CLINICAL STUDY PROTOCOL

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

Investigational Product: AAI101
Protocol Number: AT-301
EudraCT Number: 2017-004868-35
IND Number: 122269

Sponsor:
Allecra Therapeutics SAS
10 rue Alexandre Freund
68300 St Louis
France
Telephone: +33 3 89 68 9876

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SIGNATURE PAGE

STUDY TITLE: 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

Version 5.0 (Amendment 4)

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

Signature	Date
DocuSigned by: Mathias Knecht 42547E00B7E34E2...	11-Sep-18 | 19:14 CEST

Mathias Knecht, MD
Chief Development Officer
Allecra Therapeutics SAS

INVESTIGATOR AGREEMENT

By signing below, I agree that:

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

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: 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

PROTOCOL NUMBER: AT-301

EUDRACT NUMBER: 2017-004868-35

INVESTIGATIONAL PRODUCT: AAI101

PHASE: 3

INDICATION(S): Complicated urinary tract infection (cUTI), including acute pyelonephritis (AP)

OBJECTIVES:

The primary objective of this study is to assess the efficacy of cefepime-AAI101 compared to piperacillin/tazobactam in the treatment of cUTI, including 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.

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.

ENROLLMENT CRITERIA:

Inclusion Criteria

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

1. Male or female patients ≥18 years of age at the time of signing of informed consent;
2. Expectation that the patient's cUTI or AP will require hospitalization and initial treatment with at least 7 days of intravenous (i.v.) antibiotics;

3. Female patients who are no longer of childbearing potential must meet 1 of the following criteria:

   a. Women ≥50 years of age who are considered post-menopausal as they have been amenorrhoeic for ≥12 months following cessation of all pharmaceutical or exogenous hormonal treatment;

   b. Women <50 years of age who are considered post-menopausal as they have been amenorrhoeic for ≥12 months following cessation of all pharmaceutical or exogenous treatment and if follicle-stimulating hormone (FSH) levels are in the post-menopausal range. If the 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; or

   c. Permanent sterilization, defined as hysterectomy, bilateral oophorectomy, or bilateral salpingectomy;

4. Female patients of childbearing potential must have a negative urine and/or serum pregnancy test (serum β-human chorionic gonadotropin) within 1 day prior to study entry;

5. Male patients, female patients receiving hormone replacement therapy (HRT), and female patients of childbearing potential must agree to use highly effective contraception methods as defined below:

   NOTE: Female patients who are no longer of childbearing potential (*i.e.*, confirmed to be permanently sterile as defined above or post-menopausal) and patients who are exclusively in same-sex relationships will not be required to use contraception.

   a. Male patients and their partners of childbearing potential or partners sterilized by tubal ligation, female patients receiving HRT, female patients who have been sterilized by tubal ligation, and female patients of childbearing potential are required to use a condom (male or female) in conjunction with spermicidal gel, foam, cream, film, or suppository from the time of dosing until 90 days after the last dose; and

   b. Male patients and their partners of childbearing potential and female patients of childbearing potential are required to use an additional highly effective form of contraception from the time of first dose until 90 days after the last dose. Additional highly effective methods of contraception include the following:

      - Diaphragm or cervical vault cap in conjunction with spermicidal gel, foam, cream, film, or suppository;
      - Male sterilization (for female patients, the vasectomized male partner should be the sole partner for that patient);
      - Intrauterine device; or
      - Established use of oral, injected, or implanted hormonal methods of contraception;

6. Pyuria, defined as:
   a. White blood cell count >10 cells/mm^3 in unspun urine or ≥10 cells/high power field in spun urine sediment; or
   b. Urinalysis/dipstick analysis positive for leukocyte esterase;
7. Clinical signs and/or symptoms of cUTI or AP, as defined below:

   NOTE: If the criteria for both cUTI and AP are met, the infection type will be considered cUTI for randomization and analysis purposes.

cUTI	AP
At least 2 of the following new or worsening symptoms: • Dysuria, increased urinary frequency, or urinary urgency; • Fever (oral/tympanic ≥38°C [≥100.4°F] or rectal temperature ≥38.3°C [≥100.9°F]) observed and documented by a health care provider within 24 hours of Screening; • Lower abdominal pain or pelvic pain; • Suprapubic tenderness on physical examination; or • Nausea or vomiting within 24 hours of Screening as reported by the patient; **AND** At least 1 of the following complicating factors: • Male patients with documented history of urinary retention (*e.g.*, benign prostatic hypertrophy); • Use of intermittent bladder catheterization or presence of an indwelling bladder catheter; NOTE: Indwelling bladder catheters that have been in place for >24 hours prior to Screening must be removed or replaced prior to collection of the Screening visit urine for urinalysis and culture unless removal or replacement is considered unsafe or contraindicated. • Current obstructive uropathy that is scheduled to be medically or surgically relieved during i.v. study therapy and before EOT; • Any functional or anatomical abnormality of the urogenital tract (including anatomic malformations or neurogenic bladder) with voiding disturbance resulting in at least 100 mL residual urine; or • Azotemia, defined as blood urea nitrogen >20 mg/dL, blood urea >42.8 mg/dL, or serum creatinine >1.4 mg/dL, due to known prior intrinsic renal disease.	At least 2 of the following new or worsening symptoms: • Dysuria, increased urinary frequency, or urinary urgency; • Fever (oral/tympanic ≥38°C [≥100.4°F] or rectal temperature ≥38.3°C [≥100.9°F]) observed and documented by a health care provider within 24 hours of Screening; • Flank pain (onset within 7 days prior to randomization); • Costo-vertebral angle tenderness on physical examination; or • Nausea or vomiting within 24 hours of Screening, as reported by the patient.
AP = acute pyelonephritis; cUTI = complicated urinary tract infection; EOT = End of Treatment; i.v. = intravenous(ly).	

8. Have a baseline urine culture specimen obtained within 48 hours prior to randomization and the first dose of study drug; and

   NOTE: Patients may be enrolled in this study and start i.v. study drug therapy before the Investigator knows the results of the baseline urine culture.

9. Expectation, in the judgment of the Investigator, that any implanted urinary instrumentation (*e.g.*, nephrostomy tubes, ureteric stents, etc.) will be surgically removed or replaced before or within 24 hours after randomization, unless removal or replacement is considered unsafe or contraindicated.

Exclusion Criteria

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

1. Known urine culture with Gram-positive primary pathogen at $\geq 10^5$ colony-forming units (CFU)/mL (not contaminant) or suspected Gram-positive pathogen by Gram staining (Note: Gram staining is optional);
2. History of significant hypersensitivity or allergic reaction to cefepime, piperacillin/tazobactam, any of the excipients used in the respective formulations, any beta-lactam antibiotics (*e.g.*, cephalosporins, penicillins, carbapenems, or monobactams), or any beta-lactamase inhibitors (*e.g.*, tazobactam, sulbactam, or clavulanic acid);
3. In the opinion of the Investigator, the patient is considered unlikely to survive the approximately 6-week study period;
4. Weight >180 kg;
5. Concurrent infection that would interfere with evaluation of response to the study antibiotics;
6. Need for or receipt of concomitant systemic antimicrobial agents after signing of informed consent, in addition to those designated in the study-treatment groups, with the exception of a single oral dose of any antifungal treatment for vaginal candidiasis;
7. Receipt of potentially effective systemic antibacterial therapy for a continuous duration of >24 hours during the previous 72 hours before the study-qualifying baseline urine is obtained;

   EXCEPTION:

   a. Receipt up to 24 hours of short-acting antibacterial agent (see Appendix C for the list of allowed and disallowed antibiotics). No more than 25% of patients who meet this criterion will be enrolled;

   b. Patients who received prior antimicrobial therapy for the current cUTI/AP, and 1) in the Investigator's opinion, failed that prior antibiotic therapy (*i.e.,* presented with worsening signs and symptoms), AND 2) were documented to have cUTI or AP caused by a pathogen that is non-susceptible to the prior antibiotic therapy, AND 3) the causative pathogen is likely to be susceptible to the study drug;

c. Patients who received antibacterial drugs for surgical prophylaxis and then developed cUTI or AP; or

d. Patients who have received antimicrobial prophylaxis for recurrent cUTI and then presented signs and symptoms consistent with an active new cUTI or AP;

8. Complicated urinary tract infection known at study entry to be caused by pathogens resistant to the study antibiotics;
9. Likely to require the use of an antibiotic for cUTI or AP prophylaxis during the patient's participation in the study;
10. Intractable urinary tract infection (UTI) at baseline that the Investigator anticipates would require >14 days of study drug therapy;
11. Complete, permanent obstruction of the urinary tract that is not anticipated to be medically or surgically relieved during i.v. study therapy and before End of Treatment (EOT);
12. Gross hematuria requiring intervention other than administration of study drug or removal or exchange of a urinary catheter;
13. Presence of any known or suspected disease or condition that, in the opinion of the Investigator, may confound the assessment of efficacy. This includes, but is not limited to, the following:
    a. Perinephric abscess;
    b. Renal corticomedullary abscess;
    c. Uncomplicated UTI;
    d. Any recent history of trauma to the pelvis or urinary tract;
    e. Polycystic kidney disease;
    f. Chronic vesico-ureteral reflux;
    g. Previous or planned renal transplantation;
    h. Previous or planned cystectomy or ileal loop surgery;
    i. Patients receiving dialysis, including hemodialysis, peritoneal dialysis, or continuous veno-venous hemofiltration; or
    j. Known or suspected infection that is caused by pathogen(s) resistant to either study drug, including infection caused by fungi (*e.g.*, candiduria) or mycobacteria (*e.g.*, urogenital tuberculosis);
14. Suspected or confirmed acute bacterial prostatitis, orchitis, epididymitis, or chronic bacterial prostatitis as determined by history and/or physical examination;
15. Impairment of renal function with estimated glomerular filtration rate <30 mL/min/1.73 m^2 calculated by the 4-variable Modification of Diet in Renal Disease study equation (see Appendix D);

16. Urinary tract surgery within 7 days prior to randomization or urinary tract surgery planned during the study period (except surgery required to relieve an obstruction or place a stent or nephrostomy prior to EOT);
17. Any condition or circumstance that, in the opinion of the Investigator, would compromise the safety of the patient or the quality of study data;
18. Any rapidly progressing disease or immediately life-threatening illness, including acute hepatic failure and respiratory failure;
19. Presence of sepsis, producing life-threatening organ dysfunction, defined as ≥2 of the following criteria:
    a. Systolic blood pressure ≤100 mmHg that is not responsive to fluid challenge;
    b. Respiratory rate ≥22 breaths/min; and/or
    c. Altered mental status;
20. A QT interval corrected using Fridericia's formula >450 msec;
21. Immunocompromising condition, including known history of acquired immune deficiency syndrome or known recent CD4 count <200/mm^3, hematological malignancy, or bone marrow transplantation; or immunosuppressive therapy including cancer chemotherapy, medications for prevention of organ transplantation rejection, or the administration of corticosteroids ≥20 mg of prednisone or equivalent per day administered continuously for >14 days prior to randomization;
22. One or more of the following laboratory abnormalities in baseline specimens obtained at Screening: aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, or total bilirubin level >3 × upper limit of normal, or current clinically significant liver disease, including any form of known liver cirrhosis;
23. One or more of the following laboratory abnormalities at Screening: platelet count <50,000/μL, absolute neutrophil count <1,000/mm^3, or hemoglobin <8 g/dL;
24. Pregnant or expecting to conceive, breastfeeding, or plans to breastfeed within 1 month of completion of the study;
25. Currently participating in, or has participated in, any other clinical study involving the administration of investigational or experimental medication (not licensed by regulatory agencies) at the time of presentation or during the previous 30 days or 5 half-lives, whichever is longer, prior to Screening, or is anticipated to participate in such a clinical study during the course of the study; or
26. Unable or unwilling, in the judgment of the Investigator, to comply with the protocol.

STUDY DESIGN AND DURATION:

This is a randomized, double-blind, active-controlled, multi-center 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).

For dosing in patients with renal insufficiency, please see the Study Protocol, Section 5.5.3.1.

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]), see Synopsis Figure 1. 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.

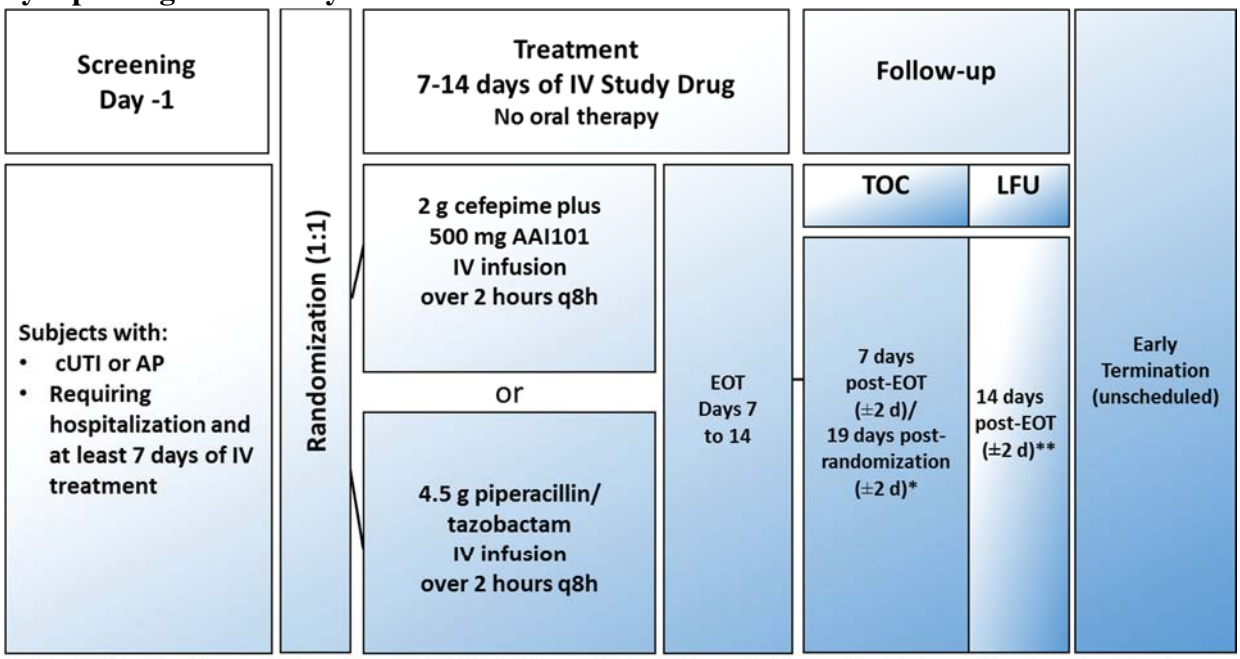
Patients with qualifying Gram-negative uropathogen co-infected with a Gram-positive uropathogen detected after randomization may be administered narrow-spectrum, open-label glycopeptide (*e.g.*, vancomycin), oxazolidinone (*e.g.*, linezolid), or daptomycin concomitantly with the blinded study drug at 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 (see Appendix F). 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 study 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.

Synopsis 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.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Study drug will be administered in a double-blind manner. Patients will be randomized in a 1:1 ratio to receive either 2 g cefepime plus 500 mg AAI101 or 4.5 g piperacillin/tazobactam (4 g piperacillin/0.5 g tazobactam) q8h, i.v.

For dosing in patients with renal insufficiency, please see the Study Protocol, Section 5.5.3.1.

EFFICACY VARIABLES:

The primary efficacy parameter is the proportion of patients in the Microbiological Modified Intent-to-Treat (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).

The secondary efficacy parameters include the following:

- The proportion of patients in the m-MITT Population with overall treatment success at 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 with a clinical outcome of Cure or Improvement (Day 3 only) in the m-MITT, Clinically Evaluable (CE), and ME Populations at Day 3, EOT, TOC, and LFU;
- Per-pathogen clinical outcome of Cure and microbiological outcome of Eradication in the m-MITT and ME Populations at Day 3, EOT, TOC, and LFU; and
- Subset of patients infected with extended-spectrum β-lactamase producing pathogens with a clinical outcome of Cure and microbiological outcome of Eradication in the m-MITT and ME Populations at Day 3, EOT, TOC, and LFU.

CLINICAL OUTCOME:

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

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

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. Clinical outcome will be determined programmatically based on patient responses in the Daily Symptom Assessment Questionnaire. **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 due to an adverse event or due to lack of clinical improvement; or • Death of the patient during the study. **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.	

MICROBIOLOGICAL OUTCOME:

The criteria for microbiological outcome are defined in the table below.

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 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. CFU = colony-forming units.	

Per-pathogen microbiological responses will also be determined (descriptive analyses) using a cut-off of <103 CFU/mL.

OVERALL RESPONSE:

Overall response is derived from a composite of the clinical and microbiological outcome, as presented below. 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.

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.				

SAFETY VARIABLES:

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

DATA AND SAFETY MONITORING BOARD:

A Data and Safety Monitoring Board (DSMB) according to international standards will be established in this study. It will consist of independent clinical experts and at least 1 independent statistical expert. The DSMB will meet to periodically review and evaluate accumulated study data for subject safety, study conduct, and progress.

The DSMB will make recommendations concerning the continuation, modification, or termination of the study.

The task, procedures, and responsibilities of the DSMB will be described in a separate DSMB Charter. The DSMB will meet at the study start, when LFU outcome is known for one-third of m-MITT patients (270 patients), and when LFU outcome is known for two-thirds of m-MITT patients (540 patients).

PHARMACOKINETIC VARIABLES:

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.

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.

ANALYSIS POPULATIONS:

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

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

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

Microbiological Modified Intent-to-Treat Population: 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 or piperacillin/tazobactam (defined as minimal inhibitory concentration [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. The m-MITT Population will be the primary efficacy population. 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. Efficacy analyses will be based on the treatment as randomized.

Clinically Evaluable 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 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.

Microbiologically Evaluable 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.

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.

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

STATISTICAL ANALYSES:

Primary Efficacy Analysis

The primary efficacy parameter is the proportion of patients in the m-MITT Population who achieve overall treatment success at TOC. 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 each 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.

Sensitivity Efficacy Analyses

Analyses of the primary efficacy endpoint will be performed for the MITT, CE, and ME Populations.

Secondary Efficacy Analyses

Descriptive statistics will be provided for secondary endpoints. Treatment differences and associated 95% CIs will also be presented.

Analyses of the secondary efficacy endpoint will be performed for the MITT, m-MITT, CE, and ME Populations.

Pharmacokinetic Analyses

Plasma concentrations and PK parameters will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequencies and percentages for discrete variables. Derived plasma PK parameters will be summarized using descriptive statistics (n, arithmetic and geometric means, coefficient of variation, standard deviation of the arithmetic mean, median, minimum, and maximum).

All PK analyses will be performed using the PK Population.

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.

SAMPLE SIZE DETERMINATION:

A trial enrolling 810 patients who are evaluable in the m-MITT 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%.

SITES:

Approximately 115 sites in Europe, North America, South America, and South Africa

SPONSOR:

Allecra Therapeutics SAS
10 rue Alexandre Freund
68300 St Louis
France
Telephone: +33 3 89 68 9876

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ALT	Alanine aminotransferase
AP	Acute pyelonephritis
AST	Aspartate aminotransferase
BLI	β-lactamase inhibitor
CE	Clinically Evaluable
CFR	Code of Federal Regulations
CFU	Colony-forming units
CI	Confidence interval
CRA	Clinical research associate
CTA	Clinical trial authorization
CTCAE	Common Terminology Criteria for Adverse Events
cUTI	Complicated urinary tract infection
DSAQ	Daily Symptom Assessment Questionnaire
DSMB	Data and Safety Monitoring Board
E. coli	*Escherichia coli*
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOT	End of Treatment
ESBL	Extended-spectrum β-lactamase
ET	Early Termination
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HRT	Hormone replacement therapy
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
i.v.	Intravenous(ly)
K. pneumoniae	*Klebsiella pneumoniae*
LFT	Liver function test
LFU	Late Follow-up
MDR	Multidrug-resistant

Abbreviation	Definition
MDRD	Modification of Diet in Renal Disease
ME	Microbiologically Evaluable
MIC	Minimal inhibitory concentration
MITT	Modified Intent-to-Treat
m-MITT	Microbiological Modified Intent-to-Treat
NS	Normal saline
OTC	Over-the-counter
PD	Pharmacodynamics
PK	Pharmacokinetic(s)
PT	Prothrombin time
PTT	Partial thromboplastin time
q#h	Once every # hours
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
TOC	Test of Cure
ULN	Upper limit of normal
UTI	Urinary tract infection

1 INTRODUCTION AND BACKGROUND INFORMATION

AAI101 is a novel penicillanic acid sulfone β-lactamase inhibitor (BLI), active against a broad range of β-lactamases, including extended-spectrum β-lactamases (ESBLs). AAI101 restores the antibacterial activity of β-lactam antibiotics such as penicillins and cephalosporins. AAI101 combined with cefepime has proven to be efficacious *in vitro* and *in vivo* against Class A ESBL-producing Enterobacteriaceae, and against Class C and some Class D β-lactamase-producing pathogens. Allecra Therapeutics SAS (hereinafter, Allecra) is sponsoring a global Phase 3 clinical development program for the cefepime-AAI101 combination.

AAI101 is an extended-spectrum BLI with broader, more potent activity than tazobactam as shown by:

- Minimal inhibitory concentration (MIC) studies using "challenge panels" comprising recent collections of multidrug-resistant (MDR) Enterobacteriaceae, as well as panels of Gram-negative clinical isolates assembled from strains with defined mechanisms of β-lactam resistance (single and multiple β-lactamases, porin defects, and efflux);
- MIC studies using isogenic panels of *Escherichia coli (E. coli)* with each strain expressing a single, defined Class A, B, or D β-lactamase; and
- Molecular enzymological studies clearly indicating differences between AAI101 and tazobactam *vis-à-vis* mode of binding to β-lactamases and reactivity within the active site.

Moreover, for an "all-comers" panel (n = 1,696) of recent (2014 to 2015) Enterobacteriaceae clinical isolates, AAI101 restored cefepime activity toward producers of ESBLs and other β-lactamases, with 94%, 100%, and 98% of *Klebsiella pneumoniae (K. pneumoniae), E. coli*, and *Enterobacter spp*, respectively, achieving MICs for cefepime-AAI101 at or below the Clinical Laboratory Standards Institute susceptibility breakpoint for cefepime.

Hollow fiber infection models with ESBL-producing Enterobacteriaceae mimicking human dosing regimens of cefepime-AAI101 demonstrated that the pharmacodynamics (PD) driver for AAI101 efficacy is time above a threshold concentration ($t > C_t$) of 2 mg/L. For AAI101 dosed once every 8 hours (q8h) across the range of 0.5 g to 1 g, Monte Carlo simulations showed a high probability of achieving the PD target associated with efficacy.[1]

Mouse septicemia and pneumonia models using *E. coli, K. pneumoniae,* and *Enterobacter cloacae* clinical isolates encoding ESBLs, AmpCs, and Class D carbapenemases demonstrated unequivocally the ability of AAI101 to restore cefepime activity *in vivo* against highly cefepime-resistant Enterobacteriaceae.[2] Moreover, in a neutropenic murine thigh infection model using a panel of predominantly MDR (cefepime-resistant) Enterobacteriaceae, simulated human doses of 2 g cefepime plus 500 mg AAI101 q8h reduced bacterial loads of 17/20 strains tested.[3]

In the completed Phase 1 study, 84 healthy male volunteers received a total of >2,500 doses of AAI101. Pharmacokinetic (PK) parameters related to AAI101 exposure (area under the curve, maximum plasma concentration) were dose-proportional and the elimination half-life for AAI101 was approximately 2 hours. In the single ascending dose cohorts, AAI101 was well tolerated, with only a few reports of headache and mostly mild local infusion site reactions, without obvious relation to dose level. A drug-drug interaction cohort showed that AAI101 does not affect the PK of cefepime, nor is the PK of AAI101 affected by cefepime.

In the multiple ascending dose cohorts (2 g and 1 g q6h administered for 14 days), dose-dependent, asymptomatic, and reversible increases of transaminases were noted at the highest AAI101 doses tested, with no functional impact on the liver observed. Two cohorts combining cefepime or piperacillin with significantly lower, but nonetheless therapeutically active, doses of AAI101 (500 mg q8h and q6h, respectively) did not lead to transaminase increases.

A Phase 2 complicated urinary tract infection (cUTI) study with the combination of cefepime and AAI101 has recently been completed. Preliminary results indicate that AAI101 doses of 500 mg to 750 mg administered q8h in combination with 1 g or 2 g of cefepime were well tolerated. None of the subjects in the study presented with increases of transaminases exceeding 2 × the upper limit of normal (ULN).

Cefepime is a fourth-generation cephalosporin with a broader spectrum and generally greater potency than other products of this β-lactam class, such as ceftazidime, cefotaxime, ceftriaxone, or ceftolozane. Whereas most β-lactam antibiotics are anionic, cefepime is zwitterionic, which likely enhances its ability to traverse the outer membrane and accumulate in the periplasm, where the targets for β-lactam antibiotics (penicillin-binding proteins) reside. Cefepime, which shows high stability towards some β-lactamases, notably AmpCs, is used as first-line monotherapy for cUTI as well as other serious bacterial infections, including bacteraemia and pneumonia.[4] However, the susceptibility of cefepime to most widespread ESBLs (*e.g.,* CTX-Ms) and, in certain regions, the prevalence of carbapenemases (*e.g., K. pneumoniae* carbapenemases), has compromised the clinical utility of this product.[5]

1.1 Rationale

For more than 2 decades piperacillin/tazobactam has been the mainstay of empiric treatment of serious hospital infections, including infections due to anaerobes, though in many regions its efficacy has eroded due to local emergence or spread of new, more aggressive ESBLs and carbapenemases.[6,7] Piperacillin/tazobactam is no longer advised for use against infections caused by ESBL-producing *E. coli* or *K. pneumoniae*.[6] There is need for new, potent β-lactam-BLI combinations with activity against ESBL- and other β-lactamase-producing strains of Enterobacteriaceae.

Combination of AAI101 with cefepime confers protection of this potent cephalosporin from hydrolysis by ESBLs and other clinically relevant β-lactamases, providing coverage of most Gram-negative clinical pathogens.

The current study will confirm the efficacy and tolerability of cefepime-AAI101 in the treatment of cUTI when compared to piperacillin/tazobactam.

1.2 Risk/Benefit

A Phase 2 study comparing the combination of cefepime and AAI101 with cefepime monotherapy for the treatment of cUTI has recently been completed. The study employed PK/PD modeling to determine the optimal cefepime-AAI101 combination dose to be used in Phase 3 studies. The study's results indicate that an AAI101 dose of 500 mg q8h provides adequate protection against cefepime-resistant Enterobacteriaceae, and is associated with a favorable safety profile. The study also provided an initial assessment of clinical efficacy in the treatment of cUTI indicating high clinical cure and microbiological eradication rates.

Cefepime is a well-established product with an adequately described safety profile and will be used in the current Phase 3 study at an approved dose.

A drug-drug interaction cohort showed that AAI101 did not affect the PK of cefepime, nor were the kinetics of AAI101 affected by cefepime.

Given the significant improvement in coverage of cefepime against the ESBL-producing pathogens when combined with AAI101, the preliminary efficacy findings and good safety profile associated with administration of AAI101 and cefepime at the targeted doses, the overall benefit-risk assessment of this combination is considered to be positive.

2 STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objectives

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 PK of cefepime-AAI101 in patients with cUTI or AP.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a randomized, double-blind, active-controlled, multi-center 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. The study will be conducted at approximately 115 sites in Europe, North America, South America, and South Africa.

Approximately 1,040 adult 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 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).

For dosing in patients with renal insufficiency, please see Section 5.5.3.1.

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 End of Treatment (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]), see Figure 1. 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 the Investigator's judgment.

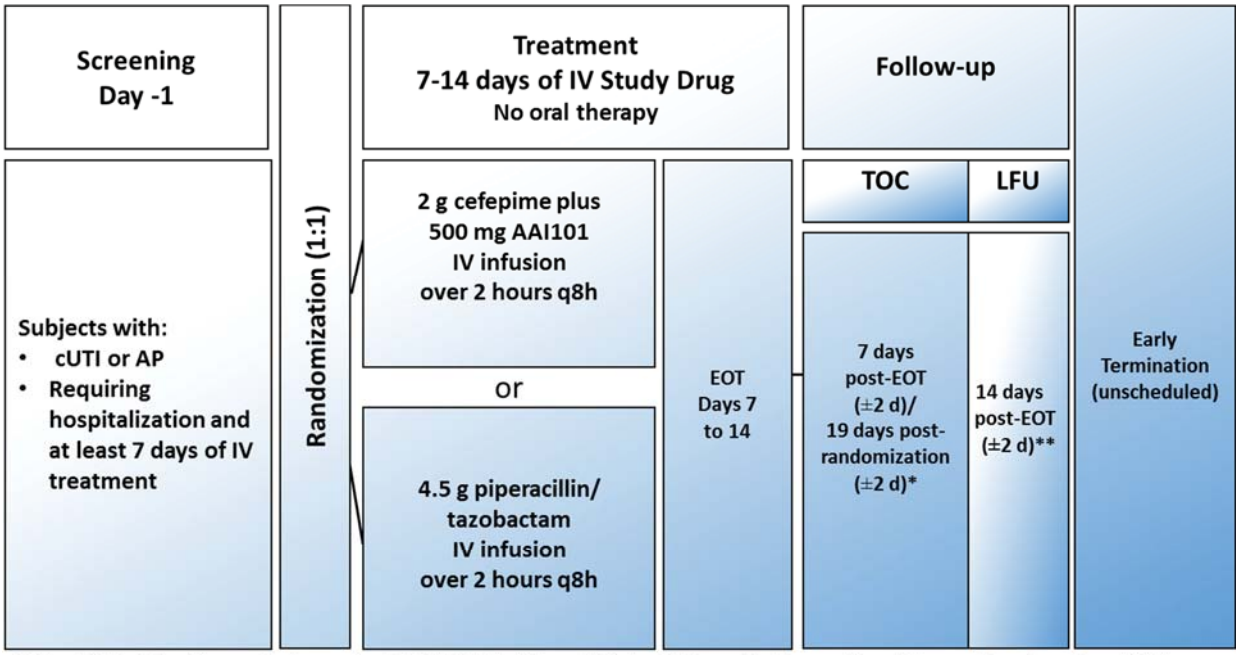
Patients with qualifying Gram-negative uropathogen co-infected with a Gram-positive uropathogen detected after randomization may be administered narrow-spectrum, open-label glycopeptide (*e.g.*, vancomycin), oxazolidinone (*e.g.*, linezolid), or daptomycin concomitantly

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 (see Appendix F). 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 study 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 Indication

Cefepime-AAI101 is indicated for the treatment of cUTI, including AP.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

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

1. Male or female patients ≥18 years of age at the time of signing of informed consent;
2. Expectation that the patient's cUTI or AP will require hospitalization and initial treatment with at least 7 days of intravenous (i.v.) antibiotics;
3. Female patients who are no longer of childbearing potential must meet 1 of the following criteria:
   a. Women ≥50 years of age who are considered post-menopausal as they have been amenorrhoeic for ≥12 months following cessation of all pharmaceutical or exogenous hormonal treatment;
   b. Women <50 years of age who are considered post-menopausal as they have been amenorrhoeic for ≥12 months following cessation of all pharmaceutical or exogenous treatment and if follicle-stimulating hormone (FSH) levels are in the post-menopausal range. If the 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; or
   c. Permanent sterilization, defined as hysterectomy, bilateral oophorectomy, or bilateral salpingectomy;
4. Female patients of childbearing potential must have a negative urine and/or serum pregnancy test (serum β-human chorionic gonadotropin) within 1 day prior to study entry;
5. Male patients, female patients receiving hormone replacement therapy (HRT), and female patients of childbearing potential must agree to use highly effective contraception methods as defined below:

   NOTE: Female patients who are no longer of childbearing potential (*i.e.*, confirmed to be permanently sterile as defined above or post-menopausal) and patients who are exclusively in same-sex relationships will not be required to use contraception.

   a. Male patients and their partners of childbearing potential or partners sterilized by tubal ligation, female patients receiving HRT, female patients who have been sterilized by tubal ligation, and female patients of childbearing potential are required to use a condom (male or female) in conjunction with spermicidal gel, foam, cream, film, or suppository from the time of dosing until 90 days after the last dose; and
   b. Male patients and their partners of childbearing potential and female patients of childbearing potential are required to use an additional highly effective form of

contraception from the time of first dose until 90 days after the last dose. Additional highly effective methods of contraception include the following:

- Diaphragm or cervical vault cap in conjunction with spermicidal gel, foam, cream, film, or suppository;
- Male sterilization (for female patients, the vasectomized male partner should be the sole partner for that patient);
- Intrauterine device; or
- Established use of oral, injected, or implanted hormonal methods of contraception;

6. Pyuria, defined as:
   a. White blood cell count >10 cells/mm^3 in unspun urine or ≥10 cells/high power field in spun urine sediment; or
   b. Urinalysis/dipstick analysis positive for leukocyte esterase;
7. Clinical signs and/or symptoms of cUTI or AP, as defined in Table 1:

   NOTE: If the criteria for both cUTI and AP are met, the infection type will be considered cUTI for randomization and analysis purposes.

Table 1. Definition of Complicated Urinary Tract Infection and Acute Pyelonephritis

cUTI	AP
At least 2 of the following new or worsening symptoms: • Dysuria, increased urinary frequency, or urinary urgency; • Fever (oral/tympanic ≥38°C [≥100.4°F] or rectal temperature ≥38.3°C [≥100.9°F]) observed and documented by a health care provider within 24 hours of Screening; • Lower abdominal pain or pelvic pain; • Suprapubic tenderness on physical examination; or • Nausea or vomiting within 24 hours of Screening as reported by the patient; **AND** At least 1 of the following complicating factors: • Male patients with documented history of urinary retention (*e.g.*, benign prostatic hypertrophy); • Use of intermittent bladder catheterization or presence of an indwelling bladder catheter; NOTE: Indwelling bladder catheters that have been in place for >24 hours prior to Screening must be removed or replaced prior to collection of the Screening visit urine for urinalysis and culture unless removal or replacement is considered unsafe or contraindicated. • Current obstructive uropathy that is scheduled to be medically or surgically relieved during i.v. study therapy and before EOT; • Any functional or anatomical abnormality of the urogenital tract (including anatomic malformations or neurogenic bladder) with voiding disturbance resulting in at least 100 mL residual urine; or • Azotemia, defined as blood urea nitrogen >20 mg/dL, blood urea >42.8 mg/dL, or serum creatinine >1.4 mg/dL, due to known prior intrinsic renal disease.	At least 2 of the following new or worsening symptoms: • Dysuria, increased urinary frequency, or urinary urgency; • Fever (oral/tympanic ≥38°C [≥100.4°F] or rectal temperature ≥38.3°C [≥100.9°F]) observed and documented by a health care provider within 24 hours of Screening; • Flank pain (onset within 7 days prior to randomization); • Costo-vertebral angle tenderness on physical examination; or • Nausea or vomiting within 24 hours of Screening, as reported by the patient.
AP = acute pyelonephritis; cUTI = complicated urinary tract infection; EOT = End of Treatment; i.v. = intravenous(ly).	

8. Have a baseline urine culture specimen obtained within 48 hours prior to randomization and the first dose of study drug; and

   NOTE: Patients may be enrolled in this study and start i.v. study drug therapy before the Investigator knows the results of the baseline urine culture.

9. Expectation, in the judgment of the Investigator, that any implanted urinary instrumentation (*e.g.*, nephrostomy tubes, ureteric stents, etc.) will be surgically removed or replaced before or within 24 hours after randomization, unless removal or replacement is considered unsafe or contraindicated.

4.2 Exclusion Criteria

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

1. Known urine culture with Gram-positive primary pathogen at $\geq 10^5$ colony-forming units (CFU)/mL (not contaminant) or suspected Gram-positive pathogen by Gram staining (Note: Gram staining is optional);
2. History of significant hypersensitivity or allergic reaction to cefepime, piperacillin/tazobactam, any of the excipients used in the respective formulations, any beta-lactam antibiotics (*e.g.*, cephalosporins, penicillins, carbapenems, or monobactams), or any BLIs (*e.g.*, tazobactam, sulbactam, or clavulanic acid);
3. In the opinion of the Investigator, the patient is considered unlikely to survive the approximately 6-week study period;
4. Weight >180 kg;
5. Concurrent infection that would interfere with evaluation of response to the study antibiotics;
6. Need for or receipt of concomitant systemic antimicrobial agents after signing of informed consent, in addition to those designated in the study-treatment groups, with the exception of a single oral dose of any antifungal treatment for vaginal candidiasis;
7. Receipt of potentially effective systemic antibacterial therapy for a continuous duration of >24 hours during the previous 72 hours before the study-qualifying baseline urine is obtained;

   EXCEPTION:

   a. Receipt up to 24 hours of short-acting antibacterial agent (see Appendix C for the list of allowed and disallowed antibiotics). No more than 25% of patients who meet this criterion will be enrolled;

   b. Patients who received prior antimicrobial therapy for the current cUTI/AP, and 1) in the Investigator's opinion, failed that prior antibiotic therapy (*i.e.*, presented with worsening signs and symptoms), AND 2) were documented to have cUTI or AP caused by a pathogen that is non-susceptible to the prior antibiotic therapy, AND 3) the causative pathogen is likely to be susceptible to the study drug;

   c. Patients who received antibacterial drugs for surgical prophylaxis and then developed cUTI or AP; or

   d. Patients who have received antimicrobial prophylaxis for recurrent cUTI and then presented signs and symptoms consistent with an active new cUTI or AP;
8. Complicated urinary tract infection known at study entry to be caused by pathogens resistant to the study antibiotics;
9. Likely to require the use of an antibiotic for cUTI or AP prophylaxis during the patient's participation in the study;
10. Intractable urinary tract infection (UTI) at baseline that the Investigator anticipates would require >14 days of study drug therapy;
11. Complete, permanent obstruction of the urinary tract that is not anticipated to be medically or surgically relieved during i.v. study therapy and before EOT;

12. Gross hematuria requiring intervention other than administration of study drug or removal or exchange of a urinary catheter;
13. Presence of any known or suspected disease or condition that, in the opinion of the Investigator, may confound the assessment of efficacy. This includes, but is not limited to, the following:
    a. Perinephric abscess;
    b. Renal corticomedullary abscess;
    c. Uncomplicated UTI;
    d. Any recent history of trauma to the pelvis or urinary tract;
    e. Polycystic kidney disease;
    f. Chronic vesico-ureteral reflux;
    g. Previous or planned renal transplantation;
    h. Previous or planned cystectomy or ileal loop surgery;
    i. Patients receiving dialysis, including hemodialysis, peritoneal dialysis, or continuous veno-venous hemofiltration; or
    j. Known or suspected infection that is caused by pathogen(s) resistant to either study drug, including infection caused by fungi (*e.g.*, candiduria) or mycobacteria (*e.g.*, urogenital tuberculosis);
14. Suspected or confirmed acute bacterial prostatitis, orchitis, epididymitis, or chronic bacterial prostatitis as determined by history and/or physical examination;
15. Impairment of renal function with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 calculated by the 4-variable Modification of Diet in Renal Disease (MDRD) study equation (see Appendix D);
16. Urinary tract surgery within 7 days prior to randomization or urinary tract surgery planned during the study period (except surgery required to relieve an obstruction or place a stent or nephrostomy prior to EOT);
17. Any condition or circumstance that, in the opinion of the Investigator, would compromise the safety of the patient or the quality of study data;
18. Any rapidly progressing disease or immediately life-threatening illness, including acute hepatic failure and respiratory failure;
19. Presence of sepsis, producing life-threatening organ dysfunction, defined as ≥2 of the following criteria:
    a. Systolic blood pressure ≤100 mmHg that is not responsive to fluid challenge;
    b. Respiratory rate ≥22 breaths/min; and/or
    c. Altered mental status;
20. A QT interval corrected using Fridericia's formula >450 msec;

21. Immunocompromising condition, including known history of acquired immune deficiency syndrome or known recent CD4 count <200/mm^3, hematological malignancy, or bone marrow transplantation; or immunosuppressive therapy including cancer chemotherapy, medications for prevention of organ transplantation rejection, or the administration of corticosteroids ≥20 mg of prednisone or equivalent per day administered continuously for >14 days prior to randomization;
22. One or more of the following laboratory abnormalities in baseline specimens obtained at Screening: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, or total bilirubin level >3 × ULN, or current clinically significant liver disease, including any form of known liver cirrhosis;
23. One or more of the following laboratory abnormalities at Screening: platelet count <50,000/µL, absolute neutrophil count <1,000/mm^3, or hemoglobin <8 g/dL;
24. Pregnant or expecting to conceive, breastfeeding, or plans to breastfeed within 1 month of completion of the study;
25. Currently participating in, or has participated in, any other clinical study involving the administration of investigational or experimental medication (not licensed by regulatory agencies) at the time of presentation or during the previous 30 days or 5 half-lives, whichever is longer, prior to Screening, or is anticipated to participate in such a clinical study during the course of the study; or
26. Unable or unwilling, in the judgment of the Investigator, to comply with the protocol.

4.3 Actions Upon Patient Withdrawal

Patients who discontinue study drug but do not withdraw from the study will be asked to complete all remaining study visits.

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

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

- The patient withdraws consent or requests discontinuation from the study for any reason;
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;
- Any serious adverse event (SAE), clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the patient;
- Pregnancy;
- Requirement of prohibited concomitant medication;
- Patient failure to comply with protocol requirements or study-related procedures; or
- Termination of the study by the Sponsor or the regulatory authority.

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records. Attempts to contact should include a minimum of 3 attempts documented in the source record over a 3-week period.

Withdrawn patients will not be replaced.

5 STUDY TREATMENTS

5.1 Treatment Groups

Approximately 1,040 patients who 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 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).

5.2 Rationale for Dosing

The rationale for the clinical doses selected for the cefepime-AAI101 combination is based on the approved cefepime dosing regimens and the clinical data obtained to date with AAI101.

The combination of 2 g cefepime plus 500 mg AAI101 infused over a period of 2 hours q8h is expected to be safe and effective for patients with cUTI, including AP.

The dose and dosing regimen for piperacillin/tazobactam is based on the current Summary of Product Characteristics and current standard clinical practice.

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

No switch to oral therapy will be permitted.

5.3 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).

5.4 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.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

AAI101 is a sterile white to off-white powder obtained by crystallization. Phase 3 drug supplies of AAI101 are manufactured by Istituto Biochimico Italiano Giovanni Lorenzini Spa in individual 10 mL Type I glass vials containing 500 mg of AAI101.

Cefepime is a white to pale yellow powder for solution for injection/infusion packaged in individual 15 mL colorless Type III glass vials containing 1 g cefepime.

Piperacillin/tazobactam is a white to off-white powder consisting of piperacillin and tazobactam as their sodium salts packaged in vials. Each vial contains sufficient drug for withdrawal of piperacillin sodium equal to 4 g piperacillin and tazobactam sodium equal to 0.5 g tazobactam. Each vial contains 217 mg of sodium.

5.5.2 Study Drug Preparation and Dispensing

An unblinded pharmacist (or qualified designee) will prepare the study drug according to the Pharmacy Manual. Cefepime-AAI101 will be reconstituted in 20 mL normal saline (NS) and immediately mixed in the 250 mL saline bag. Piperacillin/tazobactam will be reconstituted in 20 mL NS and immediately mixed in 250 mL. The i.v. bags will be labeled with the date and time of study drug preparation and patient identification number using the study supplied labels and will be transferred to the blinded study staff for administration to the patient.

The reconstituted solution should be visually inspected before use. It must only be used if the solution is free of particles. Reconstituted study drug should be administered according to the requirements outlined in the Pharmacy Manual.

5.5.3 Study Drug Administration

An unblinded pharmacist (or qualified designee) will be responsible for providing study drug to the blinded study personnel for administration. At each administration of i.v. study drug, all patients will receive a 270 mL infusion administered via a pump over a period of 2 hours. Study drug is to be administered while patients are seated or semi-recumbent in bed. The time at which each infusion is started and stopped must be collected and recorded in the eCRF. Instances where the dose is interrupted by more than 10 minutes should be noted in the source documents. Infusions that fall outside the q8h dosing (±15 minutes) will be captured as protocol deviations.

Study drug will be administered to all patients 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.

5.5.3.1 Dosing in patients with renal insufficiency

Pharmacokinetics and safety of cefepime and AAI101 in subjects with varying degrees of renal impairment are being assessed in an open-label, single-dose study.[8] The available study data indicate that in subjects with mild renal impairment (eGFR <90 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2) to moderate renal impairment (eGFR <60 mL/min/1.73 m^2 and ≥30 mL/min/1.73 m^2, as calculated using the MDRD formula), cefepime and AAI101 plasma clearance decreased to a similar extent. This similar decrease of plasma clearance allows the ratio of cefepime and AAI101 to be maintained for dose adjustment in patients with reduced renal function.

Based on the data from this trial, PK/PD modelling was performed to determine the optimal cefepime-AAI101 combination dose that would provide adequate anti-bacterial effect in renally impaired patients. The modelling confirmed no need for dose adjustment in patients with mild renal impairment (eGFR <90 mL/min/1.73 m^2 and ≥60 mL/min/1.73 m^2). In patients with moderate renal impairment (eGFR <60 mL/min/1.73 m^2 and ≥30 mL/min/1.73 m^2) the dose of cefepime-AAI101 will be adjusted to 1 g cefepime plus 250 mg AAI101, infused over a period of 2 hours q8h. In patients with moderate renal impairment, dose adjustment is applicable from Day 1 of dosing.

Dosing of piperacillin/tazobactam will follow the recommendations as per the respective summary of product characteristics, which does not require adjustment of the 4.5 g dose in patients with mild or moderate renal impairment.[9]

Patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) are excluded from study participation (see exclusion criterion 15, Section 4.2, and Appendix D).

For patients with normal renal function or mild renal impairment at baseline whose eGFR drops below 60 mL/min/1.73 m^2 after baseline, or for patients with moderate renal impairment at baseline whose eGFR drops below 30 mL/min/1.73 m^2 after baseline, serum creatinine should be repeated to confirm the initial result and estimate eGFR. The sites can perform non-programmed local and/or central laboratory tests for serum creatinine to assess if dose adjustment of study drugs may be necessary. Patients may require dose adjustment or may need to be discontinued from the study, according to the Investigator's judgment or when the patient's safety is at risk.

5.5.4 Treatment Compliance

Study drug will be administered at the study site by study staff. Dosing compliance will be recorded by the Investigator or designee at the study site. The date, start and stop times, and volume of study drug administered i.v. will be accurately logged in the source documentation.

5.5.5 Storage and Accountability

The unblinded pharmacist or designated unblinded study personnel will ensure that all study drugs are stored in a locked, secure area with limited access. The date and time of preparation of study drug will be recorded on the i.v. bags.

Refer to the Pharmacy Manual for details regarding storage of study drug (cefepime-AAI101 and piperacillin/tazobactam).

The Investigator will ensure that a current record of inventory/drug accountability is maintained. Upon completion or termination of the study, the Sponsor will provide disposition instructions for all unused and/or partially used study drugs at the study site.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

The following medications and procedures are excluded for the duration of the study:

- Concomitant systemic antimicrobial agents after signing of informed consent, in addition to those designated in the study-treatment groups, with the exception of a single oral dose of any antifungal treatment for vaginal candidiasis;
- Receipt of potentially effective systemic antibacterial therapy for a continuous duration of >24 hours during the previous 72 hours before the study-qualifying baseline urine is obtained;

  EXCEPTION:

  a. Receipt up to 24 hours of short-acting antibacterial agent (see Appendix C for list of allowed and disallowed antibiotics). No more than 25% of patients who meet this criterion will be enrolled;

  b. Patients who received prior antimicrobial therapy for the current cUTI/AP, and 1) in the Investigator's opinion, failed that prior antibiotic therapy (*i.e.*, presented with worsening signs and symptoms), AND 2) were documented to have cUTI or AP caused by a pathogen that is non-susceptible to the prior antibiotic therapy, AND 3) the causative pathogen is likely to be susceptible to the study drug;

  c. Patients who received antibacterial drugs for surgical prophylaxis and then developed cUTI or AP; or

  d. Patients who have received antimicrobial prophylaxis for recurrent cUTI and then presented signs and symptoms consistent with an active new cUTI or AP;

- Urinary tract surgery within 7 days prior to randomization, or urinary tract surgery planned during the study period (except surgery required to relieve an obstruction or place a stent or nephrostomy prior to EOT); and
- Any investigational or experimental medication (not licensed by regulatory agencies) within 30 days prior to Screening, or 5 half-lives, whichever is longer.

5.6.2 Restricted Medications and/or Procedures

Female patients receiving HRT must agree to use highly effective contraception methods (see Section 4.1).

A list of allowed and disallowed antibiotics can be found in Appendix C.

5.6.3 Allowed Medications and/or Procedures

Patients with qualifying, defined as a single Gram-positive or Gram-negative organism $\geq 10^5$ CFU/mL for urine and growth in blood culture, 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.

5.6.4 Documentation of Prior and Concomitant Medication Use

Reasonable efforts will be made to determine all relevant treatment (concomitant medications, including all prescription/non-prescription medications, herbal medications, vitamin supplements, supportive therapies, and concomitant non-pharmacologic treatments) received by the patient within 14 days before administration of study drug and during the study, which will be recorded in the eCRF. The medication name, route of administration, dose, frequency, indication, and duration of the treatment/procedure (start and stop dates) will be recorded. Concomitant treatments (non-pharmacologic treatments) include any surgical or diagnostic procedures.

6 STUDY PROCEDURES

6.1 Informed Consent

Signed informed consent must be obtained before any study-related procedures are performed.

6.2 Screening (Day -1)

The following procedures will be performed at Screening. 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 central laboratory):

- Sign informed consent;
- Record demographics;
- Record medical history;
- Record prior/concomitant medications;
- Review inclusion/exclusion criteria;
- Perform urine and/or serum pregnancy test (women of childbearing potential only);
    - 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;
- Perform triplicate 12-lead ECG;
- Assess clinical signs and symptoms;
- Collect urine samples for urine culture and send to the local microbiology laboratory for analysis;
- Collect blood samples for blood cultures and send to the local microbiology laboratory for analysis;
- Collect samples for laboratory assessments (chemistry, hematology, and urinalysis) and send to the local laboratory for analysis;
- Perform complete physical examination, including height and weight;
- Record vital signs;
- Assess adverse events; and
- Perform DSAQ interview (2 questionnaires).

6.3 Treatment Period

6.3.1 Day 1

The following procedures, with the exception of study drug administration, will be performed on Day 1 prior to the first dose of study drug (if Screening and Day 1 occur on the same day or within 24 hours, duplicate assessments do not need to be performed):

- Review and record medical history;
- Record concomitant medications;
- Review inclusion/exclusion criteria;
- Assess clinical signs and symptoms;
- Collect blood samples for PK analysis (pre-dose and at 2 and 4 hours after the start of the 2-hour infusion);
  - May be collected after any of the 3 infusions during Day 1;
- Collect urine samples for urine culture within 2 hours prior to randomization if possible and send to the local microbiology laboratory for analysis;
- Collect blood samples for blood cultures and send to the local microbiology laboratory for analysis;
- Collect samples for laboratory assessments (chemistry, hematology, coagulation, and urinalysis) and send to the central laboratory for analysis;
- Perform limited physical examination if clinically indicated;
- Record vital signs;
- Assess adverse events;
- Calculate Charlson Comorbidity Index (prior to the first dose of study drug; see Appendix E);
- Perform DSAQ interview;
- Randomize to study treatment; and
- Administer study drug.

6.3.2 Day 2

The following procedures will be performed on Day 2:

- Record concomitant medications;
- Assess clinical signs and symptoms;
- Collect blood samples for blood cultures (if clinically indicated or if previous culture was positive) and send to the local microbiology laboratory for analysis;
- Collect samples for only coagulation and send to the central laboratory for analysis. If required for the evaluation of renal function, collect a sample for laboratory assessment of serum creatinine only (may be sent to the local and/or central laboratory);

- Perform limited physical examination if clinically indicated;
- Record vital signs;
- Assess adverse events;
- Perform DSAQ interview; and
- Administer study drug.

6.3.3 Day 3

The following procedures will be performed on Day 3:

- Record concomitant medications;
- Assess clinical signs and symptoms;
- Assess clinical outcome;
- Collect blood sample for PK sampling (pre-dose and at 2 and 4 hours after the start of the 2-hour infusion);
  - May be collected after any of the 3 infusions during Day 3;
- Collect urine for urine culture and send to the local microbiology laboratory for analysis;
- Collect blood samples for blood cultures (if clinically indicated or if previous culture was positive) and send to the local microbiology laboratory for analysis;
- Collect samples for laboratory assessments (chemistry, hematology, coagulation, and urinalysis) and send to the central laboratory for analysis;
- Perform limited physical examination if clinically indicated;
- Record vital signs;
- Assess adverse events;
- Perform DSAQ interview; and
- Administer study drug.

6.3.4 Day 4 to Day 6

The following procedures will be performed on Day 4 to Day 6:

- Record concomitant medications;
- Assess clinical signs and symptoms;
- Collect blood samples for blood culture (if clinically indicated or if previous culture was positive) and send to the local microbiology laboratory for analysis;
- Collect samples for only coagulation and send to the central laboratory for analysis. If required for the evaluation of renal function, collect a sample for laboratory assessment of serum creatinine only (may be sent to the local and/or central laboratory);
- Perform limited physical examination if clinically indicated;

- Record vital signs;
- Perform triplicate 12-lead ECG (at Day 4 only);
- Assess adverse events;
- Perform DSAQ interview; and
- Administer study drug.

6.3.5 Day 7 to Day 14 (End of Treatment)

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.

End of Treatment may occur anytime from Day 7 to Day 14, depending on treatment duration. The following procedures will be performed from Day 7 to Day 14:

- Record concomitant medications;
- Assess clinical signs and symptoms;
- Assess clinical outcome (at EOT only);
- Collect blood samples for PK sampling at Day 7 and EOT (pre-dose and at 2 and 4 hours after the start of the 2-hour infusion);
  - May be collected after any of the 3 infusions at Day 7 and EOT;
- Collect urine for urine culture (at EOT only) and send to the local microbiology laboratory for analysis;
- Collect blood samples for blood cultures (if clinically indicated or if previous culture was positive) and send to the local microbiology laboratory for analysis;
- Collect samples for laboratory assessments as follows:
  - If Day 7 is EOT, collect chemistry, hematology, coagulation (prothrombin time [PT] and partial thromboplastin time [PTT]), and urinalysis;
  - If Day 7 is not EOT, collect ALT, AST, alkaline phosphatase, total and direct bilirubin, coagulation (PT and PTT), and 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 a sample for laboratory assessment of serum creatinine only (may be sent to the local and/or central laboratory);
  - If Day 10, collect chemistry, hematology, coagulation (PT and PTT), and urinalysis; or
  - If EOT (at whichever visit day it occurs), collect chemistry, hematology, coagulation (PT and PTT), and urinalysis;
- Perform limited physical examination if clinically indicated;
- Record vital signs;

- Assess adverse events;
- Perform DSAQ interview; and
- Administer study drug (study drug will be administered for 7 days [up to 14 days in patients with a positive blood culture at baseline at the discretion of the Investigator]).

6.4 Follow-up Period

Following the Treatment Period, patients will return for a TOC and LFU visit.

6.4.1 Test of Cure

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 following procedures will be performed at TOC:

- Record concomitant medications;
- Perform urine and/or serum pregnancy test (women of childbearing potential only);
- Assess clinical signs and symptoms;
- Assess clinical outcome;
- Collect urine for urine culture and send to the local microbiology laboratory for analysis;
- Collect blood samples for blood cultures (if clinically indicated or if previous culture was positive) and send to the local microbiology laboratory for analysis;
- Collect samples for laboratory assessments (chemistry, hematology, coagulation, and urinalysis) and send to the central laboratory for analysis;
- Perform limited physical examination if clinically indicated;
- Record vital signs;
- Assess adverse events; and
- Perform DSAQ interview.

6.4.2 Late Follow-up (EOT + 14 Days [±2 Days])

The LFU visit should not take place earlier than 3 days after the TOC visit. The following procedures will be performed at LFU:

- Record concomitant medications;
- Assess clinical signs and symptoms;
- Assess clinical outcome;
- Collect urine for urine culture and send to the local microbiology laboratory for analysis;
- Collect blood samples for blood cultures (if clinically indicated or if previous culture was positive) and send to the local microbiology laboratory for analysis;

- Collect samples for laboratory assessments (chemistry, hematology, coagulation, and urinalysis) and send to the central laboratory for analysis;
- Perform limited physical examination if clinically indicated;
- Record vital signs;
- Assess adverse events; and
- Perform DSAQ interview.

6.5 Early Termination Visit and Withdrawal Procedures

For patients completing the study, EOT will occur anytime from Day 7 to Day 14, depending on the duration of treatment. For patients who are withdrawn from the study prior to completion, the following procedures will be performed:

- Record concomitant medications;
- Assess clinical signs and symptoms;
- Assess clinical outcome;
- Collect blood samples for PK sampling (if ET has infusion, collect PK sampling pre-dose and at 2 and 4 hours after the start of the 2-hour infusion, otherwise collect 1 sample);
- Collect urine for urine culture and send to the local microbiology laboratory for analysis;
- Collect blood samples for blood cultures (if clinically indicated or if previous culture was positive) and send to the local microbiology laboratory for analysis;
- Collect samples for laboratory assessments (chemistry, hematology, coagulation, and urinalysis) and send to the central laboratory for analysis;
- Perform limited physical examination if clinically indicated;
- Record vital signs;
- Assess adverse events; and
- Perform DSAQ interview.

7 EFFICACY ASSESSMENTS

7.1 Primary Efficacy Assessment

The primary efficacy parameter is the proportion of patients in the Microbiological Modified Intent-to-Treat (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).

7.1.1 Clinical Outcome

Assessment of clinical outcome 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.

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

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. Clinical outcome will be determined programmatically based on patient responses in the Daily Symptom Assessment Questionnaire. **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 due to an adverse event or due to lack of clinical improvement; or • Death of the patient during the study. **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.	

7.1.2 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 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. CFU = colony-forming units.	

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

7.1.2.1 Microbiology assessments

<u>Urine culture</u>

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.

7.1.3 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.

7.2 Secondary Efficacy Assessments

The secondary efficacy parameters include the following:

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

7.3 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.

8 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]).

8.1 Adverse Events

An adverse event 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 adverse event 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 adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include laboratory test variables, will be monitored and documented from the time of informed consent until study participation is complete. Patients should be instructed to report any adverse event that they experience to the Investigator. Beginning with the signing of informed consent, investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

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

Any medical condition already present at the time of screening should not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline changes in severity or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination (*e.g.*, ECG) findings that are detected during the study or are present at the time of screening and significantly worsen during the study should be reported as adverse events. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an adverse event. Laboratory abnormalities (except liver function test [LFTs] increase) are not considered adverse events unless they are associated with clinical signs or symptoms, or require medical intervention.

Worsening of the index indication due to insufficient therapeutic effect of study drug is captured as an efficacy measure *(i.e.*, clinical failure) and in general will not be considered an adverse event. However, if the worsening of the index indication meets seriousness criteria, the event will be deemed an SAE.

8.1.1 Adverse (Drug) Reaction

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

8.1.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For AAI101, the reference safety information is included in Section 6.3 of the Investigator's Brochure currently in force. The reference safety information will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

8.1.3 Assessment of Adverse Events by the Investigator

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

Assessment of severity:

The severity of all adverse events should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. These criteria can be found at http://ctep.cancer.gov/reporting/ctc.html. For those adverse events not listed in the CTCAE, the following grading system should be used:

- Mild (CTCAE Grade 1): Transient symptoms, awareness of sign/symptom, but easily tolerated and no interference with patient's daily activities.
- Moderate (CTCAE Grade 2): Marked signs/symptoms that interfere with patient's usual activities, but still acceptable.
- Severe (CTCAE Grade 3): Incapacitating signs/symptoms which cause considerable interference with the patient's daily activities, unacceptable.
- Life-threatening (CTCAE Grade 4): Life-threatening or disabling adverse event.
- Death (CTCAE Grade 5): Death-related adverse event.

Causality assessment:

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

No (unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

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

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-
  - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases-
  - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant drug-
  - The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug-
  - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses-
  - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and PK of the study drug-
  - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.2 Adverse Events of Special Interest

Adverse events of special interest will include the following:

- Elevations of ALT
  - Percentage of subjects with ALT elevation shift from baseline to post-baseline (*e.g.*, baseline normal to post-baseline >1 × ULN, baseline >1 × ULN to post-baseline >2 × ULN, etc.).
- Elevations of AST
  - Percentage of subjects with AST elevation >1 × ULN, >2 × ULN, >3 × ULN, >5 × ULN, and >10 × ULN at Day 3, Day 10, EOT, TOC, and LFU.
- Elevations of total bilirubin
  - Percentage of subjects with total bilirubin elevation >1 × ULN, >1.5 × ULN, >2 × ULN, >3 × ULN, >5 × ULN, and >10 × ULN at Day 3, Day 10, EOT, TOC, and LFU.

8.2.1 Safety Monitoring and Assessment of Abnormal Liver Function Tests

Management and discontinuation criteria for abnormal LFTs have been designed to ensure subject safety and evaluate liver event etiology.[10] Abnormal LFTs will be monitored until resolution or return to baseline level (see Section 8.2.1.2).

8.2.1.1 Abnormal liver chemistry criteria

The Investigator or sub-Investigator must review study subject laboratory reports to identify if they meet the following criteria:

- Moderate abnormality
  - AST or ALT >3 × ULN; or
  - Total bilirubin >2 × ULN.
- Severe abnormality
  - AST or ALT >3 × ULN and total bilirubin >2 × ULN.

8.2.1.2 Action to be taken by the Investigator

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

- Obtain a detailed history of symptoms and prior or concurrent diseases. The Investigator should ensure that the medical history form captures any pre-existing illness that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including over-the-counter [OTC]/herbal/dietary supplements).
- Obtain a history of exposure to environmental chemical agents.
- Make every effort to have the subject reassessed within 48 to 72 hours following the initial observed elevation. Repeat LFTs will be performed and sent to the central laboratory. Liver function tests may also be repeated via the local laboratory, at the discretion of the Investigator.
- Monitor subjects who have an Investigator-assessed, study drug-related elevation of their LFTs 2 to 3 times per week until liver function chemistries (ALT, AST, alkaline phosphatase, direct bilirubin, and total bilirubin) completely return to normal range or return to the baseline level, and associated clinical signs and symptoms return to baseline levels. If the elevation of LFTs is attributed to a non-drug related issue (*e.g.*, pre-existing condition, concomitant treatments, etc.), the subject should be monitored until the LFTs stabilize or return to the subject's chronically baseline level and associated clinical signs and symptoms return to baseline levels. The Investigator should contact the Medical Monitor to discuss additional management and follow-up on subjects with elevation of LFTs.
- Report the event to Medpace within 48 to 72 hours after its occurrence on the Liver Event Form.
- Consider a consultation with a specialist such as a hepatologist.
- Consider performing liver imaging (*i.e.*, ultrasound, magnetic resonance imaging, computerized tomography), if required.

Hy's Law definition:

The AST or ALT >3 × ULN and total bilirubin >2 × ULN AND there is no evidence of intra-or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's Syndrome.

If the definition of Hy's Law is met, the case must be reported as an SAE (see Section 8.4).

8.2.1.3 Criteria for study drug discontinuation (severe hepatic abnormalities)

In the absence of an explanation for increased liver enzymes, the subject should be discontinued from the study drug. Discontinuation should occur if the following is observed:

- AST or ALT >5 × ULN;
- AST or ALT >3 × ULN and total bilirubin >2 × ULN or international normalized ratio (INR) >1.5;
- AST or ALT >3 × ULN with signs or symptoms compatible with hepatitis or hypersensitivity (*e.g.*, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, or eosinophilia [>5%]); or
- Close monitoring for a subject with moderate hepatic laboratory test abnormality is not possible.

8.2.1.4 Follow-up examination

If any abnormal liver chemistry criteria are met, the following assessments should be obtained at the LFU visit and documented on the Liver Event Form:

- Clinical symptoms course;
- Concomitant medications including OTC/herbal/dietary supplements (start and stop dates);
- Alcohol use;
- Risk factors for non-alcoholic steatohepatitis, such as diabetes, obesity, and hypertriglyceridemia;
- Autoimmune hepatitis/cholangitis;
- Wilson's disease; and
- Laboratory assessments - based on the subject's history, other tests may be appropriate including the following:
    - Acute viral hepatitis (A, B, C, D, E or other infectious agents); and
    - Other laboratory tests, *e.g.,* INR.

The Investigator should contact the Medical Monitor to discuss follow-up on subjects with elevation of LFTs.

8.3 Serious Adverse Events

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

- Death;
- A life-threatening adverse event;

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

- Requires hospitalization or prolongation of existing hospitalizations;

  NOTE: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (*i.e.*, no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

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

  NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.4 Serious Adverse Event Reporting – Procedures for Investigators

Initial reports

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers related to study drug occurring after the 30-day follow-up period must be reported to the Sponsor.

To report the SAE, the SAE form can be filled in electronically. When the form is completed, signed and dated, it must be sent via e-mail or fax to Medpace Safety personnel. All sites can use either of both contact details:

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

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

Follow-up reports

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

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

8.5 Pregnancy Reporting

If the patient or partner of a patient participating in the study becomes pregnant during the study or within 90 days of discontinuing study drug, the Investigator should report the pregnancy to Medpace Clinical Safety within 24 hours of being notified. Medpace Clinical Safety will then forward the Exposure In Utero form to the Investigator for completion.

A patient becoming pregnant while on study drug will immediately be withdrawn from the study and ET study procedures will be performed.

The patient or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Medpace Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (*i.e.*, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.6 Expedited Reporting

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to the Food and Drug Administration (FDA), applicable competent authorities, and Ethics Committees as required, and in any case no later than 7 days after knowledge by the Sponsor of such a case. Relevant follow-up information will subsequently be communicated within 8 days.

All other suspected unexpected serious adverse reactions will be reported to the FDA, applicable competent authorities and Ethics Committees as required as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor. Relevant follow-up information will subsequently be communicated within 15 days.

The Sponsor will also inform all investigators as required.

Expedited reporting of suspected unexpected serious adverse reactions related to cefepime or piperacillin/tazobactam (the study investigational medical product), and any other non-investigational medical products will not be necessary. Listings of cases related to cefepime or piperacillin/tazobactam will be included in the Development Safety Update Report.

8.7 Clinical Laboratory Evaluations

Blood samples for chemistry and hematology analyses will be collected as specified by the Schedule of Procedures (Appendix A). Laboratory tests that are clinically significantly abnormal will be repeated.

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 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.

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 study eligibility.

For women of childbearing potential, a urine and/or serum pregnancy test will be performed at Screening and TOC. Pregnancy testing should be performed by the local laboratory unless the site cannot perform this test, at which time pregnancy testing can be performed by the central laboratory. 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.

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

8.8 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 (Appendix A).

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.

8.9 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.

8.10 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.

8.11 Daily Symptom Assessment Questionnaire

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

8.12 Safety Assessments

A Data and Safety Monitoring Board (DSMB) according to international standards will be established in this study. It will consist of independent clinical experts and at least 1 independent statistical expert. The DSMB will meet to periodically review and evaluate accumulated study data for subject safety, study conduct, and progress.

The DSMB will make recommendations concerning the continuation, modification, or termination of the study.

The task, procedures, and responsibilities of the DSMB will be described in a separate DSMB Charter. The DSMB will meet at the study start, when LFU outcome is known for one-third of m-MITT patients (270 patients), and when LFU outcome is known for two-thirds of m-MITT patients (540 patients).

9 STATISTICS

9.1 Analysis Populations

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

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

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

Microbiological Modified Intent-to-Treat Population: 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 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. The m-MITT Population will be the primary efficacy population. 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. Efficacy analyses will be based on the treatment as randomized.

Clinically Evaluable 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 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.

Microbiologically Evaluable 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.

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.

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

9.2 Statistical Methods

9.2.1 Analysis of Efficacy

9.2.1.1 Primary efficacy analysis

The primary efficacy parameter is the proportion of patients in the m-MITT Population who achieve overall treatment success at TOC. 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 each 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.

9.2.1.2 Sensitivity efficacy analyses

Analyses of the primary efficacy endpoint will be performed for the MITT, CE, and ME Populations.

9.2.1.3 Secondary efficacy analyses

Descriptive statistics will be provided for secondary endpoints. Treatment differences and associated 95% CIs will also be presented.

Analyses of the secondary efficacy endpoint will be performed for the MITT, m-MITT, CE, and ME Populations.

9.2.1.4 Pharmacokinetic analyses

Plasma concentrations and PK parameters will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequencies and percentages for discrete variables. Derived plasma PK parameters will be summarized using descriptive statistics (n, arithmetic and geometric means, coefficient of variation, standard deviation of the arithmetic mean, median, minimum, and maximum).

All PK analyses will be performed using the PK Population.

9.2.2 Analysis of Safety

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.

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. The number and percentage of patients with TEAEs will be tabulated by System Organ Class and Preferred Term for each treatment group and by severity and relationship to treatment. Serious adverse events and adverse events leading to

discontinuation from study drug will be summarized by treatment group. Listings will also be provided for SAEs and adverse events leading to discontinuation of study drug.

Descriptive statistics will be provided for clinical laboratory data for both actual values and changes from baseline over time.

Descriptive statistics will be provided for vital sign data presented as both actual values and changes from baseline over time.

Abnormal physical examination findings will be listed.

9.2.3 Sample Size Determination

A trial enrolling 810 patients who are evaluable in the m-MITT 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%.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

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

10.1.2 Computer Systems

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

10.1.3 Data Entry

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

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- The latest version at the time of study start of the Medical Dictionary for Regulatory Activities for medical history and adverse events; and
- The latest version at the time of study start (and each subsequent update as they become available throughout the duration of the study) of the World Health Organization Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

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

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

10.2 Record Keeping

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

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

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

11.2 Institutional Review Board/Independent Ethics Committee

It is the responsibility of the Sponsor or their designee (*i.e.*, Medpace) to obtain the approval of the responsible ethics committees according to the national regulations.

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

11.3 Informed Consent

The informed consent form (ICF) and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the Institutional Review Board (IRB) prior to its use and must be in compliance with all International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP, local regulatory requirements, and legal requirements.

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

11.4 Patient Card

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

11.5 Study Monitoring Requirements

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

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

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

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

11.6 Disclosure of Data

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

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

11.7 Retention of Records

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

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

11.8 Publication Policy

After completion of the study, a clinical study report will be prepared according to the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3).

Allecra, the Sponsor, will retain ownership of all data produced in this study.

The Sponsor is committed to communicate the results of the study, positive or negative, in media of public access. With the aim of ensuring the protection of the industrial ownership derived from the study, the Sponsor keeps the right to review any manuscript before its submission.

After the multi-center publication or 12 months after completion of the study, whichever occurs first, investigators may publish the results of their data from the study. They shall provide the Sponsor or its delegate with an advance copy of any proposed publication, oral presentation, or poster at least 60 days prior to the planned date of submission or presentation, and the Sponsor or its delegate shall have 60 days to review the proposed publication for the purposes described below. The Sponsor or its delegate may request in writing, and the Investigator shall agree to, a) the deletion of any Confidential Information, b) any reasonable changes requested by the Sponsor or its delegate, or c) a delay of such proposed submission for an additional period, not to exceed 90 days, in order to protect the potential patentability of any technology described therein. The Sponsor, at its election, shall be entitled to receive in any such publication an acknowledgement of its sponsorship of the study.

Authorship in the primary multi-center publication of the study (the "Multicenter-Publication") shall be decided exclusively by Sponsor/Allecra under the guiding principle that; 1) the steering committee of the study shall have the right to offer its opinion on the Multicenter-Publication, 2) all principal investigators may be acknowledged in the Multicenter-Publication (in an appendix or similar), and 3) three of the highest recruiting principal investigators in the Study may be listed with their name in the authors list in the Multicenter-Publication.

11.9 Financial Disclosure

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

11.10 Insurance and Indemnity

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

11.11 Legal Aspects

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

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

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/Independent Ethics Committee and any applicable regulatory authorities, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

12.2 End of Study

End of Study in this study means the last visit or last study-related contact (whatever comes last) of the last patient worldwide.

12.3 Address List

12.3.1 Sponsor

Allecra Therapeutics SAS
10 rue Alexandre Freund
68300 St Louis
France
Telephone: +33 3 89 68 9876

12.3.2 Contract Research Organization

Medpace, Inc.
5375 Medpace Way
Cincinnati, OH 45227
Telephone: +1-513-579-9911
Fax: +1-513-579-0444

12.3.3 Drug Safety

Medpace Clinical Safety
5375 Medpace Way
Cincinnati, OH 45227
Telephone: +1-800-730-5779, dial 3
Fax: +1-513-336-5320
E-mail: medpace-safetynotification@medpace.com

12.3.4 Biological Specimens

Central Laboratory European Union

Medpace Reference Laboratories
Technologielaan 19
B-3001 Leuven, Belgium
Telephone: +32 16 407775
Fax: +32 16 407781

Central Laboratory United States

Medpace Reference Laboratories
5365 Medpace Way
Cincinnati, OH 45227
Telephone: +1-800-749-1737
Fax: +1-513-366-3273

Pharmacokinetics Laboratory

Aptuit Center for Drug Discovery & Development
Dr. Luciana Romanelli
Bioanalysis Sample Manager, Pharmaceutical and Preclinical Development
Via Fleming, 4
37135 Verona, Italy

Microbiology Central Laboratory

IHMA, Inc.
2122 Palmer Drive
Schaumburg, IL 60173-3817
Telephone: +1-847-303-5003
Fax: +1-847-303-5601

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APPENDIX A: SCHEDULE OF PROCEDURES

	Screening	Treatment Period							Follow-Up Period		Early Termination
									TOC	LFU	
Study Day	**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**
Procedure											
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.

APPENDIX B: CLINICAL LABORATORY ANALYTES

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.

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

APPENDIX C: ALLOWED AND DISALLOWED ANTIBIOTICS

For the purposes of this study, a short-acting antibiotic is defined as having a dosage frequency of more than once daily (*e.g.*, once every 12 hours or more frequently). If a patient received a prior short-acting systemic antibiotic that is not listed below, the Investigator must contact the Medical Monitor to ensure patient eligibility.

Antibiotic Class	Allowed Antibiotics[a]		Disallowed Antibiotics	
Penicillins	Amoxicillin	Nafcillin	Benzathine/Penicillin-G Procaine	
	Amoxicillin-Clavulanate	Oxacillin		
	Amoxicillin-Sulbactam	Penicillin-G or -V		
	Ampicillin	Piperacillin		
	Ampicillin-Sulbactam	Piperacillin-Tazobactam		
	Dicloxacillin	Ticarcillin-Clavulanate		
Cephalosporins	Cefaclor	Cefpodoxime	Cefixime (400 mg)	
	Cefadroxil	Cefprozil	Ceftriaxone	
	Cefazolin	Ceftaroline		
	Cefdinir	Ceftazidime		
	Cefepime	Ceftibuten		
	Cefixime (200 mg)	Cefuroxime		
	Cefditoren	Cephalexin		
	Cefotaxime	Loracarbef		
Carbapenems	Doripenem	Meropenem	Ertapenem	
	Imipenem			
Fluoroquinolones	Ciprofloxacin		Ciprofloxacin Extended-Release	
			Moxifloxacin	Levofloxacin
Macrolides	Clarithromycin	Erythromycin	Azithromycin	Clarithromycin XL
Tetracyclines	Doxycycline (100 mg)	Minocycline	Doxycycline (200 mg)	Tigecycline
			Minocycline Extended-Release	
Aminoglycosides	Gentamicin (1.7 mg/kg q8h)		Gentamicin (4 mg/kg to 7 mg/kg q24h)	
	Amikacin (5 mg/kg to 7.5 mg/kg q8h)		Amikacin (15 mg/kg to 20 mg/kg q24h)	
	Tobramycin (1.7 mg/kg q8h)		Tobramycin (4 mg/kg to 7 mg/kg q24h)	
Miscellaneous	Clindamycin	Metronidazole		
	Trimethoprim-sulfamethoxazole/Co-trimoxazole			
	Nitrofurantoin			

a. Receipt of effective antibacterial drug therapy for cUTI for a continuous duration of >24 hours during the previous 72 hours before the study-qualifying baseline urine is obtained.
EXCEPTION: Patients who have failed treatment, both clinically and microbiologically, are eligible for the study if they have an identified uropathogen which is non-susceptible to the empiric treatment and likely to be susceptible to the study drug; OR patients who received antibacterial drugs for surgical prophylaxis and then developed cUTI.

cUTI = complicated urinary tract infection; q8h = once every 8 hours; q24h = once every 24 hours.

APPENDIX D: MODIFICATION OF DIET IN RENAL DISEASE STUDY EQUATION

Modification of Diet in Renal Disease study equation

$eGFR = 175 \times (S_{Cr})^{-1.154} \times (age)^{-0.203} \times 0.742$ [if female] $\times$ 1.212 [if Black]

Abbreviations/units

eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2

Age = years

S_{Cr} (standardized serum creatinine) = mg/dL

Source: National Kidney Foundation® https://www.kidney.org/content/mdrd-study-equation

APPENDIX E: THE CHARLSON COMORBIDITY INDEX SCORING SYSTEM

Score	Condition
1	Myocardial infarction (history, not ECG changes only) Congestive heart failure Peripheral vascular disease (includes aortic aneurysm ≥6 cm) Cerebrovascular disease: CVA with mild or no residual or TIA Dementia Chronic pulmonary disease Connective tissue disease Peptic ulcer disease Mild liver disease (without portal hypertension, includes chronic hepatitis) Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia Moderate or severe renal disease Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes) Tumor without metastases (exclude if >5 years from diagnosis) Leukemia (acute or chronic) Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor AIDS (not just HIV positive)
For each decade >40 years of age, a score of 1 is added to the above score. AIDS = acquired immunodeficiency syndrome; CVA = cerebrovascular accident; ECG = electrocardiogram; HIV = human immunodeficiency virus; TIA = transient ischemic attack.	

APPENDIX F: DAILY SYMPTOM ASSESSMENT QUESTIONNAIRE

Interviewer Instructions for Daily Symptom Assessment Questionnaire

Interviewers must complete the symptom assessment training prior to administering the Daily Symptom Assessment Questionnaire to any study patient. Training will take place at the Investigator Meeting and at the Site Initiation Visit. A standardized procedure for the administration of the Daily Symptom Assessment Questionnaires will be applied at every site to minimize bias. To ensure standardization, please read and follow these instructions carefully before administering the questionnaire.

The questionnaire should be completed prior to other examinations, before substantial encounters with professional healthcare providers occur (*e.g.*, before exchange of clinical information such as disease status occurs).

Administer the questionnaire in a quiet place where the patient can be interviewed alone, without interference from family or study staff members.

Enter the symptom assessment date and time. **NOTE: At the Screening Visit, 2 questionnaires are required: 1 questionnaire to assess premorbid symptoms (symptoms prior to the onset of current complicated urinary tract infection [cUTI] or acute pyelonephritis [AP]) and 1 questionnaire to assess new symptoms of the cUTI or AP within 24 hours of randomization.**

Read all instructions verbatim and aloud. Note there are separate instructions for the 1st Screening Visit Questionnaire and for the 2nd Screening Visit Questionnaire plus all other visits (page 1 of questionnaire).

Read all questions and each response option verbatim and aloud *(e.g.,* "Pain or burning during urination: no symptoms, mild symptoms, moderate symptoms, or severe symptoms?"). Instruct the patient to choose only ONE response for each item and record the response selected by the patient. Definitions of mild, moderate, and severe generally follow the severity assessments for adverse events provided in Section 8.1.3, namely:

Mild: Symptom barely noticeable to the patient or does not make the patient uncomfortable; it does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of the symptom.

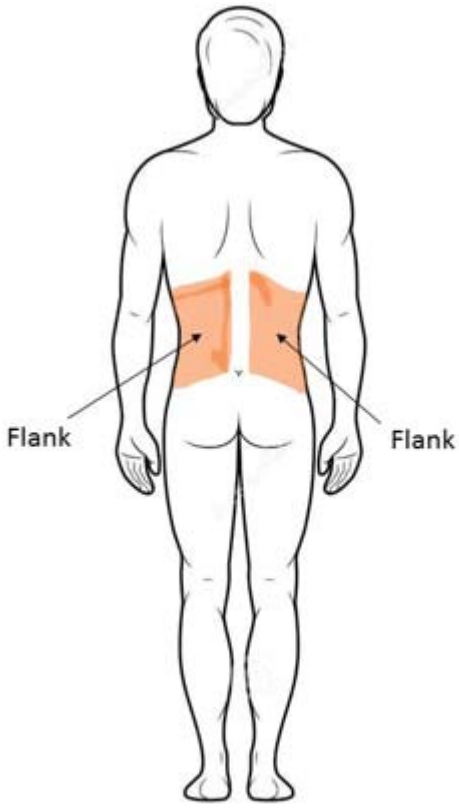
Moderate: Symptom of a sufficient severity to make the patient uncomfortable. Performance of daily activities is influenced. Treatment of the symptom may be needed.

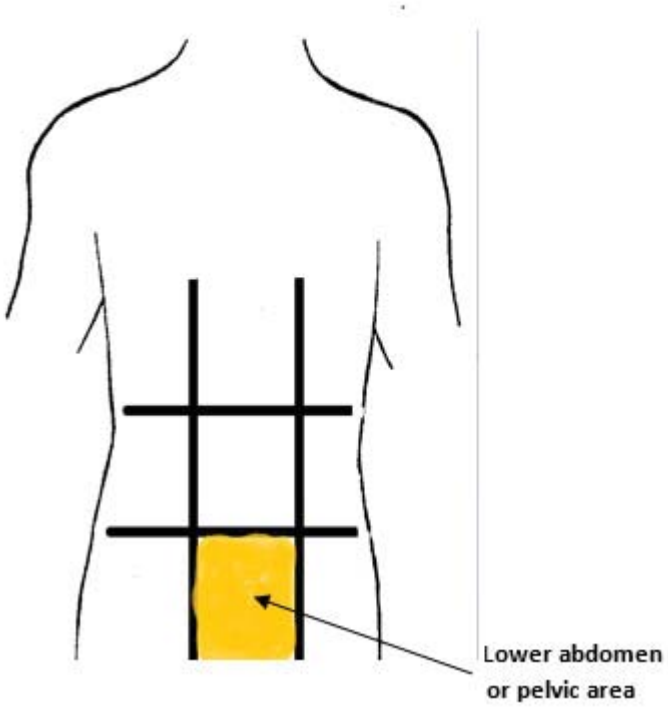
Severe: Symptom of a sufficient severity to cause the patient severe discomfort. Treatment for the symptom is needed.

The instructions, questions, and response options may be repeated at the request of the patient.

Do not interpret the questions for the patient or comment on their responses.

Please show these anatomical diagrams of the flank to the patient and the abdominal wall when reading the question about flank pain, and pain or uncomfortable pressure in the lower abdomen or pelvic pain:





Study AT-301 Daily Symptom Assessment Questionnaire [Page 1 of 2]

Site:	
Patient Number:	
Visit:	
Date (DD/MM/YYYY):	
Assessment Time (24-hour clock):	

Questionnaire Instructions for the 1st Screening Visit Questionnaire to Capture Premorbid Symptoms *(read aloud)*:

"This questionnaire asks about symptoms you might have experienced before the start of your current urinary tract infection. Some symptoms can be caused by health problems other than urinary tract infection; therefore, we want to know what symptoms you experience, if any, when you do not have a urinary tract infection.

Please respond whether you have had any of the following symptoms in the 7 days before your current urinary tract infection started and how severe those symptoms were. Answer each question by choosing only one response from the following possible options: no symptoms, mild symptoms, moderate symptoms, or severe symptoms. When answering these questions, don't think about how you feel now; think about how you felt before the start of your current urinary tract infection."

Questionnaire Instructions for the 2nd Screening Visit Questionnaire (to Capture New cUTI/AP Symptoms) and for Each Subsequent Visit (Day 1 through Days 7 to 14, EOT, TOC, and LFU) *(read aloud)*:

"This questionnaire asks about your urinary tract infection symptoms in the past 24 hours.

Please respond whether you have had any of the following symptoms or problems in the past 24 hours and how severe they were. Answer each question by choosing only 1 response from the following possible options: no symptoms, mild symptoms, moderate symptoms, or severe symptoms."

Study AT-301 Daily Symptom Assessment Questionnaire [Page 2 of 2]

Site:	
Patient Number:	
Visit:	
Date (DD/MM/YYYY):	
Assessment Time (24-hour clock):	

Symptom Assessment	No Symptom	Mild	Moderate	Severe
1. Lower back or flank pain (*Please show the figure indicating the flank area to the patient*)	☐	☐	☐	☐
2. Pain or uncomfortable pressure in the lower abdomen or pelvic area (*Please show the figure indicating the lower abdominal or pelvic area to the patient*)	☐	☐	☐	☐
3. Pain or burning during urination	☐	☐	☐	☐
4. Frequent urination or going to the toilet more often than usual	☐	☐	☐	☐
5. Urgency of urination or an uncontrollable urge to pass urine	☐	☐	☐	☐

Mild: Symptom barely noticeable to the patient or does not make the patient uncomfortable; it does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of the symptom.

Moderate: Symptom of a sufficient severity to make the patient uncomfortable. Performance of daily activities is influenced. Treatment of the symptom may be needed.

Severe: Symptom of a sufficient severity to cause the patient severe discomfort. Treatment for the symptom is needed.