at least 60% of all randomized patients.

After fulfillment of all study entry criteria, patients will be assigned a treatment assignment number via the IRT. In a randomization notification addressed only to the unblinded pharmacist (or appropriately qualified unblinded designee) at the study site, the treatment assignment number and corresponding treatment assignment will be specified. Patients will be randomized in a 2:1:1 ratio. A blinded randomization notification will be sent to the appropriate blinded site personnel.

5.3.2 Blinding

The Investigator, site personnel, Sponsor, and the Sponsor's designees involved in blinded monitoring, data management, or other aspects of the study will be blinded to treatment assignment. The site pharmacist or qualified designee who will prepare the IV infusion solution will be unblinded so that he/she may obtain the assigned drug and prepare the IV dosing solutions. The drug supply itself will not be blinded. The infusion bag containing the reconstituted study drug will be identified with the patient’s identification number, but will not identify the specific drug product. An amber IV bag cover will be placed over the infusion bag for every patient to aid in maintaining the blind. Refer to the Pharmacy Manual for further instruction on maintaining the blind during the study. The vendor who will conduct PK measurement will be also unblinded. For the details of blinding, a separate document will be prepared and followed.

There will be a limited unblinded team at the Sponsor and Contract Research Organization (CRO) to support the study pharmacists/designees who will have access to treatment assignment information. The unblinded Sponsor and CRO team will not be involved in review of the clinical database or decisions regarding patient care.

5.4 Breaking the Blind

Unblinding by request of an Investigator should occur only in the event of an emergency or AE for which it is necessary to know the study treatment to determine an appropriate course of therapy for the patient. If the Investigator must identify the treatment assignment of an individual patient, the Investigator or qualified designee should request the study drug information from the IRT. The documentation received from the IRT indicating the code break must be retained with the patient's source documents in a secure manner so as not to unblind the treatment assignment to other site or Sponsor personnel. The Investigator is also advised not to reveal the study treatment assignment to other site or Sponsor personnel.

Prior to unblinding, and if the situation allows, the Investigator should try to contact the site monitor or the Medical Monitor in order to get additional information about the study drug. If this is impractical, the Investigator must notify the site monitor or the Medical Monitor as soon as possible, without revealing the treatment assignment of the unblinded patient. The Investigator must document the patient identification and the date and time for breaking the blind and must clearly explain the reasons for breaking the code.

For patients who are unblinded and withdrawn from the study, ET procedures should be completed.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

Nacubactam is a white crystalline powder that is freely soluble in water and aqueous 0.9% sodium chloride solution. It is insoluble in ethanol and diethyl ether. Nacubactam is not hygroscopic.

Each vial of nacubactam contains 1 g of nacubactam anhydride (sterile crystalline powder).

Study drugs will be labeled according to the requirements of local law and legislation, as well as current Good Manufacturing Practices and Good Clinical Practice (GCP) guidelines.

5.5.2 Study Drug Preparation and Dispensing

An unblinded pharmacist (or qualified designee) will prepare the study drug according to the requirements outlined in the Pharmacy Manual. The IV bags will be labeled with the date and time of study drug preparation and patient identification number using the study supplied labels and will be transferred to the blinded study staff for administration to the patient. Reconstituted study drug should be administered according to the requirements outlined in the Pharmacy Manual.

5.5.3 Study Drug Administration

Study drug will be administered every 8 hours (± 1 hour) via an IV infusion over a period of 60 minutes (± 15 minutes). The administration of nacubactam requires the use of an in-line filter, according to the details outlined in the Pharmacy Manual. All patients will be treated for a minimum of 5 days (ie, 15 IV infusions) to 10 days. Duration may continue for up to 14 days in selected situations (eg, baseline bacteremia), after discussion with the Medical Monitor. The time at which each infusion is started and stopped must be collected and recorded in the eCRF. Instances where the dose is interrupted by more than 10 minutes should be noted in the source documents. Infusions that fall outside of every 8-hour dosing (± 1 hour) will be captured as protocol deviations.

5.5.3.1 Dosing in patients with renal insufficiency

If CrCl is ≥ 30 and < 60 mL/min, patients will receive 1 g cefepime/0.5 g nacubactam or 1 g aztreonam/0.5 g nacubactam or 0.5 g imipenem/0.5 g cilastatin every 8 hours. If CrCl is ≥ 60 and < 90 mL/min, patients will receive 2 g cefepime/1 g nacubactam or 2 g aztreonam/1 g nacubactam or 0.75 g imipenem/0.75 g cilastatin every 8 hours. If CrCl is ≥ 90 and ≤ 240 mL/min, patients will receive 2 g cefepime/1 g nacubactam or 2 g aztreonam/1 g nacubactam or 1 g imipenem/1 g cilastatin every 8 hours. Dosage of nacubactam, cefepime, and aztreonam, and imipenem/cilastatin according to renal function are shown in Table 4.

Table 4. Study Drug Dosage According to Renal Function

CrCl (mL/min)	Cefepime or Aztreonam (g)	Nacubactam (g)	Imipenem/Cilastatin (g)	Interval (hour)
≥ 90 and ≤ 240	2	1	1/1	8
≥ 60 and < 90	2	1	0.75/0.75	8
≥ 30 and < 60	1	0.5	0.5/0.5	8
CrCl = creatinine clearance.				

For patients with moderate renal impairment at baseline whose CrCl drops below 30 mL/min after baseline, serum creatinine should be repeated to confirm the initial result and estimate CrCl. Patients may need to be discontinued from the study, according to the Investigator's judgment or when the patient's safety is at risk.

CrCl will be calculated based on the Cockcroft-Gault formula:

- Male: Creatinine clearance mL/min = (140 – age) × weight (kg) / (72 × serum creatinine [mg/dL]); and
- Female: Creatinine clearance mL/min = 0.85 × ([140 – age] × weight [kg] / [72 × serum creatinine (mg/dL)]).

5.5.4 Treatment Compliance

The infusion date, start and stop times, and volume of study drug administered IV will be recorded in the source documents and eCRF. Treatment compliance will be calculated based on the number of doses received and expected as detailed in the Statistical Analysis Plan (SAP).

5.5.5 Storage and Accountability

The unblinded pharmacists or designated unblinded personnel will ensure that all study drugs are stored in a locked secured area (with access limited to appropriate study personnel) under recommended storage conditions and in accordance with the protocol. Study drug, nacubactam (1 g/vial, 14 vials/box), should be stored at 2 to 8°C. Concomitant drug, cefepime and aztreonam, and comparator, imipenem/cilastatin, should be stored according to the Pharmacy Manual.

Further instructions for returning and/or destroying study drugs will be provided in the Pharmacy Manual.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

Treatment with any of the following concomitant medications or procedures is prohibited from randomization to EOT:

- Valproic acid;

  Rationale: It may affect patient safety.

- Divalproex sodium;

  Rationale: It may affect patient safety.

- Probenecid; and

  Rationale: It may affect patient safety.

- Drugs listed in APPENDIX D, but if patients have used the drugs listed in APPENDIX D prior to the enrollment and need to continue using them and all entry criteria have been fulfilled, the patient can be enrolled and continue using them during the study period. These drugs should be kept at a stable dose during the study period, to the extent possible. Should dosing need to be adjusted during the study period (ie, for the treatment of an AE or for the worsening of the underlying condition), these drugs should be used with caution.

  Rationale: It may affect patient safety.

Treatment with any of the following concomitant medications or procedures is prohibited from time of obtaining informed consent to FUP:

- Receipt of antibacterial drugs for surgical prophylaxis and subsequent development of cUTI or AP;

  Rationale: It may affect the efficacy assessments.

- Receipt of antimicrobial prophylaxis for recurrent cUTI and subsequent presentation of signs and symptoms consistent with an active new cUTI or AP;

  Rationale: It may affect the efficacy assessments.

- Immunosuppressive therapy such as cancer chemotherapy or medication for rejection of transplantation;

  Rationale: It may affect the efficacy assessments.

- Bladder irrigation with antibiotics or antibiotics administered directly via urinary catheter;

  Rationale: It may affect the efficacy assessments.

- Urinary tract surgery within 7 days prior to randomization or has urinary tract surgery planned during the study period (except surgery required for relieving an obstruction or placing urinary tract instrumentation);

  Rationale: It may affect the efficacy assessments.

- Non-study antibacterial drug therapy that would potentially affect the outcome of the evaluation of cUTI/AP, including but not limited to, antibacterials with potential activity against uropathogens, antibacterial drug prophylaxis, and antibacterial bladder irrigation (see Section 5.6.3);

  Rationale: It may affect the efficacy assessments.

- Urinary anesthetics (eg, phenazopyridine hydrochloride), as these agents will interfere with clinical assessments; and

  Rationale: It may not affect the efficacy assessments directly, but it may affect some clinical symptoms because it is commonly used.

- Opioid drugs.

  Rationale: It may not affect the efficacy assessments directly, but it may affect some clinical symptoms because it is commonly used.

5.6.2 Restricted Medications and/or Procedures

Treatment with any of the following concomitant medications is restricted:

- Drugs with antipyretic and analgesic effects (eg, non-steroidal anti-inflammatory drugs and acetaminophen):

  a. For on demand use, patients should refrain from using the drugs the day of and before clinical assessment of the Early Assessment (EA)/EOT/TOC/FUP to the extent possible; and

  b. For long-term use, the drugs should be used during the clinical study period (from obtaining informed consent to FUP) at a fixed dosage before the onset of symptoms of the primary disease to extent possible.

  Rationale: It may not affect the efficacy assessments directly, but it may affect some clinical symptoms because it is commonly used.

- See APPENDIX C for a list of allowed and disallowed prior antibiotics.

  Rationale: It may affect the efficacy assessments.

5.6.3 Allowed Medications and/or Procedures

Patients with a qualifying Gram-negative uropathogen coinfected (or suspected to be coinfected) with a Gram-positive uropathogen detected after randomization may be administered narrow spectrum, open-label glycopeptide (eg, vancomycin), oxazolidinone (eg, linezolid), or daptomycin concomitantly with the blinded study drug at the Investigator's discretion. Investigators should discuss such cases with the Medical Monitor.

5.6.4 Documentation of Prior and Concomitant Medication Use

Reasonable efforts will be made to determine all relevant treatment (concomitant medications, including all prescription/non-prescription medications, herbal medications, vitamin supplements, supportive therapies, and concomitant non-pharmacologic treatments) received by the patient within 14 days before administration of study drug and during the study, which will be recorded

in the eCRF. The medication name, route of administration, dose, frequency, indication, and duration of the treatment/procedure (start and stop dates) will be recorded. Concomitant treatments (non-pharmacologic treatments) include any surgical or diagnostic procedures.

6 STUDY PROCEDURES

Study procedures will follow the Schedule of Procedures (APPENDIX A).

6.1 Informed Consent

Signed informed consent must be obtained before any study-related procedures are performed. See Section 11.3 for details on informed consent.

6.2 Screening Period

Urine culture, blood culture, blood sampling and urine sampling for clinical laboratory assessments, body temperature, and 12-lead ECG collected as part of standard of care may be used as Screening data prior to informed consent.

The following procedures will be performed at Screening on Day -1 to Day 1 (in the event that Screening and Day 1 occur on the same day or within 24 hours, duplicate assessments do not need to be performed; however, laboratory assessment samples for Day 1 chemistry, lipid, hematology, coagulation, and urinalysis need to be sent to the central laboratory in addition to local laboratory. Moreover, in case Screening culture is used as a baseline culture, it needs to be sent to the central laboratory in addition to local laboratory):

- Obtain signed informed consent;
- Record demographic information (age, sex, race, and ethnicity);
- Record medical/surgical history;
- Record prior medications;
- Review inclusion/exclusion criteria;
- Perform urine and/or serum pregnancy test at the local laboratory for female patients of childbearing potential only and postmenopausal women < 50 years of age who have been amenorrhoeic for ≥ 12 months, if the FSH level is not available at the time of randomization;
- Perform FSH test for female patients < 50 years of age who are considered postmenopausal as they have been amenorrhoeic for ≥ 12 months;
- Perform SARS-CoV-2 test (if clinically indicated);

  Note: A SARS-CoV-2 test (genetic testing will be suggested but other antigen testing is allowed) should be conducted at Screening for highly suspected COVID-19 patients at the Investigator's discretion. Patients who are tested for SARS-CoV-2 will be started on study drug only after a negative result is confirmed.

  Note: Patients eligible for the study with the exception of meeting COVID-19 criteria will be allowed to rescreen more than 2 weeks after testing positive and must have a negative test result for eligibility.

- Assess clinical signs and symptoms;

  Note: When possible, the same study personnel should complete the assessments at the same time each day. Maximum daily body temperature (defined as the maximum temperature reported on a single calendar day) will be recorded. Body temperature may be taken per the

site's preferred method (oral, tympanic, or rectal/core) and will be recorded in the appropriate eCRF. The same method of measuring the patient's body temperature should be used throughout the study. Body temperature recorded within 24 hours prior to the time of obtaining consent may be used. However, the temperature may be used only if it was measured by oral, tympanic, or rectal/core temperature, as specified in the protocol, and was observed and recorded by the site staff. The following signs and symptoms will be assigned a classification of absent, mild, moderate, or severe: chills, rigors, urinary frequency, urinary urgency, dysuria, nausea, vomiting, lower abdominal pain, suprapubic pain, pelvic pain, flank pain, and costo-vertebral angle tenderness.

- Collect urine sample for urine culture;

  Note: Urine samples will be collected by clean-catch midstream, intermittent urethral catheter (straight catheterization using sterile technique), a newly inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, suprapubic catheter, nephrostomy tube, or ureter aspiration. The local laboratory will culture each urine sample for organism identification, quantification, and susceptibility testing (only at Screening). Prior to the first dose of study drug, urine samples submitted for culture must have a urinalysis/dipstick and microscopic analysis performed at the local laboratory. Gram staining (or other possible testings) should be performed if available. Prior to the first dose of study drug, only organisms at concentrations of $\geq 10^5$ CFU/mL of urine and not deemed to be a contaminant as detailed in the Microbiology Laboratory Manual will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing; unless the same organism grows in urine (at concentrations of $\geq 10^5$ CFU/mL) and blood, these organisms should be sent to the central laboratory.

  A urine sample taken within 48 hours prior to the first dose of study drug, to support diagnosis or to treat a medical condition, can be used for screening and baseline microbiologic assessments if the organism(s) isolated from cultures is available to be sent to the central laboratory for analysis. However, all patients who had a urine sample not taken by the method specified in the protocol must have a repeat urine sample culture obtained prior to the start of study drug administration. This sample should be taken as close to randomization as possible (within 2 hours prior to the first dose of study drug, if possible). A repeat urine sample must be obtained prior to the start of study drug for any patients enrolled after receiving a single dose of a short-acting antibiotic or patients who failed preceding antimicrobial therapy.

- Collect blood sample for blood culture;

  Note: Two sets of blood culture samples from 2 separate venipuncture sites will be obtained at Screening and prior to the first dose of study drug on Day 1 for baseline blood cultures (duplicate assessments do not need to be performed if Screening and Day 1 occur on the same day or within 24 hours). The blood culture should be obtained within the allowed Screening Period and within 48 hours prior to the first dose of study drug to align with the requirement to have a urine sample taken within 48 hours. Each set of blood culture samples will include 1 aerobic and 1 anaerobic bottle (an additional aerobic bottle is allowed if anaerobic culture is not standard practice at the site). However, for cUTI and AP, a single aerobic blood culture is sufficient if it is not the institution's standard of care to obtain an anerobic culture. Specimens will be sent to the local laboratory for culture identification and susceptibility testing (only at Screening). All isolates from blood culture will be sent to the central laboratory for

confirmation of identification, susceptibility testing, and possible molecular testing as outlined in the Microbiology Laboratory Manual.

- Collect samples for clinical laboratory assessments as follows:
  a. White blood cell (WBC) with differential;
  b. Urinalysis (leukocyte esterase; microscopy will be performed only as needed, based on positive dipstick test results);
  c. Blood urea nitrogen or blood urea (if azotemia is suspected);
  d. Serum pregnancy (if female patient of childbearing potential);
  e. FSH (for female patients < 50 years of age who are considered postmenopausal as they have been amenorrhoeic for ≥ 12 months);
  f. Platelet count;
  g. Serum creatinine;
  h. AST/ALT;
  i. Total bilirubin;
  j. Electrolytes (sodium, chloride, potassium, magnesium, calcium, bicarbonate [for bicarbonate, if applicable, at the local laboratory]); and
  k. COVID-19 test (if highly suspected).

  Note: Clinical laboratory assessments for these analytes will be performed by the local laboratory.

  Note: It is permitted that these laboratory samples are obtained up to 24 hours prior to the Screening Period to determine eligibility, as long as the patient's clinical status has not changed significantly.

- Perform complete physical examination, including source documentation of skin, head and neck, heart, lung, abdomen, extremities, back/flank/costo-vertebral angle tenderness, neuromuscular assessments, height, and weight;
- Record vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature);

  Note: Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. Vital signs should be collected at the same times as assessments of signs and symptoms Patients should be resting in a semi-recumbent position for at least 5 minutes prior to and during measurement of vital signs. Body temperature may be taken per the site's preferred method (oral, tympanic, or rectal/core) and will be recorded in the appropriate eCRF. The same method of measuring the patient's body temperature should be used throughout the study. Body temperature recorded within 24 hours prior to the time of obtaining consent may be used. However, the temperature may be used only if it was measured by oral, tympanic, or rectal/core temperature, as specified in the protocol, and was observed and recorded by the site staff.

- Perform 12-lead ECG; and

  Note: If QTcF exceeds 470 msec, the ECG may be repeated 2 more times after rest and the mean of the 3 values will be used to determine the subject's eligibility.

  Note: 12-lead ECG recorded within 24 hours prior to the time of obtaining consent may be used.

- Assess AEs.

  Note: AEs will be assessed after signed informed consent is obtained. Any medical condition already present at Screening should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

6.2.1 Day 1

6.2.1.1 Pre-randomization

The following procedures will be performed on Day 1 prior to randomization (in the event that Screening and Day 1 occur on the same day or within 24 hours, duplicate assessments do not need to be performed; however, laboratory assessment samples for Day 1 chemistry, lipid, hematology, coagulation, and urinalysis need to be sent to the central laboratory in addition to local laboratory. Moreover, in case screening culture is used as a baseline culture, it needs to be sent to the central laboratory in addition to local laboratory):

- Record concomitant medications (if clinically indicated);
- Review inclusion/exclusion criteria (if clinically indicated);
- Assess clinical signs and symptoms (if clinically indicated);

  Note: When possible, the same study personnel should complete the assessments at the same time each day. Maximum daily body temperature (defined as the maximum temperature reported on a single calendar day) will be recorded. Body temperature may be taken per the site's preferred method (oral, tympanic, or rectal/core) and will be recorded in the appropriate eCRF. The same method of measuring the patient's body temperature should be used throughout the study. The following signs and symptoms will be assigned a classification of absent, mild, moderate, or severe: chills, rigors, urinary frequency, urinary urgency, dysuria, nausea, vomiting, lower abdominal pain, suprapubic pain, pelvic pain, flank pain, and costo-vertebral angle tenderness.

- Collect urine sample for urine culture within 2 hours prior to the first dose of study drug (if clinically indicated);

  Note: Urine samples will be collected by clean-catch midstream, intermittent urethral catheter (straight catheterization using sterile technique), a newly inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, suprapubic catheter, nephrostomy tube, or ureter aspiration. The local laboratory will culture each urine sample for organism identification, quantification, and susceptibility testing (only at Screening). Prior to the first dose of study drug, urine samples submitted for culture must have a urinalysis/dipstick and microscopic analysis performed at the local laboratory. Gram staining (or other possible

testings) should be performed if available. Prior to the first dose of study drug, only organisms at concentrations of ≥ 10^5 CFU/mL of urine and not deemed to be a contaminant as detailed in the Microbiology Laboratory Manual will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing; unless the same organism grows in urine (at concentrations of ≥ 10^5 CFU/mL) and blood, these organisms should be sent to the central laboratory.

A urine sample taken within 48 hours prior to the first dose of study drug, to support diagnosis or to treat a medical condition, can be used for screening and baseline microbiologic assessments if the organism(s) isolated from cultures is available to be sent to the central laboratory for analysis. However, all patients who had a urine sample not taken by the method specified in the protocol must have a repeat urine sample culture obtained prior to the start of study drug administration. A repeat urine sample must be obtained prior to the start of study drug for any patients enrolled after receiving a single dose of a short-acting antibiotic or patients who failed preceding antimicrobial therapy.

- Collect blood sample for blood culture (if clinically indicated);

  Note: Two sets of blood culture samples from 2 separate venipuncture sites will be obtained at Screening and prior to the first dose of study drug on Day 1 for baseline blood cultures (duplicate assessments do not need to be performed if Screening and Day 1 occur on the same day or within 24 hours). The blood culture should be obtained within the allowed Screening Period and within 48 hours prior to the first dose of study drug to align with the requirement to have a urine sample taken within 48 hours. Each set of blood culture samples will include 1 aerobic and 1 anaerobic bottle (an additional aerobic bottle is allowed if anaerobic culture is not standard practice at the site). However, for cUTI and AP, a single aerobic blood culture is sufficient if it is not the institution's standard of care to obtain an anerobic culture. Specimens will be sent to the local laboratory for culture identification and susceptibility testing (only at Screening). All isolates from blood culture will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing as outlined in the Microbiology Laboratory Manual.

- Collect samples for clinical laboratory assessments (chemistry, lipid, hematology, coagulation, and urinalysis) (if clinically indicated);

  Note: Clinical laboratory assessments for chemistry, lipid, hematology, coagulation, and urinalysis will be performed by the central laboratory. In principle, serum creatinine (see Section 5.5.3.1) will be performed daily at local laboratory.

- Perform a limited, symptom-directed physical examination (if clinically indicated);

- Record vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) (if clinically indicated); and

  Note: Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. Vital signs should be collected at the same times as assessments of signs and symptoms Patients should be resting in a semi-recumbent position for at least 5 minutes prior to and during measurement of vital signs. Body temperature may be taken per the site's preferred method (oral, tympanic, or rectal/core) and will be recorded in the appropriate eCRF. The same method of measuring the patient's body temperature should be used throughout the study.

- Assess AEs (if clinically indicated).

6.3 Randomization

Patients will be randomized on Day 1, after pre-randomization procedures are performed, in a 2:1:1 ratio to receive either 2 g cefepime/1 g nacubactam, 2 g aztreonam/1 g nacubactam, or 1 g imipenem/1 g cilastatin. Dosage of cefepime, aztreonam, nacubactam, and imipenem/cilastatin according to renal function is shown in Table 4. Randomization will be stratified by type of infection (AP or cUTI) and by geographic region (Japan, China, or Other).

6.4 Treatment Period

6.4.1 Day 1

6.4.1.1 Post-randomization

The following procedures will be performed on Day 1 after randomization:

- Collect blood sample for blood culture (if clinically indicated);

  Note: If a blood culture is positive at baseline for an organism obtained in a concurrently collected urine sample, blood cultures will be collected until the baseline qualifying Gram-negative pathogen(s) is negative for at least 48 hours in subsequent blood cultures. Additional blood cultures will be collected at the Investigator's discretion. In that case, 2 sets of blood culture samples from 2 separate venipuncture sites will be obtained. The frequency of repeating those blood cultures should be at the discretion of the Investigator, but there must be documentation of a negative blood culture 48 hours after any baseline blood culture or after any subsequent blood culture is found to be positive. For patients with fever spikes (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]) during the study, additional blood samples may be obtained at the time of the fever spike. Specimens will be sent to the local laboratory for culture identification and susceptibility testing (only at Screening). All isolates from blood culture will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing as outlined in the Microbiology Laboratory Manual.

- Administer study drug;

- Collect blood samples for PK analysis;

  Note: In the case the patient is assigned to multiple sampling, samples will be collected on Day 1 after the first infusion of the day: at the end of the infusion (± 5 minutes) and at 2, 4, 6,

and 8 hours (± 10 minutes) after the start of the study drug infusion. The sample will be collected prior to the start of the next infusion (Note: At least 4 time points, including 1 hour after the start of the study drug infusion (first infusion on that day) on Day 1, are needed.). If multiple PK sampling cannot be conducted on Day 1, it should be conducted on Day 3 or Day 5 instead. If sampling occurs on Day 3 or Day 5, samples can be collected after any of the 3 infusions on that day. In the case the patient is assigned to sparse sampling, samples will be collected on Day 1, Day 3, or Day 5, after any of the 3 infusions on that day: around the end of the infusion, around 2 to 4 hours after the start of the study drug infusion, and around 4 to 8 hours after the start of the study drug infusion. The sample will be collected prior to the start of the next infusion (Note: At least 2 time points after the start of the study drug infusion (for any of the 3 infusions on that day) on Day 1, Day 3, or Day 5 are needed.). Infusion start and end times, as well as PK sampling times, will be recorded in the source documents. The method of PK sample handling is detailed in the Laboratory Manual provided by the Sponsor.

- Perform 12-lead ECG (immediately after completion of the first administration of study drug); and
- Assess AEs.

6.4.2 Day 2

The following procedures will be performed on Day 2:

- Record concomitant medications;
- Assess clinical signs and symptoms;

  Note: When possible, the same study personnel should complete the assessments at the same time each day. Maximum daily body temperature (defined as the maximum temperature reported on a single calendar day) will be recorded. Body temperature may be taken per the site's preferred method (oral, tympanic, or rectal/core) and will be recorded in the appropriate eCRF. The same method of measuring the patient's body temperature should be used throughout the study. The following signs and symptoms will be assigned a classification of absent, mild, moderate, or severe: chills, rigors, urinary frequency, urinary urgency, dysuria, nausea, vomiting, lower abdominal pain, suprapubic pain, pelvic pain, flank pain, and costo-vertebral angle tenderness.

- Collect blood sample for blood culture (if clinically indicated);

  Note: If a blood culture is positive at baseline for an organism obtained in a concurrently collected urine sample, blood cultures will be collected until the baseline qualifying Gram-negative pathogen(s) is negative for at least 48 hours in subsequent blood cultures. Additional blood cultures will be collected at the Investigator's discretion. In that case, 2 sets of blood culture samples from 2 separate venipuncture sites will be obtained. The frequency of repeating those blood cultures should be at the discretion of the Investigator, but there must be documentation of a negative blood culture 48 hours after any baseline blood culture or after any subsequent blood culture is found to be positive. For patients with fever spikes (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]) during the study, additional blood samples may be obtained at the time of the fever spike. Specimens will be sent to the local laboratory for culture and identification. All isolates from blood culture will be sent to the central laboratory for confirmation of identification,

susceptibility testing, and possible molecular testing as outlined in the Microbiology Laboratory Manual.

- Collect samples for clinical laboratory assessments (chemistry, lipid, hematology, coagulation, and urinalysis) (if clinically indicated);

  Note: Clinical laboratory assessments for chemistry, lipid, hematology, coagulation, and urinalysis will be performed by the central laboratory. While the patient is receiving study drug, additional clinical laboratory assessments may be performed by the central laboratory at the Investigator's discretion. In principle, serum creatinine (see Section 5.5.3.1) will be performed daily at the local laboratory.

- Perform a limited, symptom-directed physical examination (if clinically indicated);
- Record vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature);
- Assess AEs; and
- Administer study drug.

6.4.3 Day 3

The following procedures will be performed on Day 3:

- Record concomitant medications;
- Assess clinical signs and symptoms;

  Note: When possible, the same study personnel should complete the assessments at the same time each day. Maximum daily body temperature (defined as the maximum temperature reported on a single calendar day) will be recorded. Body temperature may be taken per the site's preferred method (oral, tympanic, or rectal/core) and will be recorded in the appropriate eCRF. The same method of measuring the patient's body temperature should be used throughout the study. The following signs and symptoms will be assigned a classification of absent, mild, moderate, or severe: chills, rigors, urinary frequency, urinary urgency, dysuria, nausea, vomiting, lower abdominal pain, suprapubic pain, pelvic pain, flank pain, and costo-vertebral angle tenderness.

- Collect blood samples for PK analysis (if necessary);

  Note: In the case the patient is assigned to multiple sampling, samples will be collected on Day 1 after the first infusion of the day: at the end of the infusion (± 5 minutes) and at 2, 4, 6, and 8 hours (± 10 minutes) after the start of the study drug infusion. The sample will be collected prior to the start of the next infusion (Note: At least 4 time points, including 1 hour after the start of the study drug infusion (first infusion on that day) on Day 1, are needed.). If multiple PK sampling cannot be conducted on Day 1, it should be conducted on Day 3 or Day 5 instead. If sampling occurs on Day 3 or Day 5, samples can be collected after any of the 3 infusions on that day. In the case the patient is assigned to sparse sampling, samples will be collected on Day 1, Day 3, or Day 5, after any of the 3 infusions on that day: around the end of the infusion, around 2 to 4 hours after the start of the study drug infusion, and around 4 to 8 hours after the start of the study drug infusion. The sample will be collected prior to the start of the next infusion (Note: At least 2 time points after the start of the study drug infusion (for

any of the 3 infusions on that day) on Day 1, Day 3, or Day 5 are needed.). Infusion start and end times, as well as PK sampling times, will be recorded in the source documents. The method of PK sample handling is detailed in the Laboratory Manual provided by the Sponsor.

- Collect blood sample for blood culture (if clinically indicted);

  Note: If a blood culture is positive at baseline for an organism obtained in a concurrently collected urine sample, blood cultures will be collected until the baseline qualifying Gram-negative pathogen(s) is negative for at least 48 hours in subsequent blood cultures. Additional blood cultures will be collected at the Investigator's discretion. In that case, 2 sets of blood culture samples from 2 separate venipuncture sites will be obtained. The frequency of repeating those blood cultures should be at the discretion of the Investigator, but there must be documentation of a negative blood culture 48 hours after any baseline blood culture or after any subsequent blood culture is found to be positive. For patients with fever spikes (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]) during the study, additional blood samples may be obtained at the time of the fever spike. Specimens will be sent to the local laboratory for culture and identification. All isolates from blood culture will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing as outlined in the Microbiology Laboratory Manual.

- Collect samples for clinical laboratory assessments (chemistry, lipid, hematology, coagulation, and urinalysis) (if clinically indicted);

  Note: Clinical laboratory assessments for chemistry, lipid, hematology, coagulation, and urinalysis will be performed by the central laboratory. While the patient is receiving study drug, additional clinical laboratory assessments may be performed by the central laboratory at the Investigator's discretion. In principle, serum creatinine (see Section 5.5.3.1) will be performed daily at the local laboratory.

- Perform a limited, symptom-directed physical examination (if clinically indicated);
- Record vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature);
- Assess AEs; and
- Administer study drug.

6.4.4 Day 4 (Early Assessment)

The following procedures will be performed on Day 4 (± 1 day) at the EA visit:

- Record concomitant medications;

  Note: If the EA visit is conducted on Day 3 or Day 5 (within the allowed window), this assessment should still be conducted on Day 4 as part of the standard safety assessments.

- Assess clinical signs and symptoms;

  Note: When possible, the same study personnel should complete the assessments at the same time each day. Maximum daily temperature (defined as the maximum temperature reported on a single calendar day) will be recorded. Body temperature may be taken per the site's preferred

method (oral, tympanic, or rectal/core) and will be recorded in the appropriate eCRF. The same method of measuring the patient's body temperature should be used throughout the study. The following signs and symptoms will be assigned a classification of absent, mild, moderate, or severe: chills, rigors, urinary frequency, urinary urgency, dysuria, nausea, vomiting, lower abdominal pain, suprapubic pain, pelvic pain, flank pain, and costo-vertebral angle tenderness.

Note: If the EA visit is conducted on Day 3 or Day 5 (within the allowed window), this assessment should still be conducted on Day 4 as part of the standard safety assessments.

- Assess clinical outcome;
- Collect urine sample for urine culture;

  Note: Urine samples will be collected by clean-catch midstream, intermittent urethral catheter (straight catheterization using sterile technique), a newly inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, suprapubic catheter, nephrostomy tube, or ureter aspiration. The local laboratory will culture each urine sample for organism identification and quantification. Only organisms at concentrations of $\geq 10^3$ CFU/mL of urine and not deemed to be a contaminant as detailed in the Microbiology Laboratory Manual will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing.
- Collect blood sample for blood culture (if clinically indicted);

  Note: If a blood culture is positive at baseline for an organism obtained in a concurrently collected urine sample, blood cultures will be collected until the baseline qualifying Gram-negative pathogen(s) is negative for at least 48 hours in subsequent blood cultures. Additional blood cultures will be collected at the Investigator's discretion. In that case, 2 sets of blood culture samples from 2 separate venipuncture sites will be obtained. The frequency of repeating those blood cultures should be at the discretion of the Investigator, but there must be documentation of a negative blood culture 48 hours after any baseline blood culture or after any subsequent blood culture is found to be positive. For patients with fever spikes (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]) during the study, additional blood samples may be obtained at the time of the fever spike. Specimens will be sent to the local laboratory for culture and identification. All isolates from blood culture will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing as outlined in the Microbiology Laboratory Manual.

  Note: If the EA visit is conducted on Day 3 or Day 5 (within the allowed window), this assessment should still be conducted on Day 4 as part of the standard safety assessments.
- Collect samples for clinical laboratory assessments (chemistry, lipid, hematology, coagulation, and urinalysis);

  Note: Clinical laboratory assessments for chemistry, lipid, hematology, coagulation, and urinalysis will be performed by the central laboratory. In principle, serum creatinine (see Section 5.5.3.1) will be performed daily at the local laboratory.

  Note: If the EA visit is conducted on Day 3 or Day 5 (within the allowed window), this assessment should still be conducted on Day 4 as part of the standard safety assessments.

- Perform a limited, symptom-directed physical examination (if clinically indicated);

  Note: If the EA visit is conducted on Day 3 or Day 5 (within the allowed window), this assessment should still be conducted on Day 4 as part of the standard safety assessments.

- Record vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature);

  Note: If the EA visit is conducted on Day 3 or Day 5 (within the allowed window), this assessment should still be conducted on Day 4 as part of the standard safety assessments.

- Perform 12-lead ECG (immediately after completion of the administration of study drug);
- Assess AEs; and

  Note: If the EA visit is conducted on Day 3 or Day 5 (within the allowed window), this assessment should still be conducted on Day 4 as part of the standard safety assessments.

- Administer study drug.

6.4.5 Day 5 to Day 14

All patients will be treated for a minimum of 5 days (ie, 15 IV infusions) to 10 days. Duration may continue for up to 14 days in selected situations (eg, baseline bacteremia), after discussion with the Medical Monitor.

EOT may occur anytime from Day 5 to Day 14. Treatment may continue for up to 14 days for patients with a positive blood culture at baseline at the discretion of the Investigator. EOT assessments are to be conducted on the day of, or within 24 hours following, the day of the last dose of study drug.

The following procedures will be performed from Day 5 to Day 14:

- Record concomitant medications;
- Assess clinical signs and symptoms;

  Note: When possible, the same study personnel should complete the assessments at the same time each day. Maximum daily body temperature (defined as the maximum temperature reported on a single calendar day) will be recorded. Body temperature may be taken per the site's preferred method (oral, tympanic, or rectal/core) and will be recorded in the appropriate eCRF. The same method of measuring the patient's body temperature should be used throughout the study. The following signs and symptoms will be assigned a classification of absent, mild, moderate, or severe: chills, rigors, urinary frequency, urinary urgency, dysuria, nausea, vomiting, lower abdominal pain, suprapubic pain, pelvic pain, flank pain, and costo-vertebral angle tenderness.

- Collect blood samples for PK analysis (on Day 5 only) (if necessary);

  Note: In the case the patient is assigned to multiple sampling, samples will be collected on Day 1 after the first infusion of the day: at the end of the infusion (± 5 minutes) and at 2, 4, 6, and 8 hours (± 10 minutes) after the start of the study drug infusion. The sample will be collected prior to the start of the next infusion (Note: At least 4 time points, including 1 hour after the start of the study drug infusion (first infusion on that day) on Day 1, are needed.). If multiple PK sampling cannot be conducted on Day 1, it should be conducted on Day 3 or Day 5

instead. If sampling occurs on Day 3 or Day 5, samples can be collected after any of the 3 infusions on that day. In the case the patient is assigned to sparse sampling, samples will be collected on Day 1, Day 3, or Day 5, after any of the 3 infusions on that day: around the end of the infusion, around 2 to 4 hours after the start of the study drug infusion, and around 4 to 8 hours after the start of the study drug infusion. The sample will be collected prior to the start of the next infusion (Note: At least 2 time points after the start of the study drug infusion (for any of the 3 infusions on that day) on Day 1, Day 3, or Day 5 are needed.). Infusion start and end times, as well as PK sampling times, will be recorded in the source documents. The method of PK sample handling is detailed in the Laboratory Manual provided by the Sponsor.

- Collect blood sample for blood culture (if clinically indicated);

  Note: If a blood culture is positive at baseline for an organism obtained in a concurrently collected urine sample, blood cultures will be collected until the baseline qualifying Gram-negative pathogen(s) is negative for at least 48 hours in subsequent blood cultures. Additional blood cultures will be collected at the Investigator's discretion. In that case, 2 sets of blood culture samples from 2 separate venipuncture sites will be obtained. The frequency of repeating those blood cultures should be at the discretion of the Investigator, but there must be documentation of a negative blood culture 48 hours after any baseline blood culture or after any subsequent blood culture is found to be positive. For patients with fever spikes (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]) during the study, additional blood samples may be obtained at the time of the fever spike. Specimens will be sent to the local laboratory for culture and identification. All isolates from blood culture will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing as outlined in the Microbiology Laboratory Manual.

- Collect samples for clinical laboratory assessments (chemistry, lipid, hematology, coagulation, and urinalysis) (if clinically indicated);

  Note: Clinical laboratory assessments for chemistry, lipid, hematology, coagulation, and urinalysis will be performed by the central laboratory. While the patient is receiving study drug, additional clinical laboratory assessments may be performed by the central laboratory at the Investigator's discretion. In principle, serum creatinine (see Section 5.5.3.1) will be performed daily at the local laboratory.

- Perform a limited, symptom-directed physical examination (if clinically indicated);
- Record vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature);
- Assess AEs; and
- Administer study drug.

6.4.6 End of Treatment

EOT may occur anytime from Day 5 to Day 14. Treatment may continue for up to 14 days for patients with a positive blood culture at baseline at the discretion of the Investigator. EOT assessments are to be conducted on the day of, or within 24 hours following, the day of the last dose of study drug.

The following procedures will be performed at EOT:

- Record concomitant medications;
- Assess clinical signs and symptoms;

  Note: When possible, the same study personnel should complete the assessments at the same time each day. Maximum daily body temperature (defined as the maximum temperature reported on a single calendar day) will be recorded. Body temperature may be taken per the site's preferred method (oral, tympanic, or rectal/core) and will be recorded in the appropriate eCRF. The same method of measuring the patient's body temperature should be used throughout the study. The following signs and symptoms will be assigned a classification of absent, mild, moderate, or severe: chills, rigors, urinary frequency, urinary urgency, dysuria, nausea, vomiting, lower abdominal pain, suprapubic pain, pelvic pain, flank pain, and costo-vertebral angle tenderness.
- Assess clinical outcome;
- Collect urine sample for urine culture;

  Note: Urine samples will be collected by clean-catch midstream, intermittent urethral catheter (straight catheterization using sterile technique), a newly inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, suprapubic catheter, nephrostomy tube, or ureter aspiration. The local laboratory will culture each urine sample for organism identification and quantification. Only organisms at concentrations of $\geq 10^3$ CFU/mL of urine and not deemed to be a contaminant as detailed in the Microbiology Laboratory Manual will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing.
- Collect blood sample for blood culture (if clinically indicated);

  Note: If a blood culture is positive at baseline for an organism obtained in a concurrently collected urine sample, blood cultures will be collected until the baseline qualifying Gram-negative pathogen(s) is negative for at least 48 hours in subsequent blood cultures. Additional blood cultures will be collected at the Investigator's discretion. In that case, 2 sets of blood culture samples from 2 separate venipuncture sites will be obtained. The frequency of repeating those blood cultures should be at the discretion of the Investigator, but there must be documentation of a negative blood culture 48 hours after any baseline blood culture or after any subsequent blood culture is found to be positive. For patients with fever spikes (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]) during the study, additional blood samples may be obtained at the time of the fever spike. Specimens will be sent to the local laboratory for culture and identification. All isolates from blood culture will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing as outlined in the Microbiology Laboratory Manual.
- Collect samples for clinical laboratory assessments (chemistry, lipid, hematology, coagulation, and urinalysis);

  Note: Clinical laboratory assessments for chemistry, lipid, hematology, coagulation, and urinalysis will be performed by the central laboratory.

- Perform a limited, symptom-directed physical examination (if clinically indicated);
- Record vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature); and
- Assess AEs.

6.5 Follow-Up Period

Following the Treatment Period, patients will return for 2 follow-up visits: the TOC (7 [± 2] days after EOT [Day 10 to 23]) and the FUP (14 [±2] days after EOT [Day 17 to 30]).

6.5.1 Test of Cure Visit

The TOC will occur 7 [± 2] days after EOT [Day 10 to 23]. The following procedures will be performed at TOC:

- Record concomitant medications;
- Assess clinical signs and symptoms;

  Note: When possible, the same study personnel should complete the assessments at the same time each day. Maximum daily body temperature (defined as the maximum temperature reported on a single calendar day) will be recorded. Body temperature may be taken per the site's preferred method (oral, tympanic, or rectal/core) and will be recorded in the appropriate eCRF. The same method of measuring the patient's body temperature should be used throughout the study. The following signs and symptoms will be assigned a classification of absent, mild, moderate, or severe: chills, rigors, urinary frequency, urinary urgency, dysuria, nausea, vomiting, lower abdominal pain, suprapubic pain, pelvic pain, flank pain, and costo-vertebral angle tenderness.
- Assess clinical outcome;
- Collect urine sample for urine culture;

  Note: Urine samples will be collected by clean-catch midstream, intermittent urethral catheter (straight catheterization using sterile technique), a newly inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, suprapubic catheter, nephrostomy tube, or ureter aspiration. The local laboratory will culture each urine sample for organism identification and quantification. Only organisms at concentrations of $\geq 10^3$ CFU/mL of urine and not deemed to be a contaminant as detailed in the Microbiology Laboratory Manual will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing.
- Collect blood sample for blood culture (if clinically indicated);

  Note: If a blood culture is positive at baseline for an organism obtained in a concurrently collected urine sample, blood cultures will be collected until the baseline qualifying Gram-negative pathogen(s) is negative for at least 48 hours in subsequent blood cultures. Additional blood cultures will be collected at the Investigator's discretion. In that case, 2 sets of blood culture samples from 2 separate venipuncture sites will be obtained. The frequency of repeating those blood cultures should be at the discretion of the Investigator, but there must be documentation of a negative blood culture 48 hours after any baseline blood culture or after

any subsequent blood culture is found to be positive. For patients with fever spikes (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]) during the study, additional blood samples may be obtained at the time of the fever spike. Specimens will be sent to the local laboratory for culture and identification. All isolates from blood culture will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing as outlined in the Microbiology Laboratory Manual.

- Collect samples for clinical laboratory assessments (chemistry, lipid, hematology, coagulation, and urinalysis);

  Note: Clinical laboratory assessments for chemistry, lipid, hematology, coagulation, and urinalysis will be performed by the central laboratory.

- Perform a limited, symptom-directed physical examination (if clinically indicated);
- Record vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature); and
- Assess AEs.

6.5.2 Follow-Up Visit

The FUP will occur 14 [±2] days after EOT [Day 17 to 30] and should be performed as an in-person visit. The following procedures will be performed at the FUP:

- Record concomitant medications;
- Perform urine and/or serum pregnancy test at the local laboratory for female patients of childbearing potential only and postmenopausal women < 50 years of age who have been amenorrhoeic for ≥ 12 months, if the FSH level is not available at the time of randomization;
- Assess clinical signs and symptoms;

  Note: When possible, the same study personnel should complete the assessments at the same time each day. Maximum daily temperature (defined as the maximum temperature reported on a single calendar day) will be recorded. Body temperature may be taken per the site's preferred method (oral, tympanic, or rectal/core) and will be recorded in the appropriate eCRF. The same method of measuring the patient's body temperature should be used throughout the study. The following signs and symptoms will be assigned a classification of absent, mild, moderate, or severe: chills, rigors, urinary frequency, urinary urgency, dysuria, nausea, vomiting, lower abdominal pain, suprapubic pain, pelvic pain, flank pain, and costo-vertebral angle tenderness.

- Assess clinical outcome;
- Collect urine sample for urine culture;

  Note: Presumed eradication is assessed at FUP and categorized as eradication only if the baseline qualifying Gram-negative pathogen(s) is eradicated (reduced to < 10^3 CFU/mL) at TOC, and a urine sample cannot be collected but there is a clinical outcome of cure at FUP. Therefore, a urine sample should also be collected at FUP, unless the baseline qualifying Gram-negative pathogen(s) is eradicated (reduced to < 10^3 CFU/mL) at TOC.

Note: Urine samples will be collected by clean-catch midstream, intermittent urethral catheter (straight catheterization using sterile technique), a newly inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, suprapubic catheter, nephrostomy tube, or ureter aspiration. The local laboratory will culture each urine sample for organism identification and quantification. Only organisms at concentrations of $\geq 10^3$ CFU/mL of urine and not deemed to be a contaminant as detailed in the Microbiology Laboratory Manual will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing.

- Collect samples for clinical laboratory assessments (chemistry, lipid, hematology, coagulation, and urinalysis);

  Note: Clinical laboratory assessments for chemistry, lipid, hematology, coagulation, and urinalysis will be performed by the central laboratory.

- Perform a limited, symptom-directed physical examination (if clinically indicated);
- Record vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature); and
- Assess AEs.

6.6 Criteria for Premature Discontinuation of Study Drug or Patient Withdrawal From the Study

Patients should be encouraged to complete all study assessments. However, patients may discontinue study drug or withdraw consent to participate in this study at any time.

6.6.1 Premature Discontinuation of Study Drug Administration

Premature discontinuation of study drug administration is defined as the discontinuation of study drug before the anticipated full course of study drug required for effective treatment of a patient's infection. The minimum duration of study drug therapy is 5 days. Patients may be discontinued from study drug for any of the following reasons but will still be followed for safety assessments approximately 7 to 14 days after ET:

1. Occurrence of a TEAE that warrants study drug discontinuation in the judgment of the Investigator;
2. Occurrence of exacerbation of underlying disease that warrants study drug discontinuation in the judgment of the Investigator;
3. Patient ineligibility after the start of the study in the judgment of the Investigator;
4. Required use of prohibited concomitant medications except urinary anesthetics and opioid drugs;
5. Significant prolongation of the QT/QTc interval (QTcF > 500 msec or increase from baseline > 60 msec) as measured by the mean of 3 values after study drug administration; or
6. Occurrence of an event that warrants discontinuation in the judgment of the Investigator.

For patients who are withdrawn from the study drug prior to completion, the assessments and procedures listed below will be performed at ET. Patients who complete the ET visit but are not

discontinued from the study should continue to complete safety assessments approximately 7 to 14 days after ET.

The following assessments and procedures will be performed at the ET visit:

- Record concomitant medications;
- Perform urine and/or serum pregnancy test at the local laboratory for female patients of childbearing potential only and postmenopausal women < 50 years of age who have been amenorrhoeic for ≥ 12 months, if the FSH level is not available at the time of randomization;
- Assess clinical signs and symptoms;

  Note: When possible, the same study personnel should complete the assessments at the same time each day. Maximum daily temperature (defined as the maximum temperature reported on a single calendar day) will be recorded. Body temperature may be taken per the site's preferred method (oral, tympanic, or rectal/core) and will be recorded in the appropriate eCRF. The same method of measuring the patient's body temperature should be used throughout the study. The following signs and symptoms will be assigned a classification of absent, mild, moderate, or severe: chills, rigors, urinary frequency, urinary urgency, dysuria, nausea, vomiting, lower abdominal pain, suprapubic pain, pelvic pain, flank pain, and costo-vertebral angle tenderness.
- Assess clinical outcome;
- Collect urine sample for urine culture;

  Note: Urine samples will be collected by clean-catch midstream, intermittent urethral catheter (straight catheterization using sterile technique), a newly inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, suprapubic catheter, nephrostomy tube, or ureter aspiration. The local laboratory will culture each urine sample for organism identification and quantification. Only organisms at concentrations of ≥ 10^3 CFU/mL of urine and not deemed to be a contaminant as detailed in the Microbiology Laboratory Manual will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing.
- Collect blood sample for blood culture (if clinically indicated);

  Note: If a blood culture is positive at baseline for an organism obtained in a concurrently collected urine sample, blood cultures will be collected until the baseline qualifying Gram-negative pathogen(s) is negative for at least 48 hours in subsequent blood cultures. Additional blood cultures will be collected at the Investigator's discretion. In that case, 2 sets of blood culture samples from 2 separate venipuncture sites will be obtained. The frequency of repeating those blood cultures should be at the discretion of the Investigator, but there must be documentation of a negative blood culture 48 hours after any baseline blood culture or after any subsequent blood culture is found to be positive. For patients with fever spikes (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]) during the study, additional blood samples may be obtained at the time of the fever spike. Specimens will be sent to the local laboratory for culture and identification. All isolates from blood culture will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing as outlined in the Microbiology Laboratory Manual.

- Collect samples for clinical laboratory assessments (chemistry, lipid, hematology, coagulation, and urinalysis);

  Note: Clinical laboratory assessments for chemistry, lipid, hematology, coagulation, and urinalysis will be performed by the central laboratory.

- Perform a limited, symptom-directed physical examination (if clinically indicated);
- Record vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature);
- Perform 12-lead ECG (if clinically indicated); and
- Assess AEs.

Patients who complete the ET visit but are not discontinued from the study should continue to complete all safety assessments approximately 7 to 14 days after ET.

Note: AE assessment must be performed, but other assessments should be performed at the discretion of the Investigator, if clinically indicated.

The following safety assessments and procedures will be performed at the Safety Assessment Visit approximately 7 to 14 days after ET:

- Assess AEs;
- Collect samples for clinical laboratory assessments (chemistry, lipid, hematology, coagulation, and urinalysis) (if clinically indicated);

  Note: Clinical laboratory assessments for chemistry, lipid, hematology, coagulation, and urinalysis will be performed by the central laboratory.

- Perform a limited, symptom-directed physical examination (if clinically indicated);
- Record vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) (if clinically indicated); and
- Perform 12-lead ECG (if clinically indicated).

6.6.2 Withdrawal From the Study

Participation of a patient in this clinical study may be discontinued for any of the following reasons:

1. The patient withdraws consent or requests discontinuation from the study for any reason;
2. Pregnancy;
3. Termination of the study by the Sponsor or the regulatory authority; or
4. The patient is suspected/diagnosed with SARS-CoV-2 infection and warrants discontinuation in the judgment of the Investigator.
5. Insufficient therapeutic effect of the study drug that could lead to clinical worsening, or lack of clinical progress in the judgement of investigators;

For patients who are withdrawn from the study, the following assessments and procedures will be encouraged to be performed at ET:

- Record concomitant medications;
- Perform urine and/or serum pregnancy test at the local laboratory for female patients of childbearing potential only and postmenopausal women < 50 years of age who have been amenorrhoeic for ≥ 12 months, if the FSH level is not available at the time of randomization;
- Assess clinical signs and symptoms;

  Note: When possible, the same study personnel should complete the assessments at the same time each day. Maximum daily temperature (defined as the maximum temperature reported on a single calendar day) will be recorded. Body temperature may be taken per the site's preferred method (oral, tympanic, or rectal/core) and will be recorded in the appropriate eCRF. The same method of measuring the patient's body temperature should be used throughout the study. The following signs and symptoms will be assigned a classification of absent, mild, moderate, or severe: chills, rigors, urinary frequency, urinary urgency, dysuria, nausea, vomiting, lower abdominal pain, suprapubic pain, pelvic pain, flank pain, and costo-vertebral angle tenderness.
- Assess clinical outcome;
- Collect urine sample for urine culture;

  Note: Urine samples will be collected by clean-catch midstream, intermittent urethral catheter (straight catheterization using sterile technique), a newly inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, suprapubic catheter, nephrostomy tube, or ureter aspiration. The local laboratory will culture each urine sample for organism identification and quantification. Only organisms at concentrations of ≥ 10^3 CFU/mL of urine and not deemed to be a contaminant as detailed in the Microbiology Laboratory Manual will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing.
- Collect blood sample for blood culture (if clinically indicated);

  Note: If a blood culture is positive at baseline for an organism obtained in a concurrently collected urine sample, blood cultures will be collected until the baseline qualifying Gram-negative pathogen(s) is negative for at least 48 hours in subsequent blood cultures. Additional blood cultures will be collected at the Investigator's discretion. In that case, 2 sets of blood culture samples from 2 separate venipuncture sites will be obtained. The frequency of repeating those blood cultures should be at the discretion of the Investigator, but there must be documentation of a negative blood culture 48 hours after any baseline blood culture or after any subsequent blood culture is found to be positive. For patients with fever spikes (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]) during the study, additional blood samples may be obtained at the time of the fever spike. Specimens will be sent to the local laboratory for culture and identification. All isolates from blood culture will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing as outlined in the Microbiology Laboratory Manual.

- Collect samples for clinical laboratory assessments (chemistry, lipid, hematology, coagulation, and urinalysis);

  Note: Clinical laboratory assessments for chemistry, lipid, hematology, coagulation, and urinalysis will be performed by the central laboratory.

- Perform a limited, symptom-directed physical examination (if clinically indicated);
- Record vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature);
- Perform 12-lead ECG (if clinically indicated); and
- Assess AEs.

7 EFFICACY ASSESSMENTS

7.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients who achieve composite clinical and microbiological success at TOC in the Microbiological Modified Intent-to-Treat (m-MITT) Population. Composite clinical and microbiological success is defined as the composite clinical outcome of cure and the microbiological outcome of eradication.

7.1.1 Assessment of Clinical Signs and Symptoms

Clinical signs and symptoms will be assessed as indicated in APPENDIX A. When possible, the same study personnel should complete the assessments at the same time each day. Maximum daily body temperature (defined as the maximum temperature reported on a single calendar day) will be recorded. Body temperature may be taken per the site's preferred method (oral, tympanic, or rectal/core) and will be recorded in the appropriate eCRF. The same method of measuring the patient's body temperature should be used throughout the study.

7.1.1.1 cUTI/AP

The following signs and symptoms of cUTI/AP will be assessed:

- Chills, rigors, or fever;
- Dysuria, increased urinary frequency, or urinary urgency;
- Nausea;
- Vomiting;
- Positive leukocyte esterase;
- Suprapubic, pelvic, or lower abdominal pain;
- Elevated WBC count;
- Flank pain; and
- Costo-vertebral angle tenderness.

7.1.2 Clinical Outcome

Assessment of clinical outcome will be completed at EA, EOT, TOC, FUP, and ET. The Investigator will assign a clinical outcome as defined in Table 5.

Table 5. Clinical Outcome Criteria

Category	Criteria
Cure	The complete resolution (or return to premorbid state) of the baseline signs and symptoms of cUTI or AP that were present at Screening (and no new urinary symptoms or worsening of symptoms consistent with the specific baseline condition), such that no further antimicrobial therapy is warranted. Symptom resolution does not necessarily include pre-infection baseline symptoms associated with the patient's pre-study condition (eg, anatomic abnormalities that predispose to cUTI, such as symptoms associated with the presence of an indwelling urinary catheter). **This outcome category can be used at EA, EOT, TOC, FUP, and ET.**
Improvement	Lessening, incomplete resolution, or no worsening of baseline clinical signs and symptoms, but continued IV therapy for management is warranted. **This outcome category can only be used at EA.**
Failure	Patients who experience any 1 of the following: • At EA and EOT, worsening of baseline clinical signs and symptoms or the development of new clinical signs and symptoms of infection, sufficient to stop study drug and initiate non-study antimicrobial; • At TOC and FUP, persistence or incomplete resolution of baseline clinical signs and symptoms of infection, requiring additional antibiotic therapy; • At any visit until TOC, a change in the patient's baseline Gram-negative antimicrobial therapy to treat the baseline infection (other than dose adjustment) after randomization; • Withdrawal from the study due to an AE or due to lack of clinical improvement; or • Death of the patient during the study. **This outcome category can be used at EA, EOT, TOC, FUP, and ET.**
Recurrence	Baseline signs and symptoms were present at FUP after a response of cure. **This outcome category can only be used at FUP.**
Indeterminate	Clinical outcome cannot be determined. This outcome category can be used at EA, EOT, TOC, FUP, and ET.

AE = adverse event; AP = acute uncomplicated pyelonephritis; cUTI = complicated urinary tract infection; EA = Early Assessment; EOT = End of Treatment; ET = Early Termination; FUP = Follow-Up visit; IV = intravenous(ly); TOC = Test of Cure visit.

7.1.3 Microbiological Outcome

The criteria for microbiological outcome are defined in Table 6 and Table 7. Microbiological outcome will be determined programmatically based on the results from the site of infection.

Table 6. Microbiological Outcome Criteria for cUTI or AP

Category	Criteria
Eradication	The baseline qualifying Gram-negative pathogen(s) is reduced to $< 10^3$ CFU/mL in urine culture.
Persistence	Demonstration that 1 or more of the baseline Gram-negative pathogen(s) remains continuously present in urine culture at $\geq 10^3$ CFU/mL.
Recurrence	Isolation of the same baseline Gram-negative pathogen(s) $\geq 10^3$ CFU/mL from urine culture after a response of eradication.
Indeterminate	No urine culture is available, or the culture cannot be interpreted for any reason.

Microbiological outcome will not be evaluated in the following cases:
- New pathogen infection – the post-baseline organism is different from the baseline Gram-negative organism but is thought to be a pathogen based on a number of reasons that will be delineated in the protocol (eg, Gram-negative, obtained in multiple cultures); or
- Contaminant – the post-baseline organism is different from the baseline Gram-negative organism but is identified as a common skin flora organism and has not been cultured from another site.

Note: The qualifying pathogen is defined as a single Gram-negative organism at a concentration $\geq 10^5$ CFU/mL in a non-contaminated urine culture.

Note: Presumed eradication is assessed at FUP and categorized as eradication only if the baseline qualifying Gram-negative pathogen(s) is eradicated (reduced to $< 10^3$ CFU/mL) at TOC, and a urine sample cannot be collected but there is a clinical outcome of cure at FUP. Therefore, a urine sample should also be collected at FUP, unless the baseline qualifying Gram-negative pathogen(s) is eradicated (reduced to $< 10^3$ CFU/mL) at TOC.

AP = acute uncomplicated pyelonephritis; CFU = colony-forming unit(s); cUTI = complicated urinary tract infection; FUP = Follow-Up visit; TOC = Test of Cure visit.

Table 7. Microbiological Outcome Criteria for Secondary Bacteremia

Category	Criteria
Eradication	The baseline qualifying Gram-negative pathogen(s) is negative in blood culture. Presumed eradication is defined as eradication.
Persistence	The baseline qualifying Gram-negative pathogen(s) is positive in blood culture.
Recurrence	Isolation of the same Gram-negative pathogen(s) from blood culture after a response of eradication.
Indeterminate	No blood culture is available or the culture cannot be interpreted for any reason.
Microbiological outcome will not be evaluated in the following cases: • New pathogen infection – the post-baseline organism is different from the baseline Gram-negative organism but is thought to be a pathogen based on a number of reasons that will be delineated in the protocol (eg, Gram-negative, obtained in multiple cultures); or • Contaminant – the post-baseline organism is different from the baseline Gram-negative organism but is identified as a common skin flora organism and has not been cultured from another site. Note: Presumed eradication is assessed at TOC when the baseline qualifying Gram-negative pathogen(s) is negative for at least 48 hours in subsequent blood cultures taken during the treatment period and there is a clinical outcome of cure at TOC. TOC = Test of Cure visit.	

7.1.3.1 Microbiology assessments

Urine culture

Urine samples will be obtained at Screening, prior to the first dose of study drug on Day 1, EA, EOT, TOC, FUP (if clinically indicated), and ET.

Urine samples for microbiological testing will be collected by clean-catch midstream, intermittent urethral catheter (straight catheterization using sterile technique), a newly inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, suprapubic catheter, nephrostomy tube, or ureter aspiration.

A urine sample taken within 48 hours prior to the first dose of study drug can be used for screening and baseline microbiologic assessments if the organism(s) isolated from cultures is available to be sent to the central laboratory for analysis. However, all patients who had a urine sample not taken by the method specified in the protocol must have a repeat urine sample culture obtained prior to the start of study drug administration. This sample should be taken as close to randomization as possible (within 2 hours prior to the first dose of study drug, if possible). A repeat urine sample must be obtained prior to the start of study drug for any patients enrolled after receiving a single dose of a short-acting antibiotic or patients who failed preceding antimicrobial therapy. The sample should be collected as close to randomization as possible (within 2 hours prior to the first dose of study drug, if possible).

Up to 2 Gram-negative bacterial isolates per urine culture (at concentrations of $\geq 10^5$ CFU/mL of urine) will be considered as qualifying pathogens. If a patient grows ≥ 3 bacterial organisms $\geq 10^5$ CFU/mL in the urine, the urine culture will be considered contaminated. An organism will not be considered a contaminant if the organism grows $\geq 10^5$ CFU/mL in a urine culture and also grows in a concurrently obtained blood culture.

Prior to the first dose of study drug, urine samples submitted for culture must have a urinalysis/dipstick and microscopic analysis performed at the local laboratory. Gram staining (or other possible testings) should be performed if available.

At each sampling point, the local laboratory will culture each urine sample for organism identification, quantification, and susceptibility testing (only at Screening).

Imipenem and meropenem susceptible pathogen is defined as a Gram-negative pathogen by susceptibility data of minimum inhibitory concentration (MIC) less than 2 μg/mL to imipenem and meropenem OR imipenem and meropenem disk diffusion (zone diameter ≥ 22 mm). If MIC or disk diffusion data are not available in the local laboratory or before the availability of MIC or disk diffusion results, each site can use other susceptibility testings and criteria in the institution as the initial evidence of imipenem and meropenem susceptible pathogen for enrollment. In any case, pathogen identification and susceptibility testing performed at the central laboratory will be used to determine imipenem and meropenem susceptible pathogen in the final study analysis.

Prior to the first dose of study drug, only organisms at concentrations of ≥ 10^5 CFU/mL of urine and not deemed to be a contaminant as detailed in the Microbiology Laboratory Manual will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing; if the same organism grows in urine (at concentrations of ≥ 10^5 CFU/mL) and blood, these organisms should be sent to the central laboratory.

For all post-baseline urine cultures, only organisms at concentrations of ≥ 10^3 CFU/mL of urine and not deemed to be a contaminant as detailed in the Microbiology Laboratory Manual will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing.

If a patient's baseline urine culture is negative at the time a negative culture is confirmed but the patient is improving, the Investigator can keep the patient on treatment. If the baseline urine culture is negative at the time a negative culture is confirmed and the patient is not improving, study treatment will be stopped, and the patient will be followed for safety assessments approximately 7 to 14 days after ET.

Qualifying pathogen

A qualifying pathogen is defined as a single Gram-negative organism at a concentration ≥ 10^5 CFU/mL in a non-contaminated urine culture. If a culture grows ≥ 3 bacterial organisms ≥ 10^5 CFU/mL in the urine, the urine culture will be considered contaminated. A Gram-negative organism will not be considered a contaminant if the organism grows ≥ 10^5 CFU/mL in a urine culture and also grows in a concurrently obtained blood culture.

The list of Gram-negative uropathogens that may be considered causative in cUTI or AP is included in Table 8. Organisms identified during the study that are not listed in Table 8 as uropathogens or as contaminants in the Microbiology Laboratory Manual will be assessed on a case-by-case basis.

Table 8. Potential Uropathogens

Potential Gram-Negative Uropathogens	
Citrobacter freundii	*Citrobacter koseri*
Enterobacter cloacae	*Escherichia coli*
Klebsiella aerogenes	*Klebsiella oxytoca*
Klebsiella pneumoniae	*Morganella morganii*
Proteus mirabilis	*Proteus vulgaris*
Providencia rettgeri	*Providencia stuartii*
Pseudomonas aeruginosa	*Serratia marcescens*

Blood culture

Two sets of blood culture samples from 2 separate venipuncture sites will be obtained at Screening and prior to the first dose of study drug on Day 1 for baseline blood cultures (duplicate assessments do not need to be performed if Screening and Day 1 occur on the same day or within 24 hours). The blood culture should be obtained within the allowed Screening Period and within 48 hours prior to the first dose of study drug to align with the requirement to have a urine sample taken within 48 hours.

Each set of blood culture samples will include 1 aerobic and 1 anaerobic bottle (an additional aerobic bottle is allowed if anaerobic culture is not standard practice at the site). However, for cUTI and AP, a single aerobic blood culture is sufficient if it is not the institution's standard of care to obtain an anerobic culture. If a blood culture is positive at baseline for an organism obtained in a concurrently collected urine sample, blood cultures will be collected until the baseline qualifying Gram-negative pathogen(s) is negative for at least 48 hours in subsequent blood cultures. Additional blood cultures will be collected at the Investigator's discretion. In that case, 2 sets of blood culture samples from 2 separate venipuncture sites will be obtained. The frequency of repeating those blood cultures should be at the discretion of the Investigator, but there must be documentation of a negative blood culture 48 hours after any baseline blood culture or after any subsequent blood culture is found to be positive. For patients with fever spikes (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]) during the study, additional blood samples may be obtained at the time of the fever spike. Specimens will be sent to the local laboratory for culture identification and susceptibility testing (only at Screening). All isolates from blood culture will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing as outlined in the Microbiology Laboratory Manual.

7.1.4 Composite Clinical and Microbiological Success

The algorithm for composite clinical and microbiological success at EA, EOT, TOC, FUP, and ET is summarized in Table 9.

Table 9. Composite Clinical and Microbiological Success

Clinical Outcome	Microbiological Outcome			
	Eradication	**Persistence**	**Recurrence[1]**	**Indeterminate**
Cure	Success	Failure	Failure	Failure
Failure[2]	Failure	Failure	Failure	Failure
Indeterminate	Clinical outcome for the last visit before EA, EOT, TOC, FUP, or ET = failure; otherwise = indeterminate	Failure	Failure	Clinical outcome for the last visit before EA, EOT, TOC, FUP, or ET = failure; otherwise = indeterminate

1. For an outcome of recurrence, patients must have documented prior eradication at any prior time point.
2. In the assessment of clinical outcome at EA, category of "improvement" is included. In the assessment of clinical outcome at FUP, category of "recurrence" is included.

EA = Early Assessment; EOT = End of Treatment; ET = Early Termination; FUP = Follow-Up visit; TOC = Test of Cure visit.

7.2 Secondary Efficacy Endpoints

The clinical outcome criteria (Table 5), microbiological outcome criteria (Table 6), and composite clinical and microbiological success (Table 9) also apply to the secondary efficacy assessments.

7.2.1 Secondary Efficacy Endpoints for cUTI and AP

The secondary efficacy endpoints for cUTI and AP include the following:

- The proportion of patients with composite clinical and microbiological success at TOC in the Clinically Evaluable (CE) and Microbiologically Evaluable (ME) Populations;
- The proportion of patients with composite clinical and microbiological success at EA, EOT, and FUP in the m-MITT Population;
- The proportion of patients with a microbiological outcome of eradication at EA, EOT, TOC, and FUP in the m-MITT Population and at TOC in the ME Population;
- The proportion of patients with a clinical outcome of cure at EA, EOT, TOC, and FUP in the m-MITT Population and at TOC in the CE and ME Populations;
- The proportion of patients with a clinical outcome of cure at EA, EOT, TOC, and FUP in the m-MITT Population and at TOC in the CE and ME Populations and microbiological outcome of eradication at EA, EOT, TOC, and FUP in the m-MITT Population and at TOC in the ME Population per type of pathogen, type of resistance, and antimicrobial susceptibility; and
- The proportion of patients with composite clinical outcome of recurrence and/or microbiological outcome of recurrence at the FUP in the m-MITT, CE, and ME population.

7.2.2 Secondary Efficacy Endpoints for Secondary Bacteremia

Patients with cUTI/AP who meet the following conditions will be determined programmatically as secondary bacteremia:

- Isolation of a Gram-negative bacteria from at least 1 blood culture at baseline AND this isolated pathogen is also identified from the site of infection; AND

- At least 1 of the following within 24 hours prior to the first dose of study drug:
  a. Fever (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]) OR hypothermia (rectal/core temperature < 35°C [< 95°F]);
  b. Elevated peripheral WBC count (> 10,000/mm^3);
  c. > 15% immature polymorphonuclear neutrophils (bands) regardless of peripheral WBC count;
  d. Leukopenia (WBC < 4,500/mm^3);
  e. Tachycardia > 100 bpm;
  f. Tachypnea > 20 breaths/min;
  g. Hypotension, systolic < 90 mmHg; or
  h. C-reactive protein > 20 mg/dL.

Clinical outcome of cure from secondary bacteremia is defined as complete resolution or significant improvement of the baseline signs and symptoms of secondary bacteremia.

The secondary efficacy endpoints for secondary bacteremia include the following:

- The proportion of patients with composite clinical and microbiological success of cUTI or AP at TOC in the m-MITT, CE, and ME Populations;
- The proportion of patients with a clinical outcome of cure from cUTI or AP at TOC in the m-MITT, CE, and ME Populations;
- The proportion of patients with a microbiological outcome of eradication from cUTI or AP at TOC in the m-MITT and ME Populations;
- The proportion of patients with a clinical outcome of cure from secondary bacteremia at TOC in the m-MITT, CE, and ME Populations;
- The proportion of patients with a microbiological outcome of eradication from secondary bacteremia at TOC in the m-MITT and ME Populations;
- The proportion of patients in the m-MITT and ME Populations free from the definition of secondary bacteremia AND a clinical outcome of cure from cUTI or AP AND a microbiological outcome of eradication from cUTI or AP at TOC; and
- The proportion of patients who are free from secondary bacteremia at TOC in the m-MITT and ME Populations.

7.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include the following:

- Clinical response at EA, EOT, TOC, and FUP, as defined by the following parameters:
  a. Signs and symptoms of cUTI; and
  b. Proportion of patients in cure, improvement, failure, recurrence, or indeterminate categories for clinical response.

- Microbiological response at EA, EOT, TOC, and FUP, as defined by the following parameters:
  a. Bacterial load in CFU/mL for cUTI causative pathogens in urine; and
  b. Proportion of patients in eradication, persistence, recurrence, or indeterminate categories for microbiological response.

7.4 Pharmacokinetic Assessments

Blood samples for PK analysis will be collected from all patients. All patients will be assigned to either a multiple PK sampling or a sparse PK sampling group at the discretion of the Investigator.

Infusion start and end times, as well as PK sampling times, will be recorded in the source documents. The method of PK sample handling is detailed in the Laboratory Manual provided by the Sponsor.

In the case of multiple sampling, the PK plasma samples will be used to estimate PK parameters of nacubactam, cefepime, and aztreonam such as AUC, C_{max}, time to reach maximum observed plasma concentration, total drug clearance, $t_{½}$, C_{min}, and predicted steady-state volume of distribution using a non-compartmental model. PK parameters will be summarized using appropriate descriptive statistics.

Scatter plots of plasma concentrations of nacubactam, cefepime, and aztreonam from multiple sampling and sparse sampling will be drawn, respectively.

PK characterization and evaluation of plasma exposures of nacubactam, cefepime, and aztreonam will be performed using plasma concentrations from all patients in the cefepime/nacubactam and aztreonam/nacubactam treatment groups by means of PPK modeling methods. PK/PD analysis will be performed by analyzing the relationship between individual PK/PD parameters and individual clinical/biological efficacy data, and PPK analysis and PK/PD analysis will be conducted independently of this protocol and the results of both analyses will be reported independently of the Clinical Study Report for this study.

The PK samples will be collected from all treatment groups to maintain the blind. Only PK samples obtained from the cefepime/nacubactam and aztreonam/nacubactam groups will be analyzed (using a validated assay) by the bioanalytical laboratory. While the PK analyses will be ongoing during the study, the Sponsor and all study personnel will remain blinded to the results (see Section 5.3.2).

7.4.1 Multiple PK Sampling

In the case the patient is assigned to multiple sampling, samples will be collected on Day 1 after the first infusion of the day:

- At the end of the infusion (± 5 minutes); and
- At 2, 4, 6, and 8 hours (± 10 minutes) after the start of the study drug infusion. The sample will be collected prior to the start of the next infusion.

Note: At least 4 time points, including 1 hour after the start of the study drug infusion (first infusion on that day) on Day 1, are needed.

If multiple PK sampling cannot be conducted on Day 1, it should be conducted on Day 3 or Day 5 instead. If sampling occurs on Day 3 or Day 5, samples can be collected after any of the 3 infusions on that day.

Table 10 provides the sampling times for multiple PK assessments.

Table 10. Sampling Times for Multiple PK Assessments

Multiple PK Sampling Time (Time Allowance)	Day 1 (Post-Randomization)[1]	Day 3	Day 5
End of infusion (± 5 minutes)	X	(X)	(X)
2 hours (± 10 minutes) after the start of infusion	X	(X)	(X)
4 hours (± 10 minutes) after the start of infusion	X	(X)	(X)
6 hours (± 10 minutes) after the start of infusion	X	(X)	(X)
8 hours (± 10 minutes) after the start of infusion	X	(X)	(X)

(X) denotes samples that are only to be performed on Day 3 or Day 5 if multiple sampling could not be conducted on Day 1. If sampling occurs on Day 3 or Day 5, samples can be collected after any of the 3 infusions on that day.
1. The PK sample should be taken after the first infusion of that day.
2. Sample should be collected prior to the start of the next infusion.

Note: At least 4 time points, including 1 hour after the start of the study drug infusion (first infusion on that day) on Day 1, are needed.
PK = pharmacokinetic(s).

7.4.2 Sparse PK Sampling

In the case the patient is assigned to sparse sampling, samples will be collected on Day 1, Day 3, or Day 5, after any of the 3 infusions on that day:

- Around the end of the infusion;
- Around 2 to 4 hours after the start of the study drug infusion; and
- Around 4 to 8 hours after the start of the study drug infusion. The sample will be collected prior to the start of the next infusion.

Note: At least 2 time points after the start of the study drug infusion (for any of the 3 infusions on that day) on Day 1, Day 3, or Day 5 are needed.

Table 11 provides the sampling times for sparse PK assessments.

Table 11. Sampling Times for Sparse PK Assessments

Sparse PK Sampling Time	Day 1 (Post-Randomization)[1]	Day 3[1]	Day 5[1]
Around the end of infusion	X	(X)	(X)
Around 2 to 4 hours after the start of infusion	X	(X)	(X)
Around 4 to 8 hours after the start of infusion[2]	X	(X)	(X)

(X) denotes samples that are only to be performed on Day 3 or Day 5 if sparse sampling could not be conducted on Day 1.
1. The PK sample should be taken after any of the 3 infusions of that day.
2. Sample should be collected prior to the start of the next infusion.

Note: At least 2 time points after the start of the study drug infusion (for any of the 3 infusions on that day) on Day 1, Day 3, or Day 5 are needed.
PK = pharmacokinetic(s).

7.5 Other Assessments

The exploratory variables for this study are the minimum inhibitory concentrations for cefepime/nacubactam, aztreonam/nacubactam, and nacubactam for causative uropathogens.

Bacterial whole genome sequencing analysis, or other appropriate methods, may be conducted from purified cultures of bacterial isolates to explore type of resistance.

8 SAFETY ASSESSMENTS

The safety parameters include the incidence, severity, causality, and seriousness of TEAEs and the evaluation of changes from baseline in safety laboratory test results, 12-lead ECGs, vital signs, and physical examinations.

8.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF. All AEs will be followed until resolution, stabilization, the event is otherwise explained by the Investigator, or the patient is lost to follow-up.

AEs, which include clinical laboratory test variables, will be monitored and documented from the time of informed consent until the study participation is complete. Patients should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to study treatment. Beginning with the signing of informed consent, Investigators should make an assessment for AEs at each visit and record the event on the appropriate eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present at Screening should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (eg, 12-lead ECG) findings that are detected during the study or are present at Screening and significantly worsen during the study should be reported as AEs, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an AE. Laboratory abnormalities or other abnormal clinical findings (eg, 12-lead ECG abnormalities) should be reported as an AE if any of the following are applicable:

- If an intervention is required as a result of the abnormality;
- If action taken with the study drug is required as a result of the abnormality; or
- Based on the clinical judgment of the Investigator.

8.1.1 Treatment-Emergent Adverse Events

A TEAE is defined as a new event that occurs during or after the first dose of study treatment or any event present at baseline that worsens in either intensity or frequency after the first dose of study treatment.

8.1.2 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out.

8.1.3 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For nacubactam, the reference safety information is included in the IB currently in force. The reference safety information will be reviewed yearly, and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

8.1.4 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE as to its potential relationship to study drug using the categories of yes or no.

Assessment of severity

Mild – An event that is easily tolerated and generally not interfering with normal daily activities.

Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.

Severe – An event that is incapacitating with inability to work or perform normal daily activities.

Note: Regardless of severity, some events may also meet seriousness criteria (see Section 8.2).

Causality assessment

The relationship of an AE to the administration of the study drug is to be assessed according to the following definitions:

No (not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc) is suspected.

Yes (possibly, probably, or definitely related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

The criteria of the relationship is defined as below:

Not Related: There is no association between the study drug and the reported event.

Unlikely to be Related: The temporal sequence of the event with study drug administration makes a causal relationship improbable and/or other factors also provide plausible explanations.

Possibly Related: Treatment with the study drug caused or contributed to the AE. That is, the event follows a reasonable temporal sequence from the time of study drug administration, and/or, follows a known response pattern to the study drug, but could have been produced by other factors.

Probably Related: A reasonable temporal sequence of the event with study drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the Investigator's clinical experience, the association of the event with study drug administration seems likely.

Definitely Related: a definite causal relationship exists between the drug administration and the AE, and other conditions (eg, concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-

  The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases-

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

- Concomitant drug-

  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug-

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses-

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and PK of the study drug-

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

<u>Action taken with study drug</u>

- Drug Withdrawn;
- Dose Interrupted;
- Dose Reduced;
- Dose Increased;
- Dose Not Changed;

- Not Applicable; or
- Unknown.

8.2 Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations;

  Note: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from Baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. 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 hospitalizations, or the development of drug dependency.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial reports

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence. After the 30-day reporting window, any SAE that the Investigator considers related to study drug must be reported to Medpace Clinical Safety or the Sponsor/designee.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE reporting line (phone number listed in Section 8.6), and fax/email the completed paper SAE form to Medpace (contact information listed in Section 8.6) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-up reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to Medpace Clinical Safety via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

If a patient becomes pregnant during the study or within the safety follow up period defined in the protocol, the Investigator is to stop dosing with study drug(s) immediately and the patient should be withdrawn from the study. Procedures at ET should be implemented at that time.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to Medpace Clinical Safety.

If the female partner of a male patient becomes pregnant while the patient is receiving study drug or within the safety follow up period defined in the protocol, the Investigator should notify Medpace Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening as soon as possible to the applicable competent authorities in all the Member States concerned, and to the Central Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the applicable competent authorities concerned, and to the Central Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to investigational medicinal product.

Expedited reporting of SUSARs related to comparators is also required in line with the requirements above. Expedited reporting of SUSARs related to non-investigational medicinal products (NIMPs) (and any other NIMPs) is not required. Listings of the cases related to NIMPs will be included in the Development Safety Update Report.

8.6 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the patient has taken additional dose(s) or the Investigator has reason to suspect that the patient has taken additional dose(s).
- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of patients missing doses of investigational product are not considered reportable as medication error.
- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported on the Special Situations Report form and faxed/emailed to Medpace Clinical Safety (contact information listed below) within 24 hours of knowledge of the event. All AEs associated with these Special Situation reports should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE reporting line – United States:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-570-5196
Email: medpace-safetynotification@medpace.com

Medpace SAE reporting line – Europe:
Telephone: +49 89 89 55 718 44
Fax: +49 89 89 55 718 104
Email: medpace-safetynotification@medpace.com

8.7 Clinical Laboratory Evaluations

Samples for clinical laboratory assessments (chemistry, lipid, hematology, coagulation, and urinalysis) will be obtained as indicated in APPENDIX A.

A urine and/or serum pregnancy test will be performed as indicated in APPENDIX A for female patients of childbearing potential only and postmenopausal women, if the FSH level is not available at the time of randomization. An FSH test will be performed as indicated in APPENDIX A for female patients < 50 years of age who are considered postmenopausal as they have been amenorrhoeic for ≥ 12 months. If the FSH level is not available at the time of randomization, the patient must have a negative pregnancy test and agree to use contraception methods until the FSH result is available.

See APPENDIX B for a list of central clinical laboratory assessments.

8.8 Vital Signs

Vital signs will be measured as indicated in APPENDIX A. Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature.

Body temperature may be taken per the sites' preferred method (oral, tympanic, or rectal/core) and will be recorded in the appropriate eCRF. The same method of measuring the patient's body temperature should be used throughout the study. At Screening, body temperature recorded within 24 hours prior to the time of obtaining consent may be used. However, the temperature may be used only if it was measured by oral, tympanic, or rectal/core temperature, as specified in the protocol, and was observed and recorded by the site staff. Vital signs should be collected at the same time as assessments of signs and symptoms.

Patients should be resting in a semi-recumbent position for at least 5 minutes prior to and during measurement of vital signs.

8.9 Electrocardiograms

12-lead ECGs will be performed as indicated in APPENDIX A.

At Screening, a 12-lead ECG recorded within 24 hours prior to the time of obtaining consent may be used.

8.10 Physical Examinations

A complete physical examination will be performed as indicated in APPENDIX A and must include source documentation of skin, head and neck, heart, lung, abdomen, extremities, back/flank/costo-vertebral angle tenderness, and neuromuscular assessments. Height and weight will be measured as indicated in APPENDIX A. A limited, symptom-directed physical examination will occur as indicated in APPENDIX A if clinically indicated.

9 STATISTICS

9.1 Analysis Populations

Intent-to-Treat (ITT) Population: All patients who are randomized.

Modified Intent-to-Treat (MITT) Population: All patients who meet ITT criteria and receive any amount of study drug.

m-MITT Population: All randomized patients who meet MITT criteria and who have a baseline qualifying pathogen that susceptible to imipenem and meropenem (see Section 7.1.3.1 for the definition of a qualifying pathogen). The definition of imipenem and meropenem susceptible pathogen is described in Section 4.1 (Inclusion Criterion #5).

CE Population: All patients who meet the definition for the MITT Population and who meet the following important components of the study as specified in the protocol:

- Receive at least 80% of the intended doses of randomized study drug treatment;
- Have a clinical assessment at TOC, unless criteria for clinical failure were met at an earlier timepoint;
- Did not receive concomitant antibacterial treatment with a non-study antibacterial drug to which the uropathogen was susceptible between the time of the baseline culture and the TOC culture, unless criteria for clinical failure were met; and
- Do not have any other major protocol violations that would affect assessment of efficacy.

ME Population: Patients who meet the definition for both the m-MITT and CE Populations. In addition, to be included in the ME Population, patients must not have a microbiological outcome at TOC of Indeterminate. However, any interpretable positive urine culture obtained from EOT through TOC will be carried forward to TOC.

Safety Population: All patients who receive at least 1 dose of study drug during the study.

PK Population: All patients in the Safety Population who have at least 1 analyzable PK sample.

9.2 Statistical Methods

9.2.1 Analysis of Efficacy

The statistical and analytical plans presented below are an overview of key analysis methods. Details of the analysis will be specified in the SAP.

9.2.1.1 Primary efficacy analysis

The primary efficacy endpoint is the proportion of patients who achieve complete composite clinical and microbiological success at TOC in the m-MITT Population. The non-inferiority hypothesis test is a 1-sided hypothesis test performed at the 2.5% level of significance. This is based on the lower limit of the 2-sided 95% confidence intervals (CIs) for the observed difference in the proportion of patients with composite clinical and microbiological success (cefepime/nacubactam group minus imipenem/cilastatin group) at the TOC. Patients with missing data will be included in the denominator for the calculation of success rate. Thus, patients with missing data will be considered as failures for the analysis. The primary analysis is based on a CI

computed using the Miettinen and Nurminen method. If the lower limit of the 2-sided 95% CI for the difference between treatment groups at TOC in the m-MITT Population is > -15.0%, the null hypotheses will be rejected and non-inferiority will be concluded based on the primary efficacy endpoint.

If non-inferiority is declared for the primary efficacy endpoint, a test for superiority will be performed using a hierarchical gatekeeping approach for overall control of the Type 1 error. For this analysis, if the lower bound of the 95% CI for the treatment difference in treatment success at TOC in the m-MITT Population is > 0.0%, superiority will be declared.

Furthermore, if non-inferiority of the cefepime/nacubactam group is declared for the primary efficacy endpoint, the non-inferiority hypothesis test for the aztreonam/nacubactam group will be performed using a hierarchical gatekeeping approach for overall control of the Type 1 error. For this analysis, and for the treatment difference (aztreonam/nacubactam group minus imipenem/cilastatin group) in treatment success at TOC, the same approach as in the cefepime/nacubactam group will be used.

9.2.1.2 Secondary efficacy analyses

For the secondary efficacy endpoints, the number and percentage of patients with each response will be summarized by treatment group. The 2-sided 95% CI for the difference between treatment groups in the proportion of patients with favorable response will be presented using the same approach as for the primary analyses.

9.2.1.3 Pharmacokinetic analyses

Plasma nacubactam, cefepime, and aztreonam concentrations and PK parameters obtained by analyzing plasma concentrations of nacubactam, cefepime, and aztreonam from multiple sampling groups using non-compartmental analysis methods will be summarized using the appropriate descriptive statistics, which will be fully outlined in the SAP.

9.2.1.4 Population pharmacokinetic analyses and pharmacokinetic/pharmacodynamic analyses

PPK analyses will be performed using nacubactam, cefepime, and aztreonam plasma concentrations from all patients in the cefepime/nacubactam and aztreonam/nacubactam treatment groups. PK/PD analyses will be performed by analyzing the relationship between individual estimated PK/PD parameters and individual efficacy data. The results of both analyses will be reported independently of the Clinical Study Report for this study.

9.2.2 Analysis of Safety

Safety analyses will be performed on all patients in the Safety Population. Analyses will be based on TEAEs, vital signs, clinical laboratory assessments, physical examination findings, and 12-lead ECGs. Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

9.2.3 Interim Analysis

No interim analysis is planned for the study.

9.2.4 Data Safety Monitoring Board

An independent DSMB will review accumulated safety data and will also review SAEs on an ongoing basis. The DSMB will make recommendations based on the safety data. Further details regarding the data safety monitoring guidelines will be included in the DSMB Charter.

9.2.5 Sample Size Determination

Using a 15% non-inferiority margin, 1-sided alpha of 0.025, 80% power, a composite clinical and microbiological success rate of 70% in each treatment group (cefepime/nacubactam, imipenem/cilastatin) at TOC, and a 2:1 allocation ratio, a total of 330 patients are required in the m-MITT Population. In addition, 110 patients will be required in the m-MITT Population for the aztreonam/nacubactam group, the same as the imipenem/cilastatin group, in order to evaluate efficacy and safety of the aztreonam/nacubactam group. Assuming 75% of patients will be evaluable for the m-MITT Population, a total of approximately 600 patients will be randomized using a 2:1:1 allocation ratio (300 patients in the cefepime/nacubactam group, 150 patients in the aztreonam/nacubactam group, and 150 patients in the imipenem/cilastatin group). A review of the overall percentage of patients in the m-MITT Population will be conducted after approximately 60% of patients are randomized. Based on this assessment, the sample size may be adjusted to ensure the study remains sufficiently powered.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the clinical research associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (latest) for medical history and AEs; and
- World Health Organization Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3 End of Study

The end of the study is defined as the date when the last patient last observation (LPLO) occurs. LPLO is expected to occur at the FUP of the last patient in the study.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board/Independent Ethics Committee

The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will review all appropriate study documentation in order to safeguard the rights, safety, and wellbeing of patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, IB, informed consent form (ICF), advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB/IEC prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB/IEC.

No drug will be released to the site for dosing until clinical trial authorisation (CTA) execution has been confirmed by the Sponsor.

It is the responsibility of the Sponsor or their designee to obtain the approval of the responsible ethics committees according to the national regulations.

The study will only start in the respective sites once the respective committee's written approval has been given.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB/IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB/IEC, and/or regulatory agencies. A copy of the signed ICF will be given to the patient. The method of obtaining and documenting informed consent will comply with ICH GCP and all applicable regulatory requirement(s).

11.4 Patient Card

The patient will receive a patient card to be carried at all times from discharge to the FUP. The patient card will state that the patient is participating in a clinical research study, type of treatment, number of treatment packs received, and contact details in case of an SAE.

11.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH GCP, Directive 2001/20/EC, applicable regulatory requirements, and the Declaration of Helsinki, and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, IB, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her study staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.6 Protocol Compliance

The Investigator will conduct the study in compliance with the protocol. Modifications to the protocol should not be made without the agreement of both the Investigator and Sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion, when applicable, prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to participants. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review, and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC. The Sponsor will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to participants, the Investigator will contact the Sponsor, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented in the source documentation and must be reported to the IRB/IEC as required by applicable local requirements.

11.7 Protocol Deviations

According to ICH E3, a protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Major protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. A major deviation is an accidental or unintentional change to, or non-compliance with the protocol approved procedures without prior Sponsor and IRB approval. Major deviations include entering the study without satisfying entry criteria, developing withdrawal criteria without being withdrawn, receiving the wrong or incorrect dose, receiving excluded concomitant treatment. Minor protocol deviations are those which do not affect the scientific soundness of the protocol or the rights, safety or welfare of the participant. Minor deviations may include timing of tests and procedures, the order of testing, procedural changes, etc.

Deviations from clinical protocol requirements will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective actions put into place.

11.8 Disclosure of Data

Data generated by this study must be available for inspection by the Sponsor or their designee, applicable foreign health authorities, and the IRB/IEC as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.9 Data Protection

The conduct of this study and the processing of any personal data collected from each patient (or from a patient’s healthcare professional or other relevant third-party sources) by the Sponsor or its designee, the site, or the Investigator for use in the study will fully adhere to the requirements set out in applicable data protection and medical privacy laws or regulations, including, without limitation, the General Data Protection Regulation (GDPR) European Union (EU) 2016/679 and EU Directive 95/46/EEC. The Sponsor or its designee shall ensure that, at all times, it has an appropriate legal basis for processing personal data under applicable data protection laws. Site-based organizational and technical arrangements to avoid unauthorized access vary by site but all include access-controlled/access-limited document control and technical solutions, including passwords and security control measures to protect study-specific data, both in paper and electronic format.

The Investigators shall provide coded data to the Sponsor or its designee, which do not reveal the patient’s name, full date of birth, or any other information that can identify the patient. All personal information shall be replaced with a Subject Identification Code before any information leaves the investigative sites.

The Investigator shall report any data breaches that occur to the Sponsor or its designee, without undue delay. The Sponsor has implemented a Business Practice to address data breaches that complies with the requirements of applicable laws and regulations, including the GDPR. The data breach procedures in the Business Practice provide specific responses to actual or potential threats and involve investigation, containment, and mitigation. If applicable, the authorities and the data

patients shall be notified of a data breach within the required timeframes of the applicable laws and regulations, including those of the GDPR.

11.10 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.11 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.12 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

11.13 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out patient liability insurance for all patients who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution. Insurance cover will be maintained in accordance with the laws and regulation of the applicable countries.

11.14 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a CTA.

The study will commence (ie, initiation of study centers) when the CTA and favorable Ethics opinion have been received.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC and, where appropriate, regulatory authority, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the regulatory authority and/or the IRB/IEC, as appropriate (per country regulations).

12.2 Study Results

A summary of the results of the study will be available within 1 year of the completion of the study, unless a deferral is granted.

13 REFERENCES

OP0595 Investigator's Brochure, Edition 6, 14 January 2022.

APPENDIX A: SCHEDULE OF PROCEDURES

Day (± Visit Window)	Screening Period			Treatment Period					Follow-Up Period		ET
	Screening	1[a]							TOC	FUP	
	-1 to 1[a]	Pre-Randomization	Post-Randomization	2	3	4 (EA) (± 1 day)	5 to 14[b]	EOT[b]	7 [± 2] days after EOT [Day 10 to 23]	14 [±2] days after EOT [Day 17 to 30][c]	Unsch[y]
Informed consent[d]	X										
Inclusion/exclusion criteria	X	X[a]									
Demographic information	X										
Medical/surgical history	X										
Prior/concomitant medications[e]	X	X[a]		X	X	X	X	X	X	X	X
Physical examination[f]	X	X[a,f]		X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]
Vital signs[g]	X	X[a]		X	X	X	X	X	X	X	X
12-lead ECG[h]	X		X			X					X
Pregnancy test	X[i]									X[i]	X[i]
FSH	X[j]										
SARS-CoV-2 test	X[k]										
Clinical signs and symptoms[l]	X	X[a]		X	X	X	X	X	X	X	X
Assessment of clinical outcome						X		X	X	X	X
PK blood sampling[m]			X[n]		X[n]		X[n]				
Urine culture[o]	X	X[a,p]				X		X	X	X[q]	X
Blood culture[r]	X	X[a]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	X[s]		X[s]
Clinical laboratory assessments[t]	X	X[a]		X[u]	X[u]	X	X[u]	X	X	X	X
Randomization[v]		X									
Study drug administration[w]			X	X	X	X	X				
AEs[x]	X	X[a]	X	X	X	X	X	X	X	X	X

a. All procedures will be performed at Screening on Day -1 to Day 1. Urine culture, blood culture, blood sampling and urine sampling for clinical laboratory assessments, body temperature, and 12-lead ECG collected as part of standard of care may be used as Screening data prior to informed consent. In the event that Screening and Day 1 occur on the same day or within 24 hours, duplicate assessments do not need to be performed; however, laboratory assessment samples for Day 1 chemistry, lipid, hematology, coagulation, and urinalysis need to be sent to the central laboratory. Moreover, in case screening culture is used as a baseline culture, it needs to be sent to the central laboratory in addition to local laboratory.

b. EOT may occur anytime from Day 5 to Day 14. Treatment may continue for up to 14 days for patients with a positive blood culture at baseline at the discretion of the Investigator. EOT assessments are to be conducted on the day of, or within 24 hours following, the day of the last dose of study drug.
c. The FUP should be performed as an in-person visit.
d. Signed informed consent must be obtained before any study-related procedures are performed.
e. Reasonable efforts will be made to determine all relevant treatment (concomitant medications, including all prescription/non-prescription medications, herbal medications, vitamin supplements, supportive therapies, and concomitant non-pharmacologic treatments) received by the patient within 14 days before administration of study drug and during the study, which will be recorded in the eCRF. The medication name, route of administration, dose, frequency, indication, and duration of the treatment/procedure (start and stop dates) will be recorded. Concomitant treatments (non-pharmacologic treatments) include any surgical or diagnostic procedures. If the EA visit is conducted on Day 3 or Day 5 (within the allowed window), this assessment should still be conducted on Day 4 as part of the standard safety assessments.
f. A complete physical examination will be performed at Screening and must include source documentation of skin, head and neck, heart, lung, abdomen, extremities, back/flank/costo-vertebral angle tenderness, and neuromuscular assessments. Height and weight will be measured at Screening only. A limited, symptom-directed physical examination will occur at subsequent visits if clinically indicated. If the EA visit is conducted on Day 3 or Day 5 (within the allowed window), this assessment should still be conducted on Day 4 as part of the standard safety assessments.
g. Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. Vital signs should be collected at the same times as assessments of signs and symptoms. Patients should be resting in a semi-recumbent position for at least 5 minutes prior to and during measurement of vital signs. If the EA visit is conducted on Day 3 or Day 5 (within the allowed window), this assessment should still be conducted on Day 4 as part of the standard safety assessments.
h. 12-lead ECG at Post-Randomization on Day 1 should be done immediately after completion of the first administration of study drug.
i. For female patients of childbearing potential only and postmenopausal women < 50 years of age who have been amenorrhoeic for ≥ 12 months, if the FSH level is not available at the time of randomization, a urine and/or serum pregnancy test (serum β-human chorionic gonadotropin) will be performed within 1 day prior to study entry at the local laboratory at Screening and at FUP/ET.
j. For female patients < 50 years of age who are considered postmenopausal as they have been amenorrhoeic for ≥ 12 months. If the FSH level is not available at the time of randomization, the patient must have a negative pregnancy test and agree to use contraception methods until the FSH result is available.
k. A SARS-CoV-2 test (genetic testing will be suggested but other antigen testing is allowed) should be conducted at Screening for highly suspected COVID-19 patients at the Investigator's discretion. Patients who are tested for SARS-CoV-2 will be started on study drug only after a negative result is confirmed. Patients eligible for the study with the exception of meeting COVID-19 criteria will be allowed to rescreen more than 2 weeks after testing positive and must have a negative test result for eligibility.
l. When possible, the same study personnel should complete the assessments at the same time each day. Maximum daily body temperature (defined as the maximum temperature reported on a single calendar day) will be recorded. Body temperature may be taken per the site's preferred method (oral, tympanic, or rectal/core) and will be recorded in the appropriate eCRF. The same method of measuring the patient's body temperature should be used throughout the study. Body temperature recorded within 24 hours prior to the time of obtaining consent may be used. However, the temperature may be used only if it was measured by oral, tympanic, or rectal/core temperature, as specified in the protocol, and was observed and recorded by the site staff. If the EA visit is conducted on Day 3 or Day 5 (within the allowed window), this assessment should still be conducted on Day 4 as part of the standard safety assessments.
m. Blood samples for PK analysis will be collected from all patients. All patients will be assigned to either a multiple PK sampling or a sparse PK sampling group at the discretion of the Investigator. In the case the patient is assigned to multiple sampling, samples will be collected on Day 1 after the first infusion of the day: at the end of the infusion (± 5 minutes) and at 2, 4, 6, and 8 hours (± 10 minutes) after the start of the study drug infusion. The sample will be collected prior to the start of the next infusion. Note: At least 4 time points, including 1 hour after the start of the study drug infusion (first infusion on that day) on Day 1 are needed. If multiple PK sampling cannot be conducted on Day 1, it should be conducted on Day 3 or Day 5 instead. If sampling occurs on Day 3 or Day 5, samples can be collected after any of the 3 infusions on that day. In the case the patient is assigned to sparse sampling, samples will be collected on Day 1, Day 3, or Day 5, after any of the 3 infusions on that day: around the end of the infusion, around 2 to 4 hours after the start of the study drug infusion, and around 4 to 8 hours after the start of the study drug infusion. The sample will be collected prior to the start of the next infusion. Note: At least 2 time points after the start of the study drug infusion (for any of the 3 infusions on that day) on Day 1, Day 3, or Day 5 are needed. Infusion start and end times, as well as PK sampling times, will be recorded in the source documents. The method of PK sample handling is detailed in the Laboratory Manual provided by the Sponsor.
n. To be performed on Day 3 or Day 5 only if multiple and/or sparse sampling could not be conducted on Day 1.
o. Urine samples will be collected by clean-catch midstream, intermittent urethral catheter (straight catheterization using sterile technique), a newly inserted Foley catheter (no bag specimens allowed), bladder needle aspiration, suprapubic catheter, nephrostomy tube, or ureter aspiration. The local laboratory will culture each urine sample for organism identification, quantification, and susceptibility testing (only at Screening). Prior to the first dose of study drug, urine samples submitted for culture must have a

urinalysis/dipstick and microscopic analysis performed at the local laboratory. Gram staining (or other possible testings) should be performed if available. Prior to the first dose of study drug, only organisms at concentrations of ≥ 10^5 CFU/mL of urine and not deemed to be a contaminant as detailed in the Microbiology Laboratory Manual will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing; unless the same organism grows in urine and blood, in which case these organisms should be sent to the central laboratory regardless of CFU/mL. For all post-baseline urine cultures, only organisms at concentrations of ≥ 10^3 CFU/mL of urine and not deemed to be a contaminant as detailed in the Microbiology Laboratory Manual will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing.

p. A urine sample taken within 48 hours prior to the first dose of study drug, to support diagnosis or to treat a medical condition, can be used for screening and baseline microbiologic assessments if the organism(s) isolated from cultures is available to be sent to the central laboratory for analysis. However, all patients who had a urine sample not taken by the method specified in the protocol must have a repeat urine sample culture obtained prior to the start of study drug administration. This sample should be taken as close to randomization as possible (within 2 hours prior to the first dose of study drug, if possible). A repeat urine sample must be obtained prior to the start of study drug for any patients enrolled after receiving a single dose of a short-acting antibiotic or patients who failed preceding antimicrobial therapy. The sample should be collected as close to randomization as possible (within 2 hours prior to the first dose of study drug, if possible).

q. Presumed eradication is assessed at FUP and categorized as eradication only if the baseline qualifying Gram-negative pathogen(s) is eradicated (reduced to < 10^3 CFU/mL) at TOC, and a urine sample cannot be collected but there is a clinical outcome of cure at FUP. Therefore, a urine sample should also be collected at FUP, unless the baseline qualifying Gram-negative pathogen(s) is eradicated (reduced to < 10^3 CFU/mL) at TOC.

r. Two sets of blood culture samples from 2 separate venipuncture sites will be obtained at Screening and prior to the first dose of study drug on Day 1 for baseline blood cultures (duplicate assessments do not need to be performed if Screening and Day 1 occur on the same day or within 24 hours). The blood culture should be obtained within the allowed Screening Period and within 48 hours prior to the first dose of study drug to align with the requirement to have a urine sample taken within 48 hours. Each set of blood culture samples will include 1 aerobic and 1 anaerobic bottle (an additional aerobic bottle is allowed if anaerobic culture is not standard practice at the site). However, for cUTI and AP, a single aerobic blood culture is sufficient if it is not the institution's standard of care to obtain an anerobic culture. Specimens will be sent to the local laboratory for culture identification and susceptibility testing. All isolates from blood culture will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing as outlined in the Microbiology Laboratory Manual. If the EA visit is conducted on Day 3 or Day 5 (within the allowed window), this assessment should still be conducted on Day 4 as part of the standard safety assessments.

s. If a blood culture is positive at baseline for an organism obtained in a concurrently collected urine sample, blood cultures will be collected until the baseline qualifying Gram-negative pathogen(s) is negative for at least 48 hours in subsequent blood cultures. Additional blood cultures will be collected at the Investigator's discretion. In that case, 2 sets of blood culture samples from 2 separate venipuncture sites will be obtained. The frequency of repeating those blood cultures should be at the discretion of the Investigator, but there must be documentation of a negative blood culture 48 hours after any baseline blood culture or after any subsequent blood culture is found to be positive. For patients with fever spikes (oral or tympanic temperature ≥ 38°C [≥ 100.4°F] or rectal/core temperature ≥ 38.3°C [≥ 100.9°F]) during the study, additional blood samples may be obtained at the time of the fever spike. Specimens will be sent to the local laboratory for culture identification and susceptibility testing (only at Screening). All isolates from blood culture will be sent to the central laboratory for confirmation of identification, susceptibility testing, and possible molecular testing as outlined in the Microbiology Laboratory Manual.

t. Includes chemistry, lipid, hematology, coagulation, and urinalysis. Clinical laboratory assessments for chemistry, hematology, and urinalysis will be performed at the local laboratory at Screening and by the central laboratory at baseline and EA, EOT, TOC, FUP, and ET. It is permitted that these labs are obtained up to 24 hours prior to the Screening Period to determine eligibility, as long as the patient's clinical status has not changed significantly. In principle, serum creatinine will be performed daily at the local laboratory. See APPENDIX B for a list of clinical laboratory assessments. If the EA visit is conducted on Day 3 or Day 5 (within the allowed window), this assessment should still be conducted on Day 4 as part of the standard safety assessments.

u. While the patient is receiving study drug, additional clinical laboratory assessments may be performed by the central laboratory at the Investigator's discretion.

v. Patients will be randomized on Day 1, after pre-randomization procedures are performed, in a 2:1:1 ratio to receive either 2 g cefepime/1 g nacubactam, 2 g aztreonam/1 g nacubactam, or 1 g imipenem/1 g cilastatin. Dosage of cefepime, aztreonam, nacubactam, and imipenem/cilastatin according to renal function is shown in Table 4. Randomization will be stratified by entry diagnosis (cUTI or AP) and by geographic region (Japan, China, or Other).

w. Study drug will be administered every 8 hours (± 1 hour) via an IV infusion over a period of 60 minutes (± 15 minutes). The administration of nacubactam requires the use of an in-line filter, according to the details outlined in the Pharmacy Manual. All patients will be treated for a minimum of 5 days (ie, 15 IV infusions) to 10 days. Duration may continue for up to 14 days in selected situations (eg, baseline bacteremia), after discussion with the Medical Monitor.

x. AEs will be assessed after signed informed consent is obtained. Any medical condition already present at Screening should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should

be reported as an AE. If the EA visit is conducted on Day 3 or Day 5 (within the allowed window), this assessment should still be conducted on Day 4 as part of the standard safety assessments.

y. Patients who discontinue from study drug and complete the ET visit but are not discontinued from the study should continue to complete all safety assessments approximately 7 to 14 days after ET. AE assessment must be performed, but other assessments should be performed at the discretion of the Investigator, if clinically indicated (see Sections 6.6, 6.6.1, and 6.6.2).

AE = adverse event; AP = acute uncomplicated pyelonephritis; CFU = colony-forming unit(s); COVID-19 = Coronavirus Disease 2019; cUTI = complicated urinary tract infection; EA = Early Assessment; ECG = electrocardiogram; eCRF = electronic case report form; EOT = End of Treatment; ET = Early Termination; FSH = follicle-stimulating hormone; FUP = Follow-Up visit; IV = intravenous(ly); PK = pharmacokinetic(s); SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TOC = Test of Cure visit; Unsch = unscheduled.

APPENDIX B: CLINICAL LABORATORY ASSESSMENTS

Clinical laboratory assessments for chemistry, hematology, urinalysis, pregnancy (if applicable), follicle-stimulating hormone (if applicable), and Coronavirus Disease 2019 (COVID-19) (if applicable) will be performed by the local laboratory at Screening to determine patient eligibility. Sites can assess at least some of the laboratory tests listed in Section 6.2 at Screening. Those assessments and additional assessments listed below will be performed by the central laboratory at baseline and post-baseline to monitor patient safety. During the study period, additional clinical laboratory assessments may be performed locally at the Investigator's discretion, as needed, for management of the patient.

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate (if applicable at the local laboratory)
Blood urea/blood urea nitrogen	Calcium
Chloride	C-reactive protein
Creatine kinase	Creatinine
Estimated glomerular filtration rate	γ-glutamyl transferase
Glucose	Inorganic phosphorus
Lactate dehydrogenase	Lipase
Potassium	Sodium
Magnesium	Total bilirubin
Total protein	Uric acid

Lipid Panel

High-density lipoprotein cholesterol	Low-density lipoprotein cholesterol
Total cholesterol	Triglycerides

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count
White blood cell count and differential [1]	

1. Manual microscopic review will be performed only if white blood cell count and/or differential values are out of reference range.

Coagulation

International normalized ratio	Partial thromboplastin time
Prothrombin time	

Urinalysis

Appearance (color, clarity)	Bilirubin
Blood	Glucose
Ketones	Leukocyte esterase
Microscopy [1]	Nitrite
pH	Protein
Specific gravity	Urobilinogen

1. Microscopy will be performed only as needed based on positive dipstick test results.

Pregnancy Test

Serum β-human chorionic gonadotropin or urine pregnancy test [1]

1. Pregnancy test will be performed at the local laboratory for female patients of childbearing potential only and in postmenopausal women < 50 years of age who have been amenorrhoeic for ≥ 12 months, if follicle-stimulating hormone levels are not available at the time of randomization.

Endocrinology

Follicle-stimulating hormone [1]

1. Follicle-stimulating hormone in women < 50 years of age who are considered postmenopausal as they have been amenorrhoeic for ≥ 12 months.

Serology

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]

1. A SARS-CoV-2 test (genetic testing will be suggested but other antigen testing is allowed) should be conducted at Screening for highly suspected COVID-19 patients at the Investigator's discretion. Patients who are tested for SARS-CoV-2 will be started on study drug only after a negative result is confirmed. Patients eligible for the study with the exception of meeting COVID-19 criteria will be allowed to rescreen more than 2 weeks after testing positive and must have a negative test result for eligibility.

APPENDIX C: ALLOWED AND DISALLOWED PRIOR ANTIBIOTICS

Allowed Antibiotics (1 dose within 48 hours prior to the first dose of study drug [1])		Disallowed Antibiotics	
Penicillins			
Amoxicillin	Nafcillin	Benzathine/Penicillin-G Procaine	
Amoxicillin-clavulanate	Oxacillin		
Amoxicillin-sulbactam	Penicillin-G or -V		
Ampicillin	Piperacillin		
Ampicillin-sulbactam	Piperacillin-tazobactam		
Dicloxacillin	Ticarcillin-clavulanate		
Cephalosporins			
Cefaclor	Ceftolozane-tazobactam	Cefixime (400 mg)	
Cefadroxil	Cefpodoxime	Ceftriaxone	
Cefazolin	Cefprozil		
Cefdinir	Ceftaroline		
Cefepime	Loracarbef		
Cefixime (200 mg)	Ceftibuten		
Cefditoren	Cefuroxime		
Cefotaxime	Cephalexin		
Cefoperazone (with or without sulbactam	Ceftazidime (with or without avibactam		
Cefmetazole			
Carbapenems			
Doripenem	Meropenem	Ertapenem	
Imipenem		Meropenem-vaborbactam	
Glycopeptides			
Telavancin	Vancomycin	Dalbavancin	Oritavancin
Fluoroquinolones			
Ciprofloxacin	Ofloxacin	Levofloxacin	Prulifloxacin
Norfloxacin	Pefloxacin	Moxifloxacin	
Tosufloxacin			
Macrolides			
Clarithromycin	Erythromycin	Azithromycin	Clarithromycin XL
Tetracyclines			
Doxycycline (100 mg)	Minocycline	Doxycycline (200 mg)	Tigecycline
		Minocycline extended release	
Oxazolidinones			
Linezolid		Tedizolid	
Miscellaneous			
Clindamycin	Nitrofurantoin	Fosfomycin (intravenous and oral)	
Metronidazole	Nalidixic acid	Plazomicin	
Pipemidic acid	Amikacin		
Trimethoprim-sulfamethoxazole/ Co-trimoxazole	Gentamicin		

1. Prior (within 48 hours prior to the first dose of study drug) administration of potentially effective systemic antibacterial therapy is an Exclusion Criterion; however, patients may be eligible for the study despite prior antimicrobial therapy if they received a single dose of a single short-acting systemic antibiotic within 48 hours prior to the first dose of study drug. For the purposes of this protocol, short-acting is defined as having a dosage frequency of more than once a day. If a patient received a prior short-acting systemic antibiotic that is not listed here, the Investigator must contact the Medical Monitor to ensure patient eligibility.

APPENDIX D: DRUG LISTS CLASSIFIED AS HIGH RISK OF QT PROLONGATION

Generic Name	Drug Class
Aclarubicin	Anti-cancer
Amiodarone	Antiarrhythmic
Anagrelide	Phosphodiesterase 3 inhibitor
Arsenic trioxide	Anti-cancer
Astemizole	Antihistamine
Azithromycin	Antibiotic
Bepridil	Antianginal
Cesium Chloride	toxin
Chloroquine	Antimalarial
Chlorpromazine	Antipsychotic / Antiemetic
Chlorprothixene	Antipsychotic
Cilostazol	Phosphodiesterase 3 inhibitor
Ciprofloxacin	Antibiotic
Cisapride	GI stimulant
Citalopram	Antidepressant, SSRI
Clarithromycin	Antibiotic
Cocaine	Local anesthetic
Disopyramide	Antiarrhythmic
Dofetilide	Antiarrhythmic
Domperidone	Antiemetic
Donepezil	Cholinesterase inhibitor
Dronedarone	Antiarrhythmic
Droperidol	Antipsychotic / Antiemetic
Erythromycin	Antibiotic
Escitalopram	Antidepressant, SSRI
Flecainide	Antiarrhythmic
Fluconazole	Antifungal
Gatifloxacin	Antibiotic
Grepafloxacin	Antibiotic
Halofantrine	Antimalarial
Haloperidol	Antipsychotic
Hydroquinidine (Dihydroquinidine)	Antiarrhythmic
Hydroxychloroquine	Antimalarial, Anti-inflammatory
Ibogaine	Psychedelic
Ibutilide	Antiarrhythmic
Levofloxacin	Antibiotic
Levomepromazine (Methotrimeprazine)	Antipsychotic
Levomethadyl acetate	Opioid agonist
Levosulpiride	Antipsychotic
Meglumine antimoniate	Antiparasitic
Mesoridazine	Antipsychotic
Methadone	Opioid agonist
Moxifloxacin	Antibiotic
Nifekalant	Antiarrhythmic
Ondansetron	Antiemetic
Oxaliplatin	Anti-cancer
Papaverine hydrochloride (Intra-coronary)	Vasodilator, Coronary
Pentamidine	Antifungal

Generic Name	Drug Class
Pimozide	Antipsychotic
Probucol	Antilipemic
Procainamide	Antiarrhythmic
Propofol	Anesthetic, general
Quinidine	Antiarrhythmic
Roxithromycin	Antibiotic
Sertindole	Antipsychotic, atypical
Sevoflurane	Anesthetic, general
Sotalol	Antiarrhythmic
Sparfloxacin	Antibiotic
Sulpiride	Antipsychotic, atypical
Sultopride	Antipsychotic, atypical
Terfenadine	Antihistamine
Terlipressin	Vasoconstrictor
Terodiline	Muscle relaxant
Thioridazine	Antipsychotic
Vandetanib	Anti-cancer