STATISTICAL ANALYSIS PLAN

Protocol 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
Protocol Number:	OP0595-5
Protocol Version/Date:	Version 5.0 / 20 December 2023
Investigational Product:	1g Nacubactam for injection
Sponsor:	Meiji Seika Pharma Co., Ltd. 4-16, Kyobashi 2-chome Chuo-ku, Tokyo 104-8002 Japan [redacted]
SAP Version/Date:	Version 2.0 / 20 January 2025

Confidentiality Statement

SIGNATURE PAGE

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

[redacted]

VERSION HISTORY

Version	Version Date	Description
1.0	01Oct2024	Version 1.0
2.0	20Jan2025	• **Section 2.3.3 and Section 3.4.3:** [redacted] • **Section 2.4.3**: In Table 2.4.3, added the note that the composite outcome will be 'success' when clinical outcome is 'improvement' and microbiological outcome is 'eradication' at EA visit. • **Section 3.**2.5: for ME Population, added notes that "interpretable positive urine culture" means positive urine culture for baseline qualifying pathogen. • **Section 3.4.2**: added the analysis of "Secondary Analysis of Composite Clinical and Microbiological Success at EOT Visit by Baseline Pathogen in Microbiological Modified Intent-to-Treat Population" and "Secondary Analysis of Composite Clinical and Microbiological Success at FUP Visit by Baseline Pathogen in Microbiological Modified Intent-to-Treat Population" . • **Section 3.5.2**: change in the BLQ imputations rules to "If BLQ values occur after the last measurable concentration in a profile, the BLQ will be assigned a value of zero" • **Section 3.5.4**: added significant digits to PK parameters. • **Section 3.6.1**: added the summary of event 'e' for all AEs tables. Added the "Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity" and "Drug Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity".

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AP	Acute uncomplicated pyelonephritis
ATC	Anatomical therapeutic chemical
AUC	Area under the plasma concentration-time curve
AUC_{tau}	Area under the plasma concentration vs time curve (AUC) from over a dosing interval
AUC_{0-t}	Area under the plasma concentration vs time curve (AUC) from pre-dose (time 0) to the last quantifiable plasma concentration (C_{last})
$AUC_{\%extrap}$	Percent of AUC_{0-inf} extrapolated
AUC_{0-inf}	AUC from time 0 to infinity
AUMC	Area under the first moment of the disposition curve
BMI	Body mass index
BLQ	Below the lower limit of quantification data
CE	Clinically Evaluable
CL	Total body clearance after IV administration
CL_{ss}	Total body clearance after IV administration at steady state
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration
CI	Confidence interval
CrCl	Creatinine clearance
CRE	Carbapenem-resistant Enterobacterales
CRPA	Carbapenem-resistant *Pseudomonas aeruginosa*
CSR	Clinical Study Report
cUTI	Complicated urinary tract infection
DSMB	Data Safety Monitoring Board
EA	Early Assessment
ECG	Electrocardiogram
eCRF	Electronic case report form
EOT	End of Treatment
ESBL	Extended-spectrum beta-lactamases
ET	Early Termination
FSH	Follicle-stimulating hormone
FUP	Follow-Up visit
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	Intravenous
λz	Apparent first-order terminal elimination rate constant
LLOQ	Lower limit of quantification
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MIC	Minimum inhibitory concentration
MIC_{50}	Minimum inhibitory concentration required to inhibit the growth of 50% of organisms tested
MIC_{90}	Minimum inhibitory concentration required to inhibit the growth of 90% of organisms tested
MITT	Modified Intent-to-Treat
m-MITT	Microbiological Modified Intent-to-Treat
MRT	Mean Residence time
PK	Pharmacokinetics
R^2	Coefficient of determination
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
T_{max}	Time to reach maximum observed plasma concentration
t½	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TOC	Test of Cure
V_{ss}	Steady-state volume of distribution during terminal elimination phase after IV infusion
V_z	Volume of distribution during terminal elimination phase after IV infusion
WBC	White blood cell
WHO	World Health Organization
WGS	Whole Genomic Sequencing

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the Meiji study with protocol number OP0595-5. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary 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 complicated urinary tract infection (cUTI) or acute uncomplicated pyelonephritis (AP).

2.1.2 Secondary Objectives

- 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.

2.2 Study Design

2.2.1 Overview

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 2.2.3.

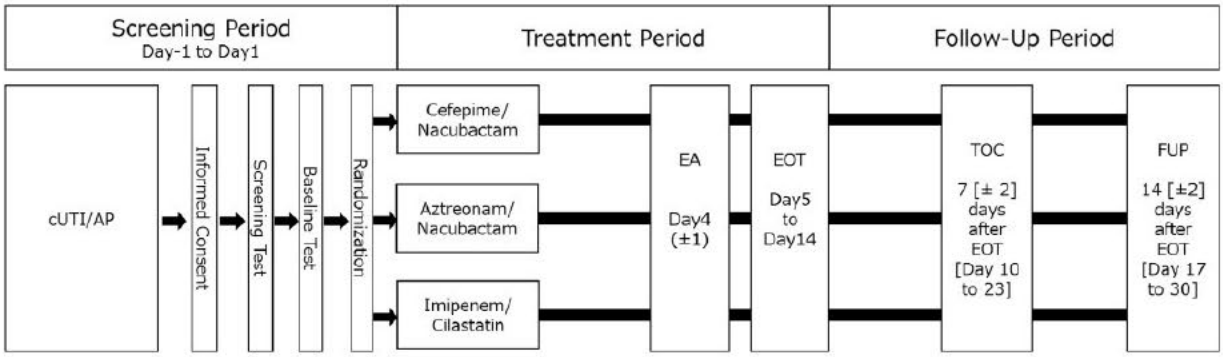
Randomization will be stratified by entry diagnosis (cUTI or AP) and by geographic region (Japan, China or Other). At least 30% of patients will have a diagnosis of AP and at least 60% will have a diagnosis of cUTI.

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.



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.

Figure 1. Study Design

Patients with a qualifying Gram-negative uropathogen co-infected (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 electrocardiograms (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 (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.

2.2.2 Randomization and Blinding

2.2.2.1 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.

2.2.2.2 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 Medpace to support the study pharmacists/designees who will have access to treatment assignment information. The unblinded Sponsor and Medpace team will not be involved in review of the clinical database or decisions regarding patient care.

2.2.3 Study Drug

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 electronic case report form (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.

If CrCl is [redacted] and [redacted] mL/min, patients will receive [redacted] g cefepime/[redacted] g nacubactam or [redacted] g aztreonam/[redacted] g nacubactam or [redacted] g imipenem/[redacted] g cilastatin every [redacted] hours. If CrCl is [redacted] and [redacted] mL/min, patients will receive [redacted] g cefepime/[redacted] g nacubactam or [redacted] g aztreonam/[redacted] g nacubactam or [redacted] g imipenem/[redacted] g cilastatin every [redacted] hours. If CrCl is [redacted] and [redacted] mL/min, patients will receive [redacted] g cefepime/[redacted] g nacubactam or [redacted] g aztreonam/[redacted] g nacubactam or [redacted] g imipenem/[redacted] g cilastatin every [redacted] hours. Dosage of nacubactam, cefepime, and aztreonam, and imipenem/cilastatin according to renal function are shown in Table 2.2.3.

Table 2.2.3. Study Drug Dosage According to Renal Function

CrCl (mL/min)	Cefepime/ Aztreonam (g)	Nacubactam (g)	Imipenem/Cilastatin (g)	Interval (hour)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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)]).

2.2.4 Schedule of Procedures

Study procedures will follow the schedule of procedures in the below Table 2.2.4.

Table 2.2.4. Schedule of Procedures

	Screening Period		Treatment Period						Follow-Up Period		ET
Day (± Visit Window)	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 $\geq 10^5$ 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 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 $\geq 10^3$ 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.
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 protocol 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 protocol 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.

2.2.5 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 Microbiological Modified Intent-to-Treat (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.

2.3 Efficacy Endpoints

2.3.1 Primary Efficacy Endpoint

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

2.3.2 Secondary Efficacy Endpoints

2.3.2.1 Secondary efficacy endpoints for cUTI and AP

- 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 Populations.

2.3.2.2 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:

- 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]);
- Elevated peripheral white blood cell (WBC) count (> $10{,}000/mm^3$);
- > 15% immature polymorphonuclear neutrophils (bands) regardless of peripheral WBC count;
- Leukopenia (WBC < $4{,}500/mm^3$);
- Tachycardia > 100 bpm;
- Tachypnea > 20 breaths/min;
- Hypotension, systolic < 90 mmHg; or
- 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.

2.3.3 Exploratory Efficacy Endpoints

[redacted]

2.4 Outcomes

2.4.1 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 2.4.1.

Table 2.4.1. 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.

2.4.2 Microbiological Outcome

The criteria for microbiological outcome are defined in Table 2.4.2 (a), Table 2.4.2 (b). Microbiological outcome will be determined programmatically based on the results from the site of infection.

Table 2.4.2 (a). 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 bacterial 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 2.4.2 (b). Microbiological Outcome 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.

2.4.3 Composite Outcome

cUTI/AP

The algorithm for composite clinical and microbiological success at EA, EOT, TOC, FUP, and ET is summarized in Table 2.4.3.

Table 2.4.3. Composite Clinical and Microbiological Success for cUTI and AP

Clinical Outcome	Microbiologic Outcome			
	Eradication	Persistence	Recurrence[1]	Indeterminate
Cured	Success	Failure	Failure	Failure
Failure[2]	Failure	Failure	Failure	Failure
Indeterminate	If clinical outcome for the last visit before EA, EOT, TOC, FUP, or ET is failure = failure; otherwise = indeterminate	Failure	Failure	If clinical outcome for the last visit before EA, EOT, TOC, FUP, or ET is failure = 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. If clinical outcome is "improvement", and microbiological outcome is "eradication", then composite outcome will be "Success" at EA visit.

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

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug or date of randomization depending on the patient's dosing status. In general, the day of the start of the study treatment infusion will be defined as Day 1, however, if not dosed, randomization date will be defined as Day 1. The day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Visit Window

Study visit periods will be windowed as applicable as shown in Section 2.2.4. Patients who discontinue from study drug and complete the ET visit but are not discontinued from the study should continue to complete safety assessments 7 to 14 days after ET. Values will be presented for all scheduled study visits according to the nominal visit obtained from the eCRF.

3.1.3 Definition of Baseline

For microbiological data, baseline pathogen(s) are determined from the specimens collected prior to the first dose of study drug. However, if the specimen taken closest to the administration of the first study drug does not meet qualifying pathogen criteria of m-MITT Population for a case in which pre-treatment with an antimicrobial agent has been administered, the specimen taken before use of antimicrobial agent that meets the qualifying pathogen criteria for the m-MITT Population and was collected within 48 hours prior to the first dose of study drug administration can be used for the acceptance/rejection decision and baseline. If more than one such specimen is available, the last of them should be used for baseline.

A baseline 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 concurrently (i.e. within 48 hours prior to the first dose of study drug administration) from a blood culture.

For all efficacy and safety endpoints, baseline is defined as the last non-missing measurement or non-missing assessment prior to the first dose of study drug. If patients are randomized but not dosed, the randomization date will be used to identify the baseline.

3.1.4 Summary Statistics

All summary statistics will be summarized by treatment group. For continuous variables, the number of observations, mean, standard deviation, median, minimum, and maximum will be provided. For categorical variables, the frequency and percentage in each category will be displayed. The denominator used for the percentage calculation will be clearly defined. In addition, 95% confidence intervals (CIs) will be computed as indicated.

Descriptive statistics will be provided for PK concentration data and PK parameters which will be fully outlined in section 3.5. All PK analyses will be performed using the PK Population.

3.1.5 Handling of Dropouts and Missing Data

For descriptive summaries in the primary efficacy analysis, patients with missing data will be included in the denominator for the calculation of success rate. For the clinical outcome, a clinical failure occurring at the last visit will be carried forward to the subsequent visits with missing outcomes or indeterminate

outcome. If there is a clinical cure or improvement at last visit, this clinical cure or improvement will not be carried forward. Descriptive summaries of safety measures will be based on observed data, no imputation of missing data will be implemented.

If it is not possible to determine whether an AE is treatment emergent or not due to completely or partially missing dates, the dates will be imputed in a conservative way so that the AE will be considered as treatment emergent, i.e., starting in on-treatment period.

Listings of the AEs, prior medications, concomitant medications, and medical history will present the actual partial dates; imputed dates will not be shown.

Data from central microbiology laboratory will be used for microbiological analysis.

If a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior or concomitant. If a medication start date is incomplete, the first day of the month will be imputed for missing day and January will be imputed for missing month. If a medication stop date is incomplete, the last day of the month will be imputed for missing day and December will be imputed for missing month. Incomplete start and stop dates will be listed as collected without imputation.

3.2 Analysis Populations

This section defines the analysis populations to be used for the planned statistical analyses.

3.2.1 Intent-to-Treat (ITT) Population

All patients who are randomized.

3.2.2 Modified Intent-to-Treat (MITT) Population

All patients who meet ITT criteria and receive any amount of study drug.

3.2.3 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 in the protocol for the definition of a qualifying pathogen). The definition of imipenem and meropenem susceptible pathogen is described in the protocol Section 4.1 (Inclusion Criterion #5).

3.2.4 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 time point;
- 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. The major protocol violations may include but are not limited to:
    a. Have key inclusion or exclusion violations;
    b. Received the wrong study drug based on the randomization assignment for any treatment visit;

c. Took restricted or prohibited concomitant medications.

3.2.5 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.

*Note: "interpretable positive urine culture" means positive urine culture for baseline qualifying pathogen.

3.2.6 Safety Population

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

3.2.7 PK Population

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

3.3 Patient Data and Study Conduct

3.3.1 Patient Disposition

Disposition will be summarized with counts and percentages by treatment group and overall for all screened patients. Disposition categories will include:

- Screened
- Randomized
- Treated
- Completed the study drug
- Discontinued the study drug early
- Primary reasons for early discontinuation of study drug
- Complete the study through the FUP visit
- Terminated the study early
- Primary reasons for early termination of study

A listing of all randomized patients who withdraw early will be provided that will specify the reason for withdrawal.

3.3.2 Protocol Deviations

Counts and percentages of patients with CSR-reportable protocol deviations by deviation category will be summarized by treatment group and in total for the ITT Population.

3.3.3 Analysis Populations

Counts and percentages of patients in each analysis population will be summarized by treatment group and in total for the ITT Population. Reasons for exclusion from each analysis population will also be summarized.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years) and age group (<65 years, 65 - 74 years, and ≥75 years; <65 years vs ≥65 years; <75 years vs ≥75 years)
- Sex
- Race (American Indian or Alaska Native, Asian-Japanese, Asian-Chinese, Asian-Other, Black or African America, Native Hawaiian or Other Pacific Islander, White, Other)
- Ethnicity
- Geographic region (Japan, China, Other; Japan vs Non-Japan; China vs Non-China)
- Height (cm) at baseline
- Weight (kg) at baseline
- Body mass index (BMI) (kg/m^2) and BMI categories (<30 kg/m^2, ≥30 kg/m^2)
- Primary infection type collected in eCRF (cUTI, AP)
- Baseline creatinine clearance and categories [redacted]
- Patients with secondary bacteremia (Yes, No)
- Prior short-acting antibacterial therapy (Yes, No)

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of patients as appropriate by treatment group and in total for each defined analysis population.

3.3.5 Medical and Surgical History

Medical history will be coded to System Organ Class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Counts and percentages of patients with medical history by SOC and preferred term will be summarized by treatment group and in total for Safety and m-MITT Populations.

At randomization, patients will be stratified into baseline diagnosis categories: cUTI or AP. The counts and percentages of patients with cUTI or AP collected via eCRF along with a frequency distribution of the signs/symptoms and evidence of pyuria criteria the patient met at enrollment, will be summarized by treatment group and in total for patients in the Safety and m-MITT Populations.

3.3.6 Baseline Clinical Signs and Symptoms

The counts and percentages of patients with each sign and symptom present at baseline of cUTI (Chills, Rigors, Suprapubic pain, Pelvic pain, Lower abdominal pain, Nausea, Vomiting, Dysuria, Urinary frequency, Urinary urgency) and AP (Chills, Rigors, Flank pain, Costo-vertebral angle tenderness, Nausea, Vomiting, Dysuria, Urinary frequency, Urinary urgency) by severity (absent, mild, moderate and severe) will be tabulated for the m-MITT, CE and ME Populations. In addition, descriptive statistics (mean, standard deviation, median, minimum and maximum value) for baseline temperature and WBC count will be presented.

3.3.7 Baseline Pathogens

All baseline qualifying pathogens will be summarized by genus and species by treatment group for the m-MITT and ME Populations. In addition, the number and percentage of patients with:

- Extended-spectrum beta-lactamases (ESBL)-Positive
- Complex infection (two or more baseline qualifying pathogens in a patient)

will be provided for the m-MITT and ME Populations.

ESBL positive is defined as resistant or intermediate to cefepime, ceftazidime, and/or aztreonam using CLSI criteria.

The MIC at baseline and each scheduled post-baseline visit will be summarized by baseline qualifying pathogen and by antimicrobial using descriptive statistics (number of patients with unique pathogens tested, 50th percentile [MIC_{50}], 90th percentile [MIC_{90}], and range) for the m-MITT Population. The MIC_{50} and MIC_{90} will only be calculated for baseline qualifying pathogens isolated from at least 10 patients at that visit within either treatment group. Contingency tables will be provided to show the number and percentage of baseline qualifying pathogens with MIC susceptibility results in the following categories: susceptible, intermediate, and resistant. Both CLSI and EUCAST interpretation will be summarized. If the same baseline qualifying pathogen is isolated from multiple samples at the same visit, only the pathogen with the highest MIC will be used.

The identification (genus and species) of organisms isolated will be done by using the central laboratories data only. Baseline pathogens are determined by a combination of programmatical derivation of qualifying baseline pathogens as defined in protocol section 7.1.3.1 followed by manual review of the study pathogens identified by the clinical/microbiological review team at the CRO according to a separate document of Pathogen Determination Algorithm, and confirmed by the Sponsor before unblinding.

3.3.8 Prior and Concomitant Medications

Prior and concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the World Health Organization (WHO) Drug Dictionary. For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of study drug and concomitant medications if they were taken at any time after the first dose of study drug (i.e. started prior to the first dose of study drug and were ongoing or started after the first dose of study drug).

Counts and percentages of patients taking prior and concomitant medications by ATC class and preferred term will be summarized by treatment group and in total based on the Safety Population. In addition, the counts and percentages of patients having concomitant surgical/diagnostic procedures will also be summarized in the Safety Population.

3.3.9 Study Drug Exposure and Compliance

The infusion start and stop dates and times, and volume of study drug administered IV will be recorded in the source documents and eCRF.

The descriptive statistics of the duration of study drug will be summarized by treatment group for the Safety and m-MITT Populations. Duration of study drug will be calculated as the last dose date - the first dose date + 1. The counts and percentages of patients receiving 1-5, 6-10 days, ≥11 days of therapy will be provided. Descriptive statistics of the total volume in the IV bag and total volume infused will be presented by treatment group, and baseline creatinine clearance categories ([redacted]).

The compliance rate of study drug will be calculated as the total number of doses received divided by the total number of doses expected then multiplied by 100, shown below.

$$\%\ \text{compliance} = \frac{\text{numer of doses received} * 100}{\text{total number of doses expected}}$$

where total number of expected doses is derived based on elapsed time between first and last doses of study drug and its prescribed frequency, i.e., ceil [(last dose ending date/time- first dose starting

date/time) /(8*3600)]. The number and percentage of patients with % compliance: < 80%, ≥ 80% will be tabulated by treatment group for the Safety and m-MITT Populations.

3.3.9.1 Calculation method for Lower dose

· If a lower dose than the dose specified in the protocol is administered, the administration will be considered as a missed dose. In case of a lower dose, the investigational drug may not be fully effective and can be considered as a missed dose.

3.3.9.2 Calculation method for Overdose

· If a higher dose than the dose specified in the protocol is administered, the administration will be considered as one dose. In case of a higher dose, the investigational drug would not affect the efficacy evaluation and can be considered as one dose.

3.4 Efficacy Analyses

Efficacy analyses will be performed on the m-MITT, CE, and ME Populations. Patients in the m-MITT Population will be analyzed according to the assigned treatment group irrespective of the treatment actually received.

3.4.1 Primary Efficacy Analyses

The primary efficacy endpoint is the proportion of patients who achieve complete composite clinical and microbiological success at TOC in the m-MITT Population. Patients will be categorized as success, failure, or indeterminate at TOC as described in Section 2.4.3. Patients with missing data or who are lost to follow-up at TOC and not failure are defined as indeterminate for the primary efficacy endpoint and will be included in the denominator for the calculation of success rate. The counts and percentages of patients in each treatment group in each response category will be reported.

The non-inferiority hypothesis test, which is a 1-sided hypothesis test, will be performed at the 2.5% level of significance. The null (H_0) and alternative (H_1) hypotheses are the following:

$$H_0: P_1 - P_2 \leq -\Delta$$

$$H_1: P_1 - P_2 > -\Delta$$

where:

Δ =15.0% is the non-inferiority margin,

P_1 = the proportion of patients with composite outcome of success at TOC in the cefepime/nacubactam treatment group,

P_2 = the proportion of patients with composite outcome of success at TOC in the imipenem/cilastatin treatment group.

This is based on the lower limit of the 2-sided 95% 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. The primary analysis is based on a CI computed using the unstratified 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.

3.4.1.1 Sensitivity Analysis

The 95% CIs for the observed difference in the proportion of patients with composite clinical and microbiological success at the TOC between treatment groups will be provided using the method of Miettinen and Nurminen stratified by baseline entry diagnosis (cUTI or AP) collected in eCRF and by geographic region (Japan, China or Other) for the m-MITT Population.

For each stratum, the counts and percentages 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 unstratified Miettinen and Nurminen method.

3.4.2 Secondary Efficacy Analyses

For the secondary efficacy endpoints, the counts and percentages 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. These summaries will be done for the outcomes/time point/population combinations shown in Table 3.4.2.

Table 3.4.2. Secondary Efficacy Endpoints

Statistical Category	Efficacy Endpoints	Conditions	Time Point	Analysis Population
Secondary	proportion of patients with composite clinical and microbiological success		TOC	CE, ME
			EA, EOT, FUP	m-MITT
		per type of resistance		
		per type of pathogen, type of resistance, and antimicrobial susceptibility	TOC	m-MITT
		per type of pathogen	EOT, FUP	m-MITT
	proportion of patients with a microbiological outcome of eradication		TOC	ME
			EA, EOT, TOC, FUP	m-MITT
		per type of pathogen, type of resistance, and antimicrobial susceptibility	TOC	ME
			EA, EOT, TOC, FUP	m-MITT
	proportion of patients with a clinical outcome of cure		TOC	CE, ME
			EA, EOT, TOC, FUP	m-MITT

		per type of pathogen, type of resistance, and antimicrobial susceptibility	TOC	ME
			EA, EOT, TOC, FUP	m-MITT
	proportion of patients with composite clinical outcome of recurrence and/or microbiological outcome of recurrence		FUP	m-MITT, ME
Secondary Bacteremia	proportion of patients with composite clinical and microbiological success	from cUTI or AP	TOC	m-MITT, CE, ME
	proportion of patients with a clinical outcome of cure	from cUTI or AP		m-MITT, CE, ME
		from secondary bacteremia		
	proportion of patients with a microbiological outcome of eradication	from cUTI or AP		m-MITT, ME
		from secondary bacteremia		
	proportion of patients who are free from the definition of secondary bacteremia AND a clinical outcome of cure AND a microbiological outcome of eradication	from cUTI or AP		m-MITT, ME
	proportion of patients who are free from secondary bacteremia			m-MITT, ME

3.4.3 Exploratory Efficacy Analyses

[redacted]

[redacted]

3.4.4 Subgroup Analyses

The following subgroups based on baseline characteristics will be used for subgroup analyses of primary efficacy endpoint. The forest plots (treatment difference between treatment groups and 95% CI) will be provided.

- Age (years) group (<65 years, 65 to 74 years, and ≥75 years; <65 years vs ≥65 years; <75 years vs ≥75 years)
- Sex (Male, Female)
- Race (American Indian or Alaska Native, Asian-Japanese, Asian-Chinese, Asian-Other, Black or African America, Native Hawaiian or Other Pacific Islander, White, Other)
- Geographic region (Japan, China, Other; Japan vs Non-Japan; China vs Non-China)
- Primary infection type collected in eCRF (cUTI, AP)

- Baseline creatinine clearance group ([redacted])

3.5 Pharmacokinetic Assessment

3.5.1 Sample Collections for Pharmacokinetic Analysis

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.

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 and prior to the next infusion.

Note: At least 4 time points, including the end of infusion collection at 1 hour are needed.

If multiple PK sampling cannot be conducted on Day 1, it will be conducted on Day 3 or Day 5 instead with sample collections following any of the 3 infusions on that day.

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 and prior to 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.

3.5.2 Handling Missing or Below the Lower Limit of Quantification Data

For PK concentration data, if the actual sampling time is missing, but a valid concentration value has been measured, the concentration value will be flagged, and the scheduled time point may be used for the calculation of PK parameters.

The pre-dose concentrations for each treatment group on Day 1 or Day 3 or Day 5 for multiple PK sampling will be assumed as zero.

For the individual concentration and PK parameter calculation of each treatment group, the following rules will be applied:

- If one or more BLQ values occur before the first measurable concentration, they will be assigned a value of zero.
- If BLQ values occur between measurable concentrations in a profile, the BLQ should be omitted (set to missing).

- If BLQ values occur after the last measurable concentration in a profile, the BLQ will be assigned a value of zero .

For the concentration summary and mean concentration plot preparation of each treatment group, the following rules will be applied:

- Mean concentration at any individual time point will only be calculated if at least half of the patients have valid values (i.e. quantifiable and not missing) at this time point for each treatment group.
- In cases where a mean value is not calculated due to the above criterion not being met, the value will be set to "NC".
- BLQ values will be set to zero.

3.5.3 Pharmacokinetic Concentration

For both multiple and sparse PK sampling, individual plasma concentrations of nacubactam, cefepime, and aztreonam will be summarized by renal function and treatment group at each nominal time point for the PK Population using descriptive statistics such as n, mean (arithmetic and geometric), standard deviation (SD), coefficient of variation (arithmetic and geometric), median, minimum and maximum. Individual plasma concentrations will also be listed by individual patient for the PK Population.

Individual plasma concentrations of nacubactam, cefepime, and aztreonam will be plotted by renal function and treatment group on a linear and semi-log scale against actual sampling time points relative to dosing time for both multiple and sparse PK sampling. Mean (±SD) concentration will be plotted on a linear and semi-logarithmic scale against nominal time points by renal function and treatment group, when available. The lower limit of quantification (LLOQ) will be plotted as a reference line in both instances.

Actual sampling times that are outside the sampling time windows will be excluded from concentration summary and mean concentration plotting but will still be used in the calculations of PK parameters and individual concentration plotting.

Individual values for PK concentration data will be reported to the same level of precision as received from bioanalytical laboratory. For PK data, N will be reported as integer, CV% and geometric CV% will be reported with 1 decimal place, and all other summary statistics will be reported with 3 significant digits. Geometric mean and geometric CV% will be calculated excluding 0 values.

3.5.4 Pharmacokinetic Parameters

The following plasma PK parameters of nacubactam, cefepime, and aztreonam will be determined for multiple PK sampling and sparse PK sampling using noncompartmental methods as appropriate:

Parameters	**Description**	**PK sampling subjects**	**Precision**
C_{max}	Maximum observed plasma concentration; determined directly from the concentration time profile; if the maximum plasma concentration occurs at more than one time point, C_{max} is defined as the first maximum value	multiple PK sampling and sparse PK sampling	sig/3

T_{max}	Time to reach maximum observed plasma concentration; If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.	multiple PK sampling and sparse PK sampling	dec/2
C_{min}	Minimum observed plasma concentration	multiple PK sampling and sparse PK sampling	sig/3
λz	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using points in the terminal log-linear phase.	multiple PK sampling	sig/3
$t_{½}$	Apparent terminal elimination half-life; calculated as ln(2)/λz	multiple PK sampling	dec/2
AUC_{0-t}	Area under the plasma concentration vs time curve (AUC) from pre-dose (time 0) to the last quantifiable plasma concentration (C_{last})	multiple PK sampling and sparse PK sampling	sig/3
AUC_{tau}	Area under the plasma concentration versus time curve over the dosing interval from time 0 to 8 hours post infusion.	multiple PK sampling	sig/3
AUC_{0-inf}	AUC from time 0 to infinity; calculated as (AUC_{0-t} + C_{last}/λz)	multiple PK sampling	sig/3
$AUC_{\%extrap}$	Percent of AUC_{0-inf} extrapolated, represented as (1 - AUC_{0-t}/AUC_{0-inf})*100	multiple PK sampling	dec/1
CL	Total body clearance (CL) after IV infusion administration; calculated as Dose/AUC_{0-inf} for day 1, day 3 and 5	multiple PK sampling	sig/3
V_z	Volume of distribution during terminal elimination phase after IV infusion administration; calculated as Dose/[λz*AUC_{inf}] for Day1.	multiple PK sampling	sig/3
V_{ss}	Volume of distribution during terminal elimination phase at steady state after IV infusion; calculated as CL x MRT (otherwise known as Dose*AUMC/$(AUC)^2$.	multiple PK sampling	sig/3

Actual collection times will be used in PK parameter calculations based on PK Population. The Linear-Log Trapezoidal method (equivalent to the Linear Up/Log Down option in WinNonlin) will be used in the computation of all AUC values. In order to estimate the apparent first-order terminal elimination constant, λz, linear regression of concentration in logarithm scale vs. time will be performed using at least 3 data

points. Uniform weighting will be selected to perform the regression analysis to estimate λz. The constant λz will not be assigned if one of the following occurs:

1. The terminal elimination phase is not linear (as it appears on a semi-logarithmic scale).
2. The terminal elimination rate constant indicates a positive slope ($\lambda z > 0$).
3. T_{max} is one of the three last data points.

The constant λz and its derived parameters will be listed but excluded from statistical analysis if one of the following occurs:

1. The adjusted coefficient of determination (R^2) is less than 0.8.
2. The $AUC_{\%extrap}$ exceeds 20%.

No value for λz, $AUC_{0\text{-}inf}$, $AUC_{\%extrap}$, CL/CL_{ss}, Vz/V_{ss}, or $t_{½}$ will be reported for cases that do not exhibit an acceptable terminal log-linear phase in the concentration-time profile.

No PK parameters will be calculated for patients with 2 or fewer detectable concentrations in their PK profile.

Pharmacokinetic parameters will be listed for individual subjects and summarized using descriptive statistics (n, mean, SD, coefficient of variation, minimum, maximum, median, geometric mean, and geometric coefficient of variation) for pooled days and separately for day 1, day 3 and day 5 by renal function and treatment group. No descriptive statistics will be determined when fewer than three individual PK parameters are available. Mean and SD will not be calculated for categorical-associated PK parameters (i.e., T_{max}) but median, min and max will be provided instead.

3.6 Safety Assessment

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

Safety data will be summarized by actual treatment received based on the Safety Population, no statistical hypothesis testing will be performed.

3.6.1 Adverse Events

AEs, which include clinical laboratory test variables, will be monitored and documented from the time of informed consent until the study participation is complete. All AEs will be coded to SOC and preferred term using the MedDRA.

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.

An overview of AEs will be provided including counts and percentages of patients (and event counts) with the following:

- Any AEs
- Any SAEs
- Any TEAEs (overall and by severity)
- Any study drug related TEAEs (overall and by severity)
- Any IV procedure related TEAEs

- Any treatment-emergent serious AEs (TESAEs)
- Any TEAEs leading to discontinuation of study drug
- Any TEAEs leading to discontinuation of study
- Any AEs leading to death

A table of any AEs by onset period will be provided including counts and percentages of patients (and event counts):

- Day 1-5
- Day 6-9
- Day 10-14
- Day 15 and after

Counts and percentages of patients (and event counts) will also be presented by SOC and preferred term for each of the categories in the overview. Counts and percentages of patients will also be presented by SOC, preferred term and maximum severity for TEAEs and study drug related TEAEs. When calculating the number of patients for specific AEs, if more than 1 event occurs with the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe or related occurrence for the summary by severity or relationship to study treatment, respectively.

Listings will be presented for AEs.

3.6.2 Clinical Laboratory Tests

Blood and urine samples for clinical laboratory assessments (chemistry, lipid, hematology, coagulation, and urinalysis) will be obtained as indicated in Table 2.2.4. A list of clinical laboratory assessments is included in Appendix B.

Values and changes from baseline will be presented at each scheduled visit and baseline by laboratory test. The incidence of abnormalities (as defined by normal ranges) prior to the first dose of study drug and after the first dose of study drug will be summarized with counts and percentages of patients.

3.6.3 Vital Signs

Vital signs will be measured as indicated in Table 2.2.4. Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature.

Values and changes from baseline will be summarized at each time point for each vital sign parameter.

3.6.4 Electrocardiograms

12-lead ECGs will be measured as indicated in Table 2.2.4. ECG parameters include heart rate (bpm), PR interval (msec), QRS duration (msec), QT interval (msec), RR interval (msec), and QTcF interval (msec).

Descriptive statistics will be provided for value and change from baseline in ECG parameters. When ECG data are collected in triplicates, the average value among three measurements will be summarized.

Counts and percentages of patients with the following potentially clinically significant abnormal QTcF results at scheduled visit and worst post-baseline visit will be summarized as follows:

- Absolute QTcF interval ≥450 msec and ≤480 msec
- Absolute QTcF interval >480 msec and ≤500 msec

- Absolute QTcF interval >500 msec
- Change from baseline QTcF interval increase >30 msec
- Change from baseline QTcF interval increase >60 msec

3.6.5 Physical Examinations

A complete physical examination will be performed as indicated in Table 2.2.4 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 Table 2.2.4. A limited, symptom-directed physical examination will occur as indicated in Table 2.2.4 if clinically indicated.

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.

5 INTERIM ANALYSIS

No interim analysis is planned for the study.

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

1) The analysis of "proportion of patients with composite clinical and microbiological success at TOC in m-MITT Population per type of pathogen, type of resistance, and antimicrobial susceptibility" was added in Section 3.4.2.
2) The analysis of "proportion of patients with composite clinical and microbiological success at EA/EOT/FUP in m-MITT Population per type of pathogen" was added in Section 3.4.2.
3) The analysis of 'proportion of composite clinical and microbiological success at EOT /FUP in m-MITT Population per baseline pathogen' was added in Section 3.4.2.

[redacted]

5) Removed the analyses from Section 3.4.2:

- Clinical cure rate at TOC by baseline pathogen and antimicrobial susceptibility category in CE Population
- Clinical cure rate at TOC by type of resistance in CE Population
- Composite clinical recurrence and/or microbiological recurrence at FUP in CE Population

7 PROGRAMMING SPECIFICATIONS

The creation of analysis datasets and all analyses will be performed using SAS® (version 9.4 or higher). PK parameters will be calculated via SAS® and confirmed with the results of Phoenix WinNonlin™ (version 8.3 or higher). All available data will be presented in patient data listings which will be sorted by

patient and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: REFERENCES

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

APPENDIX B: CLINICAL LABORATORY ASSESSMENT

Chemistry, hematology, lipid, coagulation, and urinalysis will be performed by the local laboratory at Screening and by the central laboratory at baseline and post baseline. While the patient is receiving study drug, additional clinical laboratory assessments may be performed by the central laboratory and serum creatinine will be performed daily, in principle, by the local laboratory.

Standard Safety Chemistry Panel	
Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate (if applicable at 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	
Partial thromboplastin time	Prothrombin time
International normalized ratio	
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]
• 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 $\geq$ 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 $\geq$ 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.