Statistical Analysis Plan
(SAP)

A Phase 3, Randomized, Double-Blind, Multi-Center Study to Evaluate the Efficacy, Safety, and Tolerability of Cefepime-AAI101 Compared to Piperacillin/Tazobactam in the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis, in Adults

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SAP APPROVAL FORM

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine transaminase
ALP	Alkaline phosphatase
AP	Acute pyelonephritis
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CE	Clinically evaluable
CFU	Colony forming units
CCI	Charlson Comorbidity Index
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
cUTI	Complicated urinary tract infection
DSAQ	Daily Symptom Assessment Questionnaire
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
ET	Early Termination
ESBL	Extended-spectrum β-lactamase
FSH	Follicle-stimulating hormone
ITT	Intent-to-treat
i.v.	Intravenous
LFU	Late Follow-up
LLN	Lower limit of normal
ME	Microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
m-MITT	Microbiological MITT
MITT	Modified Intent-to-treat
PK	Pharmacokinetic
PT	Prothrombin time
PTT	Partial thromboplastin time
q#h	Once every # hours

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical analysis plan
TEAE	Treatment-emergent adverse event
TOC	Test of Cure
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) is created based on Protocol AT-301 (Version 5.0, September 6, 2018) and describes in detail the statistical methodology and the statistical analyses to be conducted for the above mentioned protocol.

2. STUDY OBJECTIVES

The primary objective of this study is to assess the efficacy of cefepime-AAI101 compared to piperacillin/tazobactam in the treatment of complicated urinary tract infection (cUTI), including acute pyelonephritis (AP).

The secondary objectives of this study are the following:

- To assess the safety and tolerability of cefepime-AAI101 in hospitalized patients with cUTI or AP; and
- To characterize the pharmacokinetics (PK) of cefepime-AAI101 in patients with cUTI or AP.

3. STUDY DESIGN

3.1. General Study Design and Plan

This is a randomized, double-blind, active-controlled, multi-center, non-inferiority study to evaluate the efficacy, safety, and tolerability of the combination of cefepime plus AAI101 compared to piperacillin/tazobactam for the treatment of cUTI, including AP.

Approximately 1,040 patients ≥18 years of age who have a clinical diagnosis of cUTI or AP and meet all of the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to 1 of the following 2 treatment groups:

- 2 g cefepime plus 500 mg AAI101 infused over a period of 2 hours once every 8 hours (q8h) for 7 days (up to 14 days in patients with a positive blood culture at baseline); or
- 4.5 g piperacillin/tazobactam infused over a period of 2 hours q8h for 7 days (up to 14 days in patients with a positive blood culture at baseline).

No switch to oral therapy will be permitted. At least 50% of randomized patients will have cUTI and at least 30% will have AP.

To ensure balance among the treatment groups, randomization will be stratified by the following factors:

- Type of infection (AP versus cUTI with removable source of infection [*e.g.*, Foley catheter] versus cUTI without removable source of infection, but with other risk factors [*e.g.*, anatomical abnormality, neurogenic bladder, or azotemia]);
- Prior antibiotic therapy (short-acting antibiotic up to 24 hours versus no prior antibiotic therapy); and
- Region: Eastern Europe versus Americas (Latin America and United States) versus other countries (including Western Europe, Baltics, and South Africa).

All patients will be treated for a minimum of 7 days; however, treatment may continue for up to 14 days for patients with a positive blood culture at baseline at the discretion of the Investigator. For patients without bacteremia, treatment cannot be prolonged for more than 7 days. A Test of Cure (TOC) visit will occur 7 days after EOT (EOT + 7 days [±2 days]) for patients receiving 7 days of treatment and 19 days after randomization (randomization + 19 days [±2 days]) for patients receiving more than 7 days of treatment. A Late Follow-up (LFU) visit will occur 14 days after EOT (EOT + 14 days [±2 days]). Patients who withdraw from the study early will undergo an Early Termination (ET) visit. Patients who discontinue study drug but do not withdraw from the study will be asked to complete all remaining study visits.

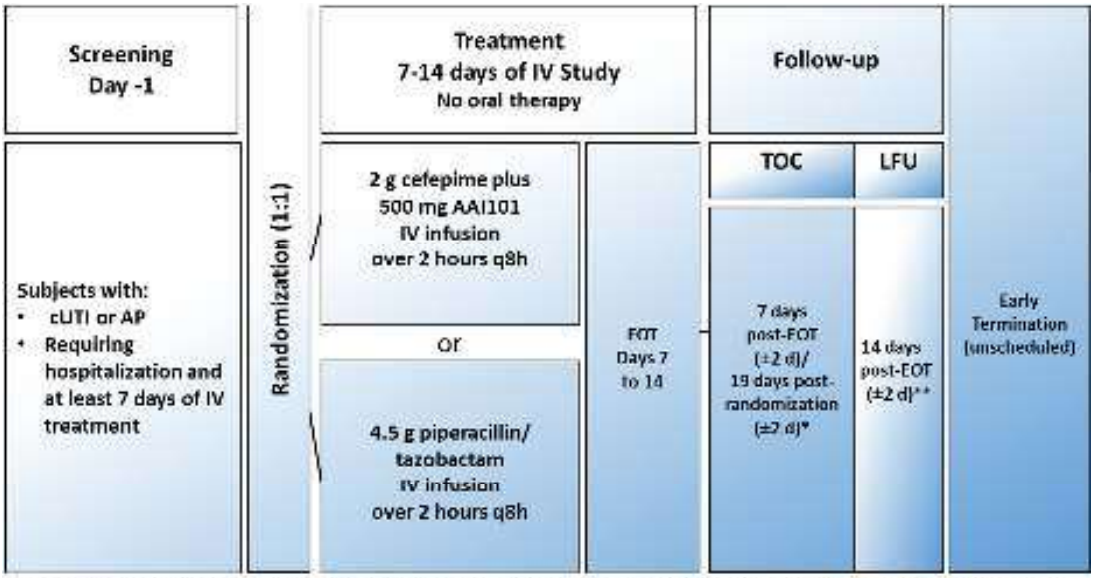
Patients with a single qualifying Gram-positive uropathogen detected in screening urine or blood culture after randomization can remain in the study if clinical signs and symptoms are improving, based on Investigator's judgment.

Patients with qualifying Gram-negative uropathogen co-infected with a Gram-positive uropathogen detected after randomization may be administered narrow-spectrum, open-label glycopeptide (*e.g.*, vancomycin), oxazolidinone (*e.g.*, linezolid), or daptomycin concomitantly with the blinded study drug at the discretion of the Investigator. Investigators should discuss such cases with the Medical Monitor.

Patients will be monitored for signs and symptoms of cUTI/AP daily during treatment and at subsequent follow-up visits. A Daily Symptom Assessment Questionnaire (DSAQ) tool will be utilized at Screening (2 questionnaires), each subsequent visit (Day 1 through Days 7 to 14), EOT, TOC, LFU, and ET. An assessment of clinical outcome will be performed by the Investigator at Day 3, EOT, TOC, LFU, and ET. Urine samples will be obtained at Screening, prior to drug administration on Day 1 (baseline), Day 3, EOT, TOC, LFU, and ET if the patient withdraws from the study early. Blood samples for culture will be collected at Screening, prior to study drug administration on Day 1, and at subsequent visits, if clinically indicated or if the previous culture was positive. Blood samples for PK analyses will be collected pre-dose and at 2 and 4 hours after the start of the 2-hour infusion (for any of the 3 infusions on that day) on Day 1, Day 3, Day 7, EOT, and ET.

Patients will be monitored for safety throughout the duration of the study. Safety assessments will include vital signs, physical examinations, laboratory assessments, adverse event assessments, and electrocardiograms (ECGs). A triplicate 12-lead ECG will be performed at Screening and Day 4. A pregnancy test will be performed at Screening and TOC for female patients of childbearing potential.

Figure 1. Study Scheme



* The TOC visit will occur 7 days after EOT (EOT + 7 days [±2 days]) for patients receiving 7 days of treatment and 19 days after randomization (randomization + 19 days [±2 days]) for patients receiving more than 7 days of treatment.

** The LFU visit should not take place earlier than 3 days after the TOC visit.

AP = acute pyelonephritis; cUTI = complicated urinary tract infection; d = day; EOT = End of Treatment; IV = intravenous; LFU = Late Follow up; q8h = once every 8 hours; TOC = Test of Cure.

3.2. Study Population

The population for this study is approximately 1,040 adult patients ≥18 years of age who require hospitalization for cUTI or AP. At least 50% of randomized patients will have cUTI and at least 30% will have AP.

3.3. Randomization and Blinding

Randomization will be coordinated through a centralized Interactive Response Technology system.

Study patients, the Sponsor, Investigators, and site personnel carrying out study procedures, evaluating patients, entering study data, and/or evaluating study data will be blinded to treatment assignment until database lock. Study site personnel involved in the preparation of the study drug (*i.e.*, pharmacist or designated staff member) will be unblinded to the patient's randomized treatment. At least 50% of randomized patients will have cUTI and at least 30% will have AP.

To ensure balance among the treatment groups, randomization will be stratified by the following factors:

- Type of infection (AP versus cUTI with removable source of infection [*e.g.*, Foley catheter] versus cUTI without removable source of infection, but with other risk factors [*e.g.*, anatomical abnormality, neurogenic bladder, or azotemia]);

- Prior antibiotic therapy (short-acting antibiotic up to 24 hours versus no prior antibiotic therapy); and
- Region: Eastern Europe versus Americas (Latin America and United States) versus other countries (including Western Europe, Baltics, and South Africa).

3.4. Breaking the Blind

Unblinding by request of an Investigator should occur only in the event of an emergency or adverse event 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 medication information from the centralized randomization system. They should not attempt to get this information from the site's unblinded pharmacist or qualified designee. The documentation received from the centralized randomization system indicating the code break must be retained with the patient's source documents in a secure manner so as not to un-blind 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 Sponsor's 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 Sponsor's 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. Patients who are unblinded and withdrawn from the study will not be replaced.

3.5. Study Assessments

Table 1 presents the schedule of procedures of the study.

Table 1: Schedule of Procedures

	Screening	Treatment Period							Follow-Up Period		Early Termination
									TOC	LFU	
Study Day / **Procedure**	**Day -1**	**Day 1[a]**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7 to Day 14 (EOT)[b]**	**EOT +7 Days (±2 Days)/ Randomization + 19 Days (±2 Days)[c]**	**EOT +14 Days (±2 Days)[d]**	**Unscheduled**
Informed consent[e]	X										
Demographics	X										
Medical history	X	X									
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X									
Pregnancy test[f]	X								X		
Triplicate 12-lead ECG[g]	X				X						
Clinical signs and symptoms	X	X	X	X	X	X	X	X	X	X	X
Assessment of clinical outcome				X				X[h]	X	X	X
Pharmacokinetic sampling[i]		X		X				X			X
Urine culture	X	X[k]		X				X[h]	X	X	X
Blood culture	X[j]	X[j]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]
Laboratory assessments (chemistry, hematology, coagulation, and urinalysis)[m]	X	X	X[n]	X	X[n]	X[n]	X[n]	X[o]	X	X	X
Physical examination[p]	X	X	X	X	X	X	X	X	X	X	X
Vital signs[q]	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Charlson Comorbidity Index[r]		X									
DSAQ	X[s]	X[t]	X	X	X	X	X	X	X	X	X
Randomization		X									
Study drug administration		X	X	X	X	X	X	X[u]			

Footnotes are on the following page.

a. Day 1 procedures will be performed prior to the first dose of study drug. 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 (but laboratory assessment samples for Day 1 need to be sent to the central laboratory).
b. The EOT may occur anytime from Day 7 to Day 14, depending on treatment duration at the discretion of the Investigator.
c. The TOC will occur 7 days after EOT (EOT + 7 days [±2 days]) for patients receiving 7 days of treatment and 19 days after randomization (randomization + 19 days [±2 days]) for patients receiving more than 7 days of treatment.
d. The LFU visit should not take place earlier than 3 days after the TOC visit.
e. Signed informed consent must be obtained before any study-related procedures are performed.
f. For women of childbearing potential, a urine and/or serum pregnancy test will be performed within 1 day prior to study entry by the local laboratory at Screening and at TOC. Women no longer of childbearing potential are defined as being ≥50 years of age and being amenorrhoeic for ≥12 months following cessation of all pharmaceutical or exogenous treatment; being <50 years of age and being amenorrhoeic for ≥12 months following cessation of all pharmaceutical or exogenous treatment and with FSH levels in the post-menopausal range; or being permanently sterile (*i.e.,* hysterectomy, bilateral oophorecotomy, or bilateral salpingectomy). If FSH levels are not available at the time of randomization, the patient must have a negative pregnancy test and agree to use highly effective contraception methods until the FSH result is available.
g. If Screening and Day 1 occur on the same day, ECG must be performed prior to study drug administration.
h. To be performed at EOT only.
i. Blood samples for PK analysis will be collected pre-dose and at 2 and 4 hours after the start of the 2-hour infusion (for any of the 3 infusions on that day) on Day 1, Day 3, Day 7, EOT, and ET. If no infusion at ET, 1 PK sample will be taken.
j. Two sets of samples from 2 separate venipuncture sites will be obtained at Screening and prior to study drug administration on Day 1 for baseline blood cultures.
k. A urine sample taken within 48 hours prior to randomization as part of standard of care, to support diagnosis or to treat a medical condition, can be used for baseline microbiologic assessments if the organism(s) cultured were sent to the designated central laboratory. However, all patients who had a urine sample taken previously as part of standard of care should have a repeat urine sample for culture obtained prior to the start of study drug treatment. This sample should be taken as close to randomization as possible (within 2 hours prior to randomization, if possible).
l. If a blood culture is positive at baseline for an organism obtained in a concurrently collected urine sample, daily blood cultures will be collected until the first negative blood culture (culture reading at ≥24 hours). Additional blood cultures will be collected if clinically indicated. For patients with fever spikes (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal temperature ≥38.3°C [≥100.9°F]) during the study, additional blood samples may be obtained at the time of the fever spike.
m. Screening laboratory tests for eligibility will include, at a minimum, serum creatinine (for eGFR), platelet count, ALT, AST, alkaline phosphatase, total bilirubin, absolute neutrophil count, hemoglobin, and urinalysis with microscopy. Coagulation (PT and PTT) will not be collected at Screening. All screening laboratory assessments will be performed at the local laboratory and may have been collected as standard of care within 24 hours prior to randomization. Laboratory assessments (chemistry, hematology, coagulation, and urinalysis) collected after Screening (also when Day 1 is on the same day as Screening) will be sent to the central laboratory for analysis. If the urine sample is obtained within 48 hours as part of the patient's standard of care in order to support a diagnosis or treat a medical condition, the result may be used for confirming study eligibility. If azotemia is suspected, obtain blood urea nitrogen (or urea).
n. Collect samples for only coagulation (PT and PTT) and send to the central laboratory. If required for the evaluation of renal function, collect sample for laboratory assessment of serum creatinine only; may be sent to local and/or central laboratory.
o. Collect samples for laboratory assessments at Day 10 (if applicable) and EOT (chemistry, hematology, coagulation [PT and PTT], and urinalysis). If Day 7 is not EOT, collect ALT, AST, alkaline phosphatase, total and direct bilirubin, coagulation (PT and PTT), and a full urinalysis. If Days 8, 9, 11, 12, or 13 are not EOT, collect samples for only coagulation (PT and PTT) and send to the central laboratory for analysis. If required for the evaluation of renal function, collect sample for laboratory assessment of serum creatinine only; may be sent to local and/or central laboratory.
p. 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.
q. Vital signs include body temperature, systolic and diastolic blood pressure, and heart rate. Patients should be resting in a semi-recumbent position for at least 5 minutes prior to and during measurement of vital signs. Vital signs are only to be taken once (no repeats required). Vitals signs should be collected at the same time as assessments of signs and symptoms.
r. The Charlson Comorbidity Index will be calculated at baseline, prior to the first dose of study drug on Day 1.

s. At Screening, 2 questionnaires are required: 1 questionnaire to assess premorbid symptoms (symptoms prior to the onset of current cUTI or AP), and 1 questionnaire to assess new symptoms of the cUTI or AP within 24 hours of randomization.
t. In the event that Screening and Day 1 occur on the same day, the Day 1 DSAQ will not be collected.
u. Study drug will be administered for 7 treatment days; however, treatment may continue up to 14 days in patients with a positive blood culture at baseline at the discretion of the Investigator. For patients without bacteremia, treatment cannot be prolonged for more than 7 days.

ALT = alanine aminotransferase; AP = acute pyelonephritis; AST = aspartate aminotransferase; cUTI = complicated urinary tract infection; DSAQ = Daily Symptom Assessment Questionnaire; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOT = End of Treatment; ET = Early Termination; FSH = follicle-stimulating hormone; LFU = Late Follow-up; PK = pharmacokinetic(s); PT = prothrombin time; PTT = partial thromboplastin time; TOC = Test of Cure.

4. SAMPLE SIZE DETERMINATION

A trial enrolling 810 patients who are evaluable in the Microbiological Modified Intent-to-Treat (m-MITT; see Section 6 for definition) Population will provide 90% power to demonstrate the non-inferiority of cefepime-AAI101 to piperacillin/tazobactam in the m-MITT Population, assuming the overall success rate is 74% in both groups and the non-inferiority margin is 10 percentage points. This trial will continue until 810 patients are evaluable in the m-MITT Population. It is estimated that approximately 1,040 patients will be recruited to achieve 810 evaluable patients, assuming an evaluability rate of 78%.

5. STUDY ASSESSMENT

5.1. Efficacy Assessments

5.1.1. Primary Efficacy Assessment

The primary efficacy parameter is the proportion of patients in the m-MITT Population who achieve overall treatment success at TOC. Overall treatment success is defined as the composite of clinical outcome of Cure and the microbiological outcome of Eradication ($<10^3$ CFU/mL in urine culture).

5.1.1.1. Daily Symptom Assessment Questionnaire

A Daily Symptom Assessment Questionnaire (DSAQ) tool will be utilized at Screening (2 questionnaires), each subsequent visit (Day 1 through Days 7 to 14), EOT, TOC, LFU, and ET. In the event that Screening and Day 1 occur on the same day, the Day 1 DSAQ will not be collected.

At the Screening Visit, 2 questionnaires are required: 1 questionnaire to assess premorbid symptoms (symptoms prior to the onset of current cUTI or AP) and 1 questionnaire to assess new symptoms of the cUTI or AP within 24 hours of randomization.

The following symptoms will be assessed:

- Lower back or flank pain,
- Pain or uncomfortable pressure in the lower abdomen or pelvic area,
- Pain or burning during urination,
- Frequent urination or going to the toilet more often than usual, and
- Urgency of urination or an uncontrollable urge to pass urine.

For each symptom, there is only 1 response from the following possible options: no symptom, mild, moderate, or severe.

5.1.1.2. Assessment of Clinical Signs and Symptoms

Patients will be monitored for signs and symptoms of cUTI/AP daily during treatment and at subsequent follow-up visits.

The following signs and symptoms will be assessed:

- Dysuria,
- Increased urinary frequency,
- Urinary urgency,
- Fever (oral/tympanic ≥38°C [≥100.4°F] or rectal temperature ≥38.3°C [≥100.9°F]),
- Maximum daily temperature of previous 24 hours,
- Lower abdominal pain or pelvic pain (only for cUTI),
- Suprapubic tenderness on physical examination (only for cUTI),
- Flank pain (only for AP),
- Costo-vertebral angle tenderness on physical examination (only for AP),
- Nausea, and
- Vomiting.

5.1.1.3. Clinical Outcome

Clinical outcome is based on the assessment of signs and symptoms and will be completed on Day 3, and at EOT, TOC, LFU, and ET. The Investigator will assign a clinical outcome as defined in Table 2. If the clinical outcome is "Failure," the patient may initiate non-study antimicrobial therapy as per standard of care.

Table 2 presents clinical outcome criteria for this study.

Table 2. 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), such that no further antimicrobial therapy to treat the cUTI/AP is warranted. Symptom resolution does not necessarily include baseline symptoms associated with 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 Day 3, EOT, TOC, LFU, and ET.**
Improvement	Lessening, incomplete resolution, or no worsening of baseline clinical signs and symptoms of cUTI or AP, but continued i.v. therapy for management of cUTI/AP is warranted. **This outcome category can only be used at Day 3.**
Failure	Patients who experience any 1 of the following: • At Day 3 and EOT, worsening of baseline clinical signs and symptoms of cUTI or AP or the development of new clinical signs and symptoms of infection, sufficient to stop study drug and initiate non-study antimicrobial; • At TOC and LFU visits, persistence, incomplete resolution of baseline clinical signs and symptoms of infection, requiring additional antibiotic therapy; • Withdrawal from the study drug due to an adverse event or due to lack of clinical improvement; or • Death of the patient during the study. Note: Withdrawal from the study drug due to an adverse event or due to lack of clinical improvement or death of the patient during the study will lead to clinical failure for the subsequent time points but will not change the previous time point assessment. **This outcome category can be used at Day 3, EOT, TOC, LFU, and ET.**
Indeterminate	Clinical outcome cannot be determined. **This outcome category can be used at Day 3, EOT, TOC, LFU, and ET.**

AP = acute pyelonephritis; cUTI = complicated urinary tract infection; EOT = End of Treatment; ET = Early Termination; i.v. = intravenous(ly); LFU = Late Follow-up; TOC = Test of Cure.

5.1.1.4. Microbiological Outcome

Table 3 presents microbiological outcome criteria for this study.

Table 3. Microbiological Outcome Criteria

Category	Criteria
Eradication	• The baseline qualifying Gram-negative pathogen(s) is reduced to $<10^3$ CFU/mL in urine culture; AND • A negative blood culture for a Gram-negative pathogen that is identified as a uropathogen (if repeated after positive baseline blood 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; OR • A continuously positive blood culture with an organism that is identified as a Gram-negative uropathogen.
Recurrence	• Isolation of the same baseline Gram-negative pathogen(s) from urine culture after a response of Eradication; OR • A positive blood culture with the same baseline Gram-negative pathogen that was identified as a uropathogen after a response of Eradication.
Indeterminate	No urine culture is available, or the culture cannot be interpreted for any reason.

NOTE: The baseline qualifying pathogen is defined as a non-contaminated baseline Gram negative organism $\geq 10^5$ CFU/mL for urine or growth in blood culture concurrently.
CFU = colony-forming units.

Per-pathogen microbiological responses will also be determined (descriptive analyses) using a cut-off of $<10^3$ CFU/mL.

5.1.1.4.1. Microbiology assessments

Urine culture

Urine samples will be obtained at Screening, prior to drug administration on Day 1 (baseline), Day 3, at EOT, at TOC, at LFU, and at ET if the patient withdraws from the study early.

Urine samples for microbiological testing will be collected by clean-catch midstream, from 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 randomization as part of standard of care, to support diagnosis or to treat a medical condition, can be used for baseline microbiologic assessments if the organism(s) cultured were sent to the designated central laboratory. However, all patients who had a urine sample taken previously as part of standard of care should have a repeat urine sample for culture obtained prior to the start of study drug treatment. This sample should be taken as close to randomization as possible (within 2 hours prior to randomization, if possible).

Patients with a single qualifying Gram-positive uropathogen detected in screening urine or blood culture after randomization can remain in the study if clinical signs and symptoms are improving, based on the Investigator's judgment.

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 or more bacterial organisms in the urine, the urine culture will be considered contaminated. An organism will not be considered a contaminant if it also grows in a concurrently obtained blood culture.

Prior to randomization, urine samples submitted for culture must have a urinalysis/dipstick and microscopic analysis performed by the local laboratory.

The local laboratory will culture each sample for organism identification, quantification (urine culture only), and susceptibility testing.

Prior to randomization, only organisms that grow $\geq 10^5$ CFU/mL of urine, and are not deemed a contaminant as detailed in the Microbiology Procedures Manual, will be sent to the central laboratory for confirmation of identification and susceptibility testing, as well as further characterization of the organism(s), unless the same organism grows concurrently in urine and blood, in which case these pathogens should be sent to the central laboratory regardless of CFU/mL.

For all post-baseline urine cultures, only organisms that grow $\geq 10^3$ CFU/mL of urine, and are not deemed a contaminant as detailed in the Microbiology Procedures Manual, will be sent to the central laboratory for confirmation of identification and susceptibility testing, as well as further characterization of the organism(s).

For instances where local susceptibility testing indicates resistance to the study drug, but the patient is clinically improving, the patient should remain on the study drug at the Investigator's discretion.

Blood culture

Two sets of samples from 2 separate venipuncture sites will be obtained at Screening and prior to study drug administration 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). If a blood culture is positive at baseline for an organism obtained in a concurrently collected urine sample, daily blood cultures will be collected until the first negative blood culture is obtained (culture reading at ≥24 hours). Additional blood cultures will be collected if clinically indicated. For patients with fever spikes (oral or tympanic temperature ≥38°C [≥100.4°F] or rectal 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 susceptibility testing.

5.1.1.5. Overall Response

Overall response is derived from a composite of the clinical and microbiological outcome, as presented in Table 4. Overall treatment success is defined as the composite of the clinical outcome of Cure and the microbiological outcome of Eradication. Overall treatment success at TOC is the primary efficacy endpoint, and the proportion of patients with overall treatment success at EOT and LFU will be evaluated as secondary endpoints.

Table 4. Determination of Overall Response

Clinical Outcome	Microbiological Outcome			
	Eradication	Persistence	Recurrence[a]	Indeterminate
Cure	Success	Failure	Failure	Indeterminate
Failure	Failure	Failure	Failure	Failure
Indeterminate	Failure if clinical outcome at any prior visit was Failure, otherwise Indeterminate.	Failure	Failure	Failure if clinical outcome at any prior visit was Failure, otherwise Indeterminate.

a. For an outcome of Recurrence, patients must have documented prior Eradication.

5.1.2. Secondary Efficacy Assessments (see Section 6 for analysis populations)

The secondary efficacy parameters include the following:

- The proportion of patients in the m-MITT Population with overall treatment success at Day 3, EOT and LFU;
- The proportion of patients in the m-MITT and Microbiologically Evaluable (ME) Populations with a microbiological outcome of Eradication at Day 3, EOT, TOC, and LFU;
- The proportion of patients in the m-MITT+R and ME+R Populations with a microbiological outcome of Eradication at Day 3, EOT, TOC, and LFU;
- The proportion of patients with a clinical outcome of Cure or Improvement (Day 3 only) in the m-MITT, m-MITT+R, Clinically Evaluable (CE), ME, and ME+R Populations at Day 3, EOT, TOC, and LFU;
- Per-pathogen overall treatment success, clinical outcome of Cure, and microbiological outcome of Eradication in the m-MITT, m-MITT+R, ME, ME+R, and CE Populations at Day 3, EOT, TOC, and LFU;

- Subset of patients with a baseline isolate of Enterobacteriaceae, MICs ≥1 for ceftazidime, ceftriaxone, cefepime, meropenem, or cefepime-AAI101, and genotyped as
    - ESBL co-producing (ESBL-genotype, combined with or without any other non-ESBL genotype)
    - ESBL-only producing (ESBL-genotype only, no other genotype)
    - ESBL co-producing (CTX-M-type)
    - ESBL-only producing (CTX-M-type)
    - ESBL co-producing (non-CTX-M-type)
    - ESBL-only producing (non-CTX-M-type)
    - Carbapenemase (Class A) co-producing
    - Carbapenemase (Class A)-only producing
    - Carbapenemase (Class B) co-producing
    - Carbapenemase (Class B)-only producing
    - Carbapenemase (Class D) co-producing
    - Carbapenemase (Class D)-only producing
    - AmpC co-producing
    - AmpC-only producing
    - non-ESBL-, non-carbapenemase-, and non-AmpC-producing

  with overall treatment success, clinical outcome of Cure, and microbiological outcome of Eradication in the m-MITT, m-MITT+R, ME, ME+R, and CE Populations at Day 3, EOT, TOC, and LFU.
- The proportion of patients with overall treatment success, clinical outcome of Cure, and microbiological outcome of Eradication at each discrete cefepime/AAI101 baseline MIC value by baseline pathogen in the m-MITT, m-MITT+R,ME, and ME+R, at TOC;
- The proportion of patients with overall treatment success, clinical outcome of Cure, and microbiological outcome of Eradication at each discrete piperacillin/tazobactam baseline MIC by baseline pathogen value in the m-MITT, m-MITT+R,ME, and ME+R at TOC.

5.1.3. Pharmacokinetic Assessments

Blood samples for PK analyses will be collected from all patients pre-dose and at 2 and 4 hours after the start of the 2-hour infusion (for any of the 3 infusions on that day) on Day 1, Day 3, Day 7, EOT, and ET. If no infusion at ET, 1 PK sample will be taken. The exact times of PK sampling are to be collected and recorded in the eCRF.

The PK plasma samples will be used to estimate PK parameters, such as area under the concentration-time curve, maximum plasma concentration, time to maximum plasma concentration, drug clearance, half-life, minimum plasma concentration, and steady-state volume of distribution using a structural population PK model.

Pharmacokinetic characterization and evaluation of plasma exposures of cefepime and AAI101 will be performed using both non-compartmental and modeling methods. Using a sparse sampling approach, PK samples on Day 1, Day 3, Day 7, EOT, and ET will be obtained from all patients at the specified time points. If no infusion at ET, 1 PK sample will be taken. The PK samples will be collected from both treatment groups to maintain the blind. Only PK samples obtained from the cefepime-AAI101 group will be analyzed (using a validated assay) by the central bioanalytical laboratory. While the PK analysis will be ongoing during the study, the Sponsor and all study personnel will remain blinded to the results.

5.2. Safety Assessments

The safety and tolerability profile will be determined by incidence and severity of adverse events and SAEs, vital signs, laboratory tests, ECGs, and physical examinations from Screening through LFU (EOT + 14 days [±2 days]).

5.2.1. 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. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 21.0). The severity of all AEs should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

5.2.2. Clinical Laboratory Evaluations

Screening laboratory tests for eligibility will include, at a minimum, serum creatinine (for eGFR), platelet count, ALT, AST, alkaline phosphatase, total bilirubin, absolute neutrophil count, hemoglobin, and urinalysis with microscopy. All screening laboratory assessments will be performed at the local laboratory and may have been collected as standard of care within 24 hours prior to randomization. Laboratory assessments collected after Screening (also when Day 1 is on the same day as Screening) will be sent to the central laboratory for analysis.

Coagulation (PT and PTT) will be collected at randomization and at each subsequent visit and will be sent to the central laboratory for analysis.

See below for a list of all local and central clinical laboratory analytes to be assessed in this study.

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	C-reactive protein
Calcium	Chloride
Creatinine	Creatine kinase
Creatinine clearance	Direct bilirubin
Glucose	Lipase

Phosphorus	Potassium
Sodium	Lactate dehydrogenase
Total protein	Total bilirubin
Uric acid	

Hematology

Hematocrit	Hemoglobin
Mean cell hemoglobin	MCH concentration
Mean cell volume	Platelets
Red blood cell count	White blood cell count and differential, including absolute neutrophil count

Coagulation

Prothrombin time	Partial thromboplastin time

Pregnancy Testing

Human chorionic gonadotropin (urine and/or serum)
Follicle-stimulating hormone

Urinalysis

Bilirubin	Blood
Bacteria	Casts
Glucose	Ketones
Leukocyte esterase	Microscopy, including white blood cell count
Nitrite	pH
Protein	Specific gravity
Urobilinogen	

5.2.3. Vital Signs

Vital signs will be collected at Screening and at each subsequent visit. Vital signs are only to be taken once (no repeats required) and will include systolic and diastolic blood pressure, heart rate, and body temperature.

Body temperature may be taken via tympanic, rectal, or oral only. The method of measuring body temperature will be recorded in the appropriate eCRF. The same method of measuring a patient's body temperature should be used throughout the study. Vitals 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.

5.2.4. Electrocardiograms

A triplicate 12-lead ECG will be performed at Screening and Day 4. If Screening and Day 1 occur on the same day, the ECG must be performed prior to study drug administration. The ECG reading and analysis will be done centrally by an ECG reading expert and be reported separately as attachment to the clinical study report.

5.2.5. Physical Examinations

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 physical examination will be completed at subsequent visits, if clinically indicated. If a patient does not display symptoms, no limited physical examination needs to be performed. Physical examinations may be performed at various unscheduled time points if deemed necessary by the Investigator. All physical examinations may be performed by physicians, physician's assistants, or nurse practitioners.

5.3. Medical History

Medical history will be collected at Screening and Day 1 and coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 21.0).

5.4. Prior and Concomitant Medication/Procedures/Non-drug Therapies

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.

Prior and concomitant medication will be coded using the World Health Organization Drug Dictionary (WHO-DD version B2 March 2018).

Prior and concomitant procedures/non-drug therapies will be coded using MedDRA, Version 21.0.

6. ANALYSIS POPULATIONS

The following analysis populations will be used for analyses.

6.1. Intent-to-Treat Population (ITT)

The ITT Population includes all patients who are randomized.

6.2. PK Population

The PK Population includes all patients in the ITT Population who have at least 1 PK sample taken. Pharmacokinetic analyses will be based on actual treatment received.

6.3. Modified Intent-to-Treat Population (MITT)

The MITT Population includes all patients who meet ITT criteria and receive any amount of study drug.

6.4. Microbiological Modified Intent-to-Treat Population (m-MITT)

The m-MITT Population includes all randomized patients who meet MITT criteria and who have a baseline Gram-negative pathogen $\geq 10^5$ CFU/mL in urine culture or the same pathogen present in concurrent blood and urine cultures that causes the cUTI that is not resistant to cefepime/AAI101 (MIC determined with AAI101 at a fixed concentration of 8 μg/mL) or piperacillin/tazobactam (defined as MIC ≤8 μg/mL or MIC ≤64 μg/mL, respectively). If ≥3 bacterial isolates are identified, the culture will be considered contaminated regardless of colony count unless 1 of the isolates that grows in the urine, even if $\leq 10^5$ CFU/mL, is also isolated from a blood culture obtained within 48 hours prior to randomization. Any patient with only a Gram-positive pathogen or a bacterial species typically not expected to respond to both study drugs at $\geq 10^5$ CFU/mL will be excluded from the m-MITT Population. Patients with contaminated Screening and baseline samples will be excluded from the m-MITT Population. The m-MITT Population will be the primary efficacy population. Efficacy analyses will be based on the treatment as randomized.

6.5. Microbiological Modified Intent-to-Treat Population Including Patients with Resistant Isolates (m-MITT+R)

The m-MITT Population includes all randomized patients who meet MITT criteria and who have a baseline Gram-negative pathogen $\geq 10^5$ CFU/mL in urine culture or the same pathogen present in concurrent blood and urine cultures that causes the cUTI, including isolates resistant to cefepime/AAI101 (MIC determined with AAI101 at a fixed concentration of 8 μg/mL) or piperacillin/tazobactam (defined as MIC >8 μg/mL or MIC >64 μg/mL, respectively). If ≥3 bacterial isolates are identified, the culture will be considered contaminated regardless of colony count unless 1 of the isolates that grows in the urine, even if $\leq 10^5$ CFU/mL, is also isolated from a blood culture obtained within 48 hours prior to randomization. Any patient with only a Gram-positive pathogen at Baseline will be excluded from the m-MITT+R Population. Patients with contaminated Screening and baseline samples will be excluded from the m-MITT+R Population.

6.6. Clinically Evaluable (CE) Population

The CE Population includes 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 a total duration of antibacterial therapy of at least 15 consecutive doses of study drug or are classified as clinical failures after completing at least 9 doses of i.v. study drug therapy;
- Have a clinical assessment at TOC, unless criteria for clinical failure were met at an earlier time point;
- Did not receive concomitant antibacterial therapy 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.

6.7. Microbiologically Evaluable (ME) Population

The ME Population includes all 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.

Concomitant administration of narrow-spectrum Gram-positive active agents to patients who have Gram-positive and Gram-negative co-infection will not affect patient evaluability in the CE or ME Populations.

6.8. Microbiologically Evaluable Population Including Patients with Resistant Isolates (ME+R)

The ME+R Population includes all patients who meet the definition for both the m-MITT+R and CE Populations. In addition, to be included in the ME+R Population, patients must not have a microbiological outcome at TOC of Indeterminate.

Concomitant administration of narrow-spectrum Gram-positive active agents to patients who have Gram-positive and Gram-negative co-infection will not affect patient evaluability in the CE or ME+R Populations.

6.9. Safety Population

The Safety Population includes all patients who receive at least 1 dose of study drug during the study. All safety analyses will be based on actual treatment received.

7. STATISTICAL ANALYSIS

7.1. General Statistical Considerations

Summary statistics will be presented by treatment group. For continuous variables, the number of observations (n), mean, standard deviation, median, minimum, and maximum will be provided. For categorical variables, the frequency and percentage in each category will be displayed.

For summary statistics, the mean and median will be displayed to one decimal place greater than the original value and the measure of variability (e.g. standard deviation) will be displayed to two decimal places greater than the original value.

7.2. Handling of Dropouts/Missing Data

For the primary efficacy outcome measure of overall response, patients with missing data or who are lost to follow-up will be considered as an indeterminate response and are included in the denominator for the calculation of overall success rate. Thus, patients with an indeterminate outcome are considered as failures for the primary analysis. A clinical failure occurring at an earlier time point will be carried forward to the subsequent visits.

In cases of missing or incomplete dates (e.g. AE and concomitant medications), the missing component(s) will be assumed as the most conservative value possible. For example, AEs with missing start dates, but with stop dates either overlapping into the treatment period or missing, will be counted as treatment-emergent, taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the AE started prior to the start of study drug or ended prior

to the start of study drug. If the above cannot be conclusively established based on the partial and/or present dates, then the AE will be considered as treatment-emergent. Actual data values as they appear in the original eCRF will be presented in the data listings.

Missing values for other variables will not be imputed and only observed values will be used in data analyses and summaries.

Missing start dates of lab AEs will be queried for sites to insert the lab sampling date.

7.3. Baseline Definition

For microbiological data, baseline pathogen(s) are determined from all specimens collected prior to the first dose of study drug.

For all efficacy and safety endpoints, baseline is defined as the last measurement or assessment prior to the first dose of study drug.

7.4. Patient Disposition

Patient disposition will be summarized for the ITT and MITT Populations for each treatment group and in total. The following patient disposition categories will be included in the summary for the ITT and MITT Populations:

- Patients who were randomized,
- Patients who received study drug,
- Patients who did not receive study drug,
- Patients who completed the study treatment,
- Patients who did not complete the study treatment,
- Patients who completed the study, and
- Patients who did not complete the study.

For patients who did not complete the treatment, and patients who did not complete the study, a summary will be provided by reason of discontinuation. In addition, the total number of patients for each defined population will be tabulated.

The number and percent of patients with reasons leading to exclusion from the m-MITT, m-MITT+R, CE, ME, and ME+R Populations will also be presented.

Patient disposition will be listed by patient.

7.5. Protocol Deviations

The number of patients with at least one reportable protocol deviation, and the number of patients with at least one reportable deviation in each category will be presented by treatment group and overall for the ITT Population.

Protocol deviations will be listed by patient.

7.6. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate by treatment group and in total for the ITT, MITT, m-MITT, m-MITT+R, CE, ME, and ME+R Populations. The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (<65, 65 - < 75, or ≥75 years);
- Sex;
- Race;
- Ethnicity;
- Height (cm);
- Weight (kg);
- Body mass index (BMI) (kg/m2) ;
- Creatinine clearance at baseline and categories (Severe - <30 mL/min, Moderate - 30-59 mL/min, Mild - 60-89 mL/min, or Normal - ≥90 mL/min);
- Randomization stratification factor 1: Type of infection (AP, cUTI with removable source of infection, or cUTI without removable source of infection, but with other risk factors);
- Randomization stratification factor 2: Prior antibiotic therapy (Short-acting antibiotic up to 24 hours or No prior antibiotic therapy);
- Randomization stratification factor 3: Region (Eastern Europe, Americas, or Other countries);
- Charlson Comorbidity Index (CCI) at baseline (<3 or ≥3);
- Presence of concurrent bacteremia at baseline (Yes or No);
- Country Category: US or Non-US;
- Baseline diabetic status (from medical history) (Yes or No); and
- Presence of beta-lactamase-producing isolates of Enterobacteriaceae at Baseline
    - ESBL co-producing (ESBL-genotype, combined with or without any other non-ESBL genotype)
    - ESBL-only producing (ESBL-genotype only, no other genotype)
    - ESBL co-producing (CTX-M-type)
    - ESBL-only producing (CTX-M-type)
    - ESBL co-producing (non-CTX-M-type)
    - ESBL-only producing (non-CTX-M-type)
    - Carbapenemase (Class A) co-producing
    - Carbapenemase (Class A)-only producing
    - Carbapenemase (Class B) co-producing
    - Carbapenemase (Class B)-only producing

- Carbapenemase (Class D) co-producing
- Carbapenemase (Class D)-only producing
- AmpC co-producing
- AmpC-only producing
- non-ESBL-, non-carbapenemase-, and non-AmpC-producing

Demographics and baseline characteristics, including CCI, will be listed by patient.

7.6.1. Definition of beta-lactamase-producing isolates of Enterobacteriaceae

Enterobacteriaceae baseline isolates with MICs ≥1 for ceftazidime, ceftriaxone, cefepime, meropenem, or cefepime-AAI101 will be screened by multiplex PCR for the presence of genes encoding

- ESBLs (TEM, SHV, CTX-Ms [including 5 subtypes: CTX-M-1-type, CTX-M-2-type, CTX-M-8-type, CTX-M-9-type, and CTX-M-25-type], GES, VEB, and PER),
- AmpC beta-lactamases (ACC, ACT, CMY, DHA, FOX, MIR, MOX), and
- carbapenemases (Class A KPC, Class D OXA-48-like, and Class B IMP, VIM, NDM, SPM, and GIM).

All detected beta-lactamase genes will be amplified with flanking, extragenic primers and sequenced in their entirety with the following exceptions_

- TEM and SHV beta-lactamases will be screened first by limited sequencing to identify genes encoding TEM-type and SHV-type enzymes containing amino acid substitutions common to ESBLs at the following positions: SHV a.a. 146, 179, 238, 240; TEM a.a. 104, 164, 238, 240.
  - TEM and SHV beta-lactamases containing amino acid substitutions common to ESBLs will be fully sequenced
  - Remaining TEM and SHV beta-lactamase variants will be reported as SHV-OSBL or TEM-OSBL (original spectrum beta-lactamase)
- AmpC beta-lactamases intrinsic to particular species (i.e. ACT/MIR detected in Enterobacter spp., CMY detected in Citrobacter spp., ACC in Hafnia alvei and DHA detected in M. morganii) will be confirmed by singleplex PCR with flanking primers.

Isolates of Enterobacteriaceae will be classified by ESBL-, carbapenemase-, and AmpC-producers, ignoring OSBL genotypes:

- Enterobacteriaceae ESBL-producing
  - Enterobacteriaceae ESBL co-producing (ESBL-genotype, combined with or without any other non-ESBL genotype)
  - Enterobacteriaceae ESBL-only producing (ESBL-genotype only, no other genotype)
  - Enterobacteriaceae ESBL co-producing (CTX-M-type)
  - Enterobacteriaceae ESBL-only producing (CTX-M-type)
  - Enterobacteriaceae ESBL co-producing (non-CTX-M-type)

    - Enterobacteriaceae ESBL-only producing (non-CTX-M-type)
- Enterobacteriaceae Carbapenemase-producing
    - Enterobacteriaceae Carbapenemase (Class A) co-producing
    - Enterobacteriaceae Carbapenemase (Class A)-only producing
    - Enterobacteriaceae Carbapenemase (Class B) co-producing
    - Enterobacteriaceae Carbapenemase (Class B)-only producing
    - Enterobacteriaceae Carbapenemase (Class D) co-producing
    - Enterobacteriaceae Carbapenemase (Class D)-only producing
- Enterobacteriaceae AmpC-producing
    - Enterobacteriaceae AmpC co-producing
    - Enterobacteriaceae AmpC-only producing
- Enterobacteriaceae non-ESBL-, non-carbapenemase-, and non-AmpC-producing

7.7. Baseline Infection Characteristics

Baseline infection characteristics will be summarized with descriptive statistics for the ITT, MITT, m-MITT, m-MITT+R, CE, ME, and ME+R Populations. Clinical signs and symptoms at baseline, and evidence of pyuria criteria at baseline will be summarized by infection type with contingency tables. Risks associated with cUTI will also be summarized for patients with cUTI.

All baseline pathogens will also be summarized for the m-MITT, m-MITT+R, ME, and ME+R Populations.

7.8. Medical History

Medical history will be summarized for the MITT, m-MITT, and m-MITT+R Populations for each treatment group and in total by system organ class (SOC) and preferred term (PT).

All medical history will be listed by patient.

7.9. Prior and Concomitant Medications

Prior medications are medications used before the first dose of study drug. Concomitant medications are medications that were taken on or after first dose of study drug.

The prior and concomitant medications will be summarized with the number and percentages by Anatomical Therapeutic Chemical (ATC) class and preferred term for each treatment group and overall for the MITT, m-MITT, m-MITT+R, CE, ME and ME+R Populations. Concomitant antibiotics will also be summarized in the same manner. In addition, for the prior medications, the patients who received antibiotic therapy within 72 hours before entry will be summarized in the same manner for the m-MITT and m-MITT+R Populations. Although a patient may have taken two or more medications, the patient is counted only once within an ATC classification. The same patient may contribute to two or more preferred terms in the same classification or to two different classifications.

All prior and concomitant medications and procedures will be listed by patient.

7.10. Dosing and Extent of Exposure

Descriptive statistics for the duration of study drug will be summarized by treatment group for the MITT, m-MITT, m-MITT+R, CE, ME, and ME+R Populations. Treatment duration is defined as the date of the last dose of study medication - first dose of study mediation +1 day. The number and percentage of patients receiving 1-3, 4-6, 7, 8-10 and 11-14 days of study drug will be provided. The total number of doses of study drug received will also be summarized by treatment group using descriptive statistics.

The compliance rate will be calculated as the total number of doses received divided by the total number of doses expected then multiplied by 100. The total number of expected doses is the number of medication days multiplied by the number of expected doses per day. Number of medication days is the total number of days from the date of the first infusion of study drug to the date of the last infusion of study drug.

Percent compliance with study drug will be calculated using the following formula:

$$\%\,\text{compliance} = \frac{\text{no. of doses received} * 100}{\text{expected doses per day} * \text{total number of medication days}}$$

The compliance rate will be summarized with summary statistics by treatment group and overall for the MITT, m-MITT, m-MITT+R, CE, ME, and ME+R Populations. In addition, contingency tables will be provided to show the number and percentage of patients in each treatment group with compliance in the following categories: <80% and ≥80%.

Study drug administration will be listed by patient.

7.11. Efficacy Analyses

7.11.1. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients in the m-MITT Population who achieve overall treatment success (clinical cure and microbiological eradication) at the TOC Visit.

Patients will be programmatically categorized as a success, failure, or indeterminate response. Patients with missing data or who are lost to follow-up are defined as indeterminate for the primary analysis and are included in the denominator for the calculation of overall success rate. Thus, patients with an indeterminate outcome are considered failures for the primary analysis. The number and percentage of patients in each treatment group in each response category will be summarized.

The non-inferiority assessment will be based on the stratified Newcombe 2-sided 95% confidence interval (CI) for the difference in the proportions of patients with overall treatment successes, calculated as the rate in the cefepime-AAI101 group minus that of the piperacillin/tazobactam group. The non-inferiority margin will be a difference of 10 percentage points. Non-inferiority will be concluded if the lower limit of the 2-sided 95% CI is >-10. Stratification will be applied for type of infection, prior therapy category, and region. If non-inferiority is demonstrated, an assessment for superiority on the primary endpoint will be performed as a secondary objective without the need for type I error alpha correction. Superiority will be shown if the treatment difference is positive and the lower bound of the 95% CI around this difference is greater than zero.

Overall response, including the microbiologic response and clinical response will be listed by patient.

Additional Analyses of Primary Efficacy Endpoint

Additional analyses of the primary efficacy endpoint will be performed for the MITT, CE, and ME Populations. A 95% CI will be computed for the treatment difference in the overall success rates based on the stratified Newcombe method.

In addition, the primary efficacy endpoint will be performed for a subset of MITT Population without exclusion based on susceptibility results, i.e. all randomized patients who meet MITT criteria and who have a baseline Gram-negative pathogen $\geq 10^5$ CFU/mL in urine culture or the same pathogen present in concurrent blood and urine cultures. These MITT subsets are referred to as m-MITT+R and ME+R Populations (see Section 6).

7.11.2. Analysis of Secondary Efficacy Endpoints

Descriptive statistics will be provided for secondary efficacy endpoints as follows:

The number and percentage of patients in the m-MITT, m-MITT+R, ME, and ME+R Populations with overall responses (Success, Failure, or Indeterminate) at Day 3, EOT and LFU Visits will be summarized by treatment group. The treatment differences in overall success rates and the stratified Newcombe 95% CIs will be presented.

The number and percentage of patients in the m-MITT, m-MITT+R, ME, and ME+R Populations with clinical outcomes (Cure, Improvement [Day 3 only], Failure, and Indeterminate) at Day 3, EOT, TOC, and LFU Visits will be summarized by treatment group. The treatment differences in clinical cure rates and the stratified Newcombe 95% CIs will be presented.

The number and percentage of patients in the m-MITT, m-MITT+R, ME, and ME+R Populations with per-patient microbiological outcomes (Eradication, Persistence, Recurrence, and Indeterminate) at Day 3, EOT, TOC, and LFU Visits will be summarized by treatment group. The treatment differences in per-patient microbiological eradication rates and the stratified Newcombe 95% CIs will be presented.

The per-pathogen microbiological outcomes (Eradication, Persistence, Recurrence, and Indeterminate) at Day 3, EOT, TOC, and LFU Visits by baseline pathogen will be summarized by treatment group in the m-MITT, m-MITT+R, ME, and ME+R Populations.

Clinical cure rates at Day 3, EOT, TOC, and LFU Visits by baseline pathogen will be summarized in the m-MITT, m-MITT+R, ME, and ME+R Populations as the proportion of patients with a clinical cure for each baseline pathogen isolated.

Clinical outcomes at Day 3, EOT, TOC, and LFU Visits will be summarized for the subset of patients infected with baseline ESBL-producing isolates of Enterobacteriaceae in the m-MITT, m-MITT+R, ME, and ME+R. The treatment differences in clinical cure rates and the stratified Newcombe 95% CIs will be presented.

Per-patient microbiological outcomes at Day 3, EOT, TOC, and LFU Visits will be summarized for the subset of patients infected with baseline ESBL-producing isolates of Enterobacteriaceae in the m-MITT, m-MITT+R, ME, and ME+R Populations. The treatment differences in microbiological eradication rates and the stratified Newcombe 95% CIs will be presented.

Overall responses (Success, Failure, or Indeterminate) at Day 3, EOT, TOC, and LFU Visits will be summarized for the subset of patients infected with baseline ESBL-producing isolates of Enterobacteriaceae in the m-MITT, m-MITT+R, ME, and ME+R Populations. The treatment differences in overall success rates and the stratified Newcombe 95% CIs will be presented.

For definitions of ESBL-producing Enterobacteriaceae refer to Section 7.6.1.

Clinical cure at TOC Visit will be summarized for discrete MIC values in the m-MITT, m-MITT+R, ME, and ME+R.

Per-patient microbiological Eradication at TOC Visit will be summarized for discrete cefepime/AAI101 and piperacillin/tazobactam baseline MIC values by baseline pathogen in the m-MITT, m-MITT+R, ME, and ME+R Populations.

Overall success at TOC Visit will be summarized for discrete cefepime/AAI101 and piperacillin/tazobactam baseline MIC values by baseline pathogen in the m-MITT, m-MITT+R, ME, and ME+R Populations.

7.11.3. Subgroup Analyses

Subgroup analyses will be performed for the primary efficacy endpoint and secondary efficacy endpoints as the follows:

- The proportion of patients in the m-MITT and m-MITT+R Populations with overall responses (Success, Failure, or Indeterminate) at the TOC Visit;
- The proportion of patients in the m-MITT and m-MITT+R Populations with clinical outcomes (Cure, Failure, and Indeterminate) at the TOC Visit;
- The proportion of patients in the m-MITT and m-MITT+R Populations with per-patient microbiological outcomes (Eradication, Persistence, Recurrence, and Indeterminate) at the TOC Visit;

The following subgroups will be performed:

- Age (<65, 65 - < 75, or ≥75 years);
- Sex (Male or Female);
- Creatinine clearance at baseline (Severe - <30 mL/min, Moderate - 30-59 mL/min, Mild - 60-89 mL/min, or Normal - ≥90 mL/min);
- Randomization stratification factor 1: Type of infection (AP, cUTI with removable source of infection, or cUTI without removable source of infection, but with other risk factors);
- Randomization stratification factor 2: Prior antibiotic therapy (Short-acting antibiotic up to 24 hours or No prior antibiotic therapy);
- Randomization stratification factor 3: Region (Eastern Europe, Americas, or Other countries);
- Charlson Comorbidity Index (CCI) at baseline (<3 or ≥3);
- Presence of concurrent bacteremia at baseline (Yes or No);
- Race: White, Black or African American, Other (these categories may be combined depending on the distribution of patients in each category.);
- Country Category: US or Non-US;

- Baseline diabetic status (from medical history) (Yes or No); and
- Presence of beta-lactamase-producing isolates of Enterobacteriaceae at Baseline
    - ESBL co-producing (ESBL-genotype, combined with or without any other non-ESBL genotype)
    - ESBL-only producing (ESBL-genotype only, no other genotype)
    - ESBL co-producing (CTX-M-type)
    - ESBL-only producing (CTX-M-type)
    - ESBL co-producing (non-CTX-M-type)
    - ESBL-only producing (non-CTX-M-type)
    - Carbapenemase (Class A) co-producing
    - Carbapenemase (Class A)-only producing
    - Carbapenemase (Class B) co-producing
    - Carbapenemase (Class B)-only producing
    - Carbapenemase (Class D) co-producing
    - Carbapenemase (Class D)-only producing
    - AmpC co-producing
    - AmpC-only producing
    - non-ESBL-, non-carbapenemase-, and non-AmpC-producing

Forest plots will be performed for each endpoint and subgroup analysis.

7.12. Pharmacokinetic analyses

All pharmacokinetic analyses will be performed by another vendor and described in a standalone PK analysis plan.

A listing of the PK concentrations by patient will be provided.

7.13. Safety Analyses

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

7.13.1. Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an adverse event with a start date and time on or after the administration of study drug.

An overview of adverse events will be provided which summarizes the number and percentage of patients with the incidence of the following information:

- All AEs,

- All TEAEs,
- Drug-related TEAEs
- Maximum severity of TEAEs,
- Deaths,
- Serious adverse events (SAEs),
- Treat-emergent SAEs,
- Drug-related treatment-emergent SAEs,
- Discontinuation of study drug due to TEAEs,
- Discontinuation of study drug due to drug-related TEAEs.

In addition, the above incidences in the overview of adverse events will also be summarized in the following subgroups:

- Age group (<65, 65 - < 75, or ≥75 years);
- Sex (Male or Female);
- Race: White, Black or African American, Other (these categories may be combined depending on the distribution of patients in each category.);
- Baseline diabetic status (from medical history) (Yes or No); and
- Creatinine clearance at baseline (Severe - <30 mL/min, Moderate - 30-59 mL/min, Mild - 60-89 mL/min, or Normal - ≥90 mL/min).

The number and percentage of patients who experienced at least one TEAE will be presented by system organ class and preferred term. Drug-related TEAEs, study drug withdrawals due to TEAEs, and all SAEs will be summarized in the same manner.

Summaries will be provided by worst grade for the number and percentage of patients with TEAEs and for patients with drug-related TEAEs by system organ class and preferred term.

In addition, the number and percentage of patients with TEAEs which are classified as adverse events of special interest (AESI) by category, subcategory and preferred term will be presented. The following AESI will be summarized:

- Hypersensitivity reactions: identified with SMQs of anaphylactic reactions, angioedema, and hypersensitivity
- Symptoms of encephalopathy and seizures: identified with SMQs of convulsions, noninfectious encephalopathy/delirium
- SMQ of hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions.
- SMQ for pseudomembranous colitis / clostridium difficile infection.

Although a patient may have two or more TEAEs, the patient is counted only once within a System Organ Class and Preferred Term category. The same patient may contribute to two or more preferred terms in the same System Organ Class category or to two different System Organ Class categories.

A list of patients who have serious adverse events (SAEs), a list of patients who discontinue from study drug, and a list of death will be provided. All adverse events will be listed.

7.13.2. Clinical Laboratory Evaluations

Central laboratory test results (chemistry, hematology, coagulation, and urinalysis) at each scheduled visit and change from baseline will be summarized with descriptive statistics by treatment group.

Shift tables from baseline to each scheduled post-baseline visit will be provided for selected chemistry parameters (ALT, AST, Total Bilirubin, Creatinine, Creatinine kinase, Alkaline phosphatase, Potassium) and hematology parameters (Hematocrit, Hemoglobin, Platelets, White blood cell count and differential). For chemistry parameters, the following categories will be used: < the lower limit of normal (LLN), normal, >ULN to ≤2×ULN, >2×ULN to ≤3×ULN, >3×ULN to ≤5×ULN, >5×ULN, and missing. For hematology parameters, the following categories will be used: low, normal, high, and missing.

The number and percentage of patients with the following abnormal liver function tests will be summarized at baseline and each scheduled post-baseline visit:

- ALT >ULN
- ALT >2×ULN
- ALT >3×ULN
- ALT >5×ULN
- ALT >10×ULN
- AST >ULN
- AST >2×ULN
- AST >3×ULN
- AST >5×ULN
- AST >10×ULN
- ALT or AST >3×ULN
- Total bilirubin >1.5×ULN and >2×ULN
- Total bilirubin >ULN to ≤1.5×ULN
- Total bilirubin >1.5×ULN to ≤3×ULN
- Total bilirubin >3×ULN to ≤10×ULN
- Total bilirubin >10×ULN
- ALP >1.5×ULN and >3×ULN
- ALT or AST >3×ULN and Total bilirubin ≤2×ULN
- ALT or AST >3×ULN and Total bilirubin >2×ULN
- Potential Hy's Law cases: ALT or AST >3×ULN and Total bilirubin >2×ULN, and ALP ≤ 2×ULN

A listing of patients with any baseline and post-baseline abnormal liver function tests will be presented.

All clinical laboratory data will be listed. Values outside the normal ranges will be flagged.

7.13.3. Vital Signs

Descriptive statistics will be provided for vital sign data (systolic and diastolic blood pressure, heart rate, and body temperature) presented as both actual values and changes from baseline over time.

A listing of all vital signs will be provided by patient.

7.13.4. 12-Lead ECG

ECG analysis will be done from blinded central assessment and not local readings and reported in a separate report.

7.13.5. Physical Examination

The number and percentage of patients at baseline and each scheduled post-baseline visit will be summarized using the following categories: normal, abnormal not clinically significant, abnormal clinically significant, and not done.

Physical examination findings will be listed by patient.

7.14. Interim Analysis

No interim analysis has been planned.

8. CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

The following changes are made in Table 2 (Clinical Outcome Criteria) in SAP compared to the description in the protocol as clarification:

- Removed “Clinical outcome will be determined programmatically based on patient responses in the Daily Symptom Assessment Questionnaire” from Table 2 to be consistent with the language “The Investigator will assign a clinical outcome as defined in Table 2” in SAP;

- Changed “Withdrawal from the study due to an adverse event or due to lack of clinical improvement” to be “Withdrawal from the study drug due to an adverse event or due to lack of clinical improvement” in Table 2.

- Added a clarification in Table 2 “Note: Withdrawal from the study drug due to an adverse event or due to lack of clinical improvement or death of the patient during the study will lead to clinical failure for the subsequent time points but will not change the previous time point assessment.”.

- Changed "NOTE: The qualifying pathogen is defined as a single Gram-positive or Gram-negative organism $\geq 10^5$ CFU/mL for urine and growth in blood culture." to be "NOTE: The baseline qualifying pathogen is defined as a non-contaminated baseline Gram negative organism ≥105 CFU/mL for urine or growth in blood culture concurrently." in Table 3 note to be consistent with other sections.

- The efficacy analysis has been added based on the following genotype data:

    - ESBL co-producing (ESBL-genotype, combined with or without any other non-ESBL genotype)
    - ESBL-only producing (ESBL-genotype only, no other genotype)
    - ESBL co-producing (CTX-M-type)
    - ESBL-only producing (CTX-M-type)
    - ESBL co-producing (non-CTX-M-type)
    - ESBL-only producing (non-CTX-M-type)
    - Carbapenemase (Class A) co-producing
    - Carbapenemase (Class A)-only producing
    - Carbapenemase (Class B) co-producing
    - Carbapenemase (Class B)-only producing
    - Carbapenemase (Class D) co-producing
    - Carbapenemase (Class D)-only producing
    - AmpC co-producing
    - AmpC-only producing
    - non-ESBL-, non-carbapenemase-, and non-AmpC-producing

9. PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.3 or higher. All available data will be presented in patient data listings which will be sorted by patient as applicable. Detailed Programming Specifications will be provided in a separate document.