Statistical Analysis Plan: IT001-310

Study Title:	A prospective, Phase 3, randomized, multi-center, double-blind study of the efficacy, tolerability, and safety of oral sulopenem etzadroxil/probenecid versus oral amoxicillin/clavulanate for treatment of uncomplicated urinary tract infections (uUTI) in adult women.
Study Number:	IT001-310
Study Phase:	Phase 3
Product Name:	Sulopenem etzadroxil/probenecid tablets (500 mg/500 mg)
Indication:	Uncomplicated urinary tract infection
Sponsor:	Iterum Therapeutics International Limited
Study Statistician:	Jayanti Gupta, PhD
Study Clinician:	Steven I. Aronin, MD
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SIGNATURE PAGE

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I have read this document and confirm that to the best of my knowledge it accurately describes the statistical analysis plan for the study.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
BID	bis in die (Twice a Day)
BMI	Body Mass Index
BPM	Beats Per Minute
BUN	Blood Urea Nitrogen
CE	Clinically Evaluable
CFU	Colony Forming Unit
CI	Confidence Interval
Cr	Creatinine
CRF	Case Report Form
CSR	Clinical Study Report
dL	Deciliter
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
e-CRF	Electronic Case Report Form
EOT	End of Treatment Visit
ESBL	Extended-Spectrum-β-Lactamases
FDA	Food and Drug Administration
FV	Final Visit
GFR	Glomerular Filtration Rate
GGT	Gamma Glutamyltransferase
Hg	Mercury
HPF	High Power Field
IA	Interim Analysis
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
Kg	Kilogram
LLN	Lower Limit of Normal
ME	Microbiological Evaluable

MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MIC	Minimum Inhibitory Concentration
micro-MITT	Microbiological Modified Intent-to-Treat
micro-MITTR	Microbiological Modified Intent-to-Treat Resistant
micro-MITTS	Microbiological Modified Intent-to-Treat Susceptible
MITT	Modified Intent-to-Treat
MM	Millimeter
NI	Non-inferiority or Non-inferior
NTF	Nitrofurantoin
PCR	Polymerase Chain Reaction
PFGE	Pulsed Field Gel Electrophoresis
PSAQ	Patient Symptom Assessment Questionnaire
QNS	Quinolone Non-Susceptible
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
TEAE	Treatment Emergent Adverse Event
TOC	Test of Cure Visit
ULN	Upper Limit of Normal
uUTI	Uncomplicated Urinary Tract Infection
WBC	White Blood Cell
WGS	Whole Genome Sequencing
WHODRUG	World Health Organization (WHO) Drug Dictionary

1. INTRODUCTION

This document presents the Statistical Analysis Plan (SAP) for the protocol IT001-310, "A prospective, Phase 3, randomized, multi-center, double-blind study of the efficacy, tolerability, and safety of oral sulopenem etzadroxil/probenecid versus oral amoxicillin/clavulanate for treatment of uncomplicated urinary tract infections (uUTI) in adult women". The statistical plan described is an a priori plan, and the unblinded analyses outlined here have not been conducted prior to the preparation of this plan. This SAP summarizes the design and objectives of protocol IT001-310 and provides details of the definitions of analysis populations, the endpoints and statistical methodology that will be used to analyze the data from the study.

Any deviation from the planned analysis will be documented in the clinical study report (CSR). This SAP is based on study protocol Amendment 1 dated December 5, 2022.

2. STUDY DESIGN

This trial is a prospective Phase 3, randomized, multicenter, double-blind, double dummy, controlled study to compare oral sulopenem etzadroxil/probenecid to oral amoxicillin/clavulanate for the treatment of patients with uUTI. Approximately 1966 adult women with uUTI are to be randomized in a 1:1 fashion to receive either an oral bilayer tablet with sulopenem etzadroxil/probenecid 500 mg/500 mg twice daily for 5 days or oral amoxicillin/clavulanate 875 mg/125 mg twice daily for 5 days.

Visits occur on Screening (Day -1 to Day 1, within 24 hours of first dose), Day 5 (+ 1 day), Day 12 (± 1 day), and Day 28 (± 2 days). The Day 5 visit is the End of Treatment (EOT) visit, Day 12 is the Test of Cure (TOC) visit, and Day 28 is the Final Visit (FV). The schedule of activities at each visit is provided in Appendix A.

3. STUDY OBJECTIVES

3.1 Primary Objective

To compare the overall response (clinical and microbiologic combined response) of oral sulopenem etzadroxil/probenecid versus oral amoxicillin/clavulanate for the treatment of uUTI in adult women at the primary timepoint, Day 12 (± 1 day)/TOC.

3.2 Secondary Objectives

- To evaluate the clinical efficacy at Day 12 (±1 day)/TOC
- To evaluate the microbiologic efficacy at Day 12 (±1 day)/TOC
- To further evaluate the safety profile of oral sulopenem etzadroxil/probenecid tablets when used for treatment of uUTI in adult women

3.3 Additional Objectives

- To evaluate the clinical efficacy at Day 5 (+1 day) and Day 28 (±2 days)
- To evaluate the rate of post-treatment asymptomatic bacteriuria at Day 5 (+1 day), Day 12 (±1 day)/TOC and Day 28 (±2 days)

- To evaluate the microbiologic efficacy at Day 5 (+1 day) and Day 28 (±2 days)
- To evaluate overall response at other relevant timepoints
- To evaluate the investigator determined clinical response
- To evaluate overall success, clinical success, and microbiologic success by key baseline pathogens

4. DEFINITION OF ANALYSIS POPULATIONS

The definitions of the analysis populations included in this study are as follows:

4.1 Intent-to-Treat (ITT)

The ITT population is comprised of all randomized patients regardless of whether or not the patient received study drug.

4.2 Modified Intent-to-Treat (MITT)

The MITT population includes all patients in the ITT population who received at least a single dose of study medication.

4.3 Microbiological Modified Intent-to-Treat (micro-MITT)

The micro-MITT population includes all MITT patients with a positive study entry urine culture defined as $\geq 10^5$ colony forming units (CFU)/mL of a uropathogen (Enterobacterales only) and no more than 2 species of microorganisms identified in the study entry urine culture, regardless of colony count.

4.3.1 Susceptible (micro-MITTS)

All micro-MITT patients with a baseline uropathogen susceptible (defined as MIC ≤ 8/4 mg/L) to the comparator drug, amoxicillin/clavulanate, and no baseline pathogen non-susceptible to amoxicillin/clavulanate. If a patient has 2 uropathogens at baseline, both need to be susceptible.

4.3.2 Resistant (micro-MITTR)

All micro-MITT patients with a baseline uropathogen non-susceptible (defined as intermediate (MIC ≥ 16/8 mg/L) or resistant (MIC ≥ 32/16 mg/L)) to the comparator drug, amoxicillin/clavulanate.

4.4 Clinically Evaluable (CE)

Three CE populations are defined based on the timing of the outcome assessment, CE-EOT, CE-TOC and CE-FV. The term "CE population" is used to refer to all CE populations. CE is a subset of MITT and follows the rules below.

a. Received at least 80% of their active study medication up to the timepoint of assessment unless a failure at the time of discontinuing study drug due to insufficient therapeutic effect or need for concomitant systemic antibacterial therapy

b. Met the following inclusion criteria:

Inclusion Criterion 1. Female patients ≥18 years of age with ≥24 hours and ≤96 hours of urinary symptoms attributable to a UTI

Inclusion Criterion 2. Two of the following signs and symptoms of uUTI: urinary frequency, urinary urgency, pain or burning on micturition, suprapubic pain;

Inclusion Criterion 3 (if randomized under protocol dated Dec 5, 2022). A mid-stream urine specimen with:

i. a machine-read dipstick positive for nitrite and any positive leucocyte esterase or

ii. evidence of pyuria as defined by either:

   a. a machine-read dipstick positive for large leukocyte esterase OR

   b. at least 10 white blood cells per cubic millimeter on microscopic analysis of unspun urine OR

   c. White blood cell count ≥10 cells/HPF in the sediment of a spun urine

Inclusion Criterion 3 (if randomized under protocol dated July 7, 2022). A mid-stream urine specimen with evidence of pyuria as defined by either:

i. a machine-read dipstick positive for leucocyte esterase OR

ii. at least 10 white blood cells per cubic millimeter on microscopic analysis of unspun urine OR

iii. White blood cell count ≥10 cells/HPF in the sediment of a spun urine

and did not meet any of the following exclusion criteria:

Exclusion Criterion 1. Presence of signs and symptoms suggestive of acute pyelonephritis defined as: fever (temperature > 38° Celsius), chills, costovertebral angle tenderness, flank pain, nausea, and/or vomiting

Exclusion Criterion 2. Receipt of antibacterial drug therapy potentially effective as treatment of uUTI within the prior 7 days (note, this will be checked against both the inclusion/exclusion and the prior concomitant medication eCRF pages)

Exclusion Criterion 3. Patients requiring concurrent use of non-study treatments that would have a potential effect on outcome evaluations in patients with uUTI, including analgesics (e.g., non-steroidal anti-inflammatory drugs, aspirin, paracetamol etc.), phenazopyridine, and cranberry products

Exclusion Criterion 4. Any anatomical abnormality of the urinary tract, including surgically modified urinary tract anatomy, and obstructive uropathy due to nephrolithiasis, stricture, tumor or fibrosis

Exclusion Criterion 5. Ongoing urinary retention

Exclusion Criterion 6. Neurogenic bladder

Exclusion Criterion 9. Patients with an indwelling urinary catheter, ureteral stent or other foreign material in the urinary tract

Exclusion Criterion 10. Any history of trauma to the pelvis or urinary tract

Exclusion Criterion 11. Patient's current urine culture, if available while evaluating

eligibility, that is positive for more than 2 microorganisms regardless of colony count or patient has a confirmed fungal UTI

Exclusion Criterion 16. Patients with poorly controlled diabetes mellitus, including the presence of ketoacidosis and hyperosmolar hyperglycemia

Note: Fulfillment of inclusion and exclusion criteria is based on version of protocol that subject was randomized under.

c. Had no major protocol deviations that would affect the assessment of efficacy prior to the visit as indicated in the protocol deviation log (see Section 8.10)

d. Had a patient-determined clinical response of success or failure (and not indeterminate) at the timepoint of the visit (i.e., within the SAP defined allowed visit window)

e. For CE-EOT and CE-TOC, did not receive any systemic antibiotic therapy with potential activity against any of the uropathogens collected at baseline, between the time of the baseline culture and the EOT or TOC visits, respectively. This excludes the protocol defined study therapy and patients who were considered clinical failures and required additional antibiotic therapy and patients who received a rescue antibiotic to which the baseline pathogen was found to be non-susceptible by susceptibility testing performed by the central laboratory. Patients with coinfection with a gram-positive uropathogen resistant to study drugs are allowed to receive agents with narrow spectrum gram-positive coverage (i.e., such as oral linezolid, daptomycin and vancomycin).

   For CE-FV, did not receive any antibiotic therapy with potential activity against any of the baseline uropathogen(s) collected at baseline through FV, except resuming oral antibiotic prophylaxis therapy after the Day 12 urine culture was obtained. This does not include antibiotic therapy taken for the treatment of uUTI by patients who were considered investigator-assessed clinical failures.

f. Received appropriate adjunctive antibacterial coverage (i.e., such as linezolid, daptomycin or vancomycin) if the patient had a culture-documented Enterococcus spp. or other gram-positive resistant pathogens at baseline and has symptoms at the post-baseline visit.

g. Site personnel involved in the assessment of efficacy parameters remained blinded to study treatment up to the time of the efficacy assessment.

h. Patients who receive study drug therapy beyond the protocol defined number of 10 doses as a result of the investigator's assessment that additional drug therapy is needed for treatment of the underlying urinary tract infection will be defined as failures for patient determined clinical response at TOC. Thus, these patients will be included in the CE populations, if all other criteria are met.

4.5 Microbiologically Evaluable (ME)

All patients included in both the micro-MITT and CE populations at the Day 5 visit (ME-EOT), Day 12 visit (ME-TOC) and at the Day 28 visit (ME-FV) and have an appropriately collected urine culture specimen and interpretable urine culture result at the Day 5, Day 12 and Day 28 visits (i.e., within the SAP defined allowed visit window), respectively.

4.5.1 Susceptible (ME-S)

All ME patients with a baseline uropathogen susceptible (defined as MIC ≤ 8/4 mg/L) to the comparator drug, amoxicillin/clavulanate, and no baseline pathogen non-susceptible (defined as intermediate [MIC 16/8 mg/L] or resistant [MIC ≥ 32/16 mg/L]) to amoxicillin/clavulanate. If a patient has 2 uropathogens at baseline, both need to be susceptible.

4.5.2 Resistant (ME-R)

All ME patients with a baseline uropathogen non-susceptible (defined as intermediate [MIC 16/8 mg/L] or resistant [MIC ≥ 32/16 mg/L]) to the comparator drug, amoxicillin/clavulanate.

4.6 Safety

The safety population is comprised of all patients in the ITT population who received at least one dose of study medication.

4.7 Determination of Inclusion in Analysis Populations

Inclusion into the ITT, MITT and Safety populations will be determined programmatically from the e-CRF data and as needed by manual review.

Inclusion into the CE populations will be determined programmatically from the e-CRF data and through a manual review conducted by the Sponsor. The Sponsor will review clinical data for determination of criteria used to assess inclusion in the CE populations. The Sponsor will be blinded to treatment assignment and will review the data concurrent with the conduct of the study.

Inclusion into the micro-MITT, micro-MITTS, micro-MITTR, ME, ME-S and ME-R populations will be determined programmatically and through a manual review conducted by the Sponsor.

5. DEFINITION OF ENDPOINTS

5.1 Overall Response

The primary endpoint in the study is overall success (combined clinical and microbiologic) at TOC.

A patient will be defined as a success at a given timepoint (EOT, TOC and FV) if the following criteria are met (programmatically, based on the data on the e-CRF):

- The patient is alive
- The patient has received no non-study antibacterial therapy for uUTI. (Note: If an antibiotic is started after a visit, then for that visit's assessment the patient will be considered as not having received non-study antibiotic therapy)
    - If an antibiotic active against the urinary tract pathogen is given for non-uUTI reasons and the baseline pathogen is susceptible to the antibiotic, then the patient will be considered indeterminate
- The patient has resolution of the symptoms of uUTI present at trial entry and no new UTI

symptoms (based on the Patient Symptom Assessment Questionnaire (PSAQ)). Missing answers to PSAQ severity questions are treated as missing, thus the outcome will be indeterminate.

  - Baseline symptoms associated with another known condition (e.g., overactive bladder) do not need to be resolved.

- The patient's urine culture demonstrates $<10^3$ CFU/mL of each of the baseline study uropathogens based on results of quantitative cultures performed on the urine sample collected at the visit. If the urine culture is contaminated (defined in Appendix D), baseline pathogen(s) is/are considered eradicated.

A patient will be defined as a failure if at least one of the following criteria is met:

- Patient died due to uUTI
- Patient received non-study antibacterial therapy for uUTI.
- Patient has no resolution or has worsening of symptoms of uUTI present at trial entry and/or has new uUTI symptoms. Missing answers to PSAQ severity questions are treated as missing, thus the outcome will be indeterminate.
- The patient's urine culture at the visit demonstrates $\geq 10^3$ CFU/mL of any of the baseline study uropathogens.

Patients will be defined to have an indeterminate outcome if any data needed to determine whether the outcome is success or failure are missing. Patients with missing answers to PSAQ severity questions will be considered as indeterminate for overall response at TOC (unless the urine culture demonstrates $\geq 10^3$ CFU/mL of the baseline uropathogen, then the patient is a failure). Patients who died due to other reasons than the uUTI will have an indeterminate outcome. If an antibiotic that is active against the urinary tract pathogen based on susceptibility results is given for non-uUTI reasons, then the patient will be considered indeterminate. If urine culture data at TOC is missing, the patient will be considered as indeterminate for overall response at TOC (unless the PSAQ response at TOC shows failure, then the patient is a failure). Patients with an indeterminate response are included in the denominator for determination of the response rate.

5.2 Microbiologic Response

Per pathogen microbiologic response is assessed using the definitions listed below. It will be analyzed at each timepoint (EOT, TOC and FV). It is assessed for each study uropathogen that a patient has at baseline.

Per patient microbiologic response is a patient level response determined by the outcome of all baseline study uropathogens, and will be analyzed at each timepoint (EOT, TOC and FV).

Note, if a patient did not have a positive culture at baseline, she is not included in the micro-MITT or ME populations even if a pathogen is isolated post-baseline.

5.2.1 Baseline Pathogens

Microbiologic response	Definition
Eradication (success)	The urine culture demonstrates $<10^3$ CFU/mL of the baseline study uropathogen at the timepoint of analysis (contaminated results are considered a negative culture and therefore an eradication)
Persistence	A study uropathogen present at baseline grew at $\geq 10^3$ CFU/mL at the time-point of analysis*
Persistence with increasing MIC	A urine culture taken after at least 2 full days of treatment grew $\geq 10^3$ CFU/mL of the baseline study uropathogen and displayed $\geq$ 4-dilutions higher MIC, as compared to baseline, to study drug received at the timepoint of analysis (i.e., when a post-baseline study uropathogen displays a MIC of $\geq$2 mg/L when the baseline MIC was 0.12 mg/L).
Indeterminate	Patient was lost to follow-up or an assessment was not undertaken such that no urine culture was obtained (or culture results could not be interpreted for any reason) at the timepoint of analysis

* The genus and species need to match. Additional molecular testing by pulsed field gel electrophoresis (PFGE), polymerase chain reaction (PCR) or whole genome sequencing (WGS) may be performed to be used as sensitivity analysis of the primary endpoint

A per pathogen microbiologic success is termed as ‘eradication’. A pathogen failure is termed as ‘persistence’ or ‘persistence with increasing MIC’.

A per patient microbiologic success is when all pathogen responses for a patient are ‘eradication’. A per patient microbiologic failure is when one or more pathogens for a patient are ‘persistence’ or ‘persistence with increasing MIC’. Otherwise, the patient will have an indeterminate outcome.

5.2.2 Post-Baseline Pathogens

For patients with a baseline study uropathogen, the following outcomes based on post-baseline uropathogens will be determined.

Microbiologic response	Definition
Superinfection	A uropathogen not present at baseline grew with $\geq 10^5$ CFU/mL from the first dose of study drug through the EOT visit in the setting of recurrent/persistent/new uUTI symptoms requiring non-study systemic antibacterial treatment (patient determined clinical failure at EOT)
New Infection	Isolation of a non-baseline pathogen from a culture post-EOT visit from a urine culture specimen with $\geq 10^5$ CFU/mL in a patient with one or more new uUTI signs/symptoms requiring new systemic antibacterial treatment after the EOT visit (patient determined clinical failure post-EOT)
Recurrence	In a patient with clinical and microbiologic success at EOT, isolation of a baseline study pathogen from a urine culture specimen with $\geq 10^5$ CFU/mL post-EOT visit, along with new or recurrence of one or more uUTI signs/symptoms requiring new systemic antibacterial treatment after the EOT visit (patient determined clinical failure post-EOT)
Colonization	Isolation of a pathogen from the urine culture after EOT in a patient without one or more signs and symptoms of uUTI and not requiring new systemic antibiotic therapy (patient determined clinical success post-EOT)

5.3 Patient-Determined Clinical Response (Clinical Response)

A patient will be defined as a clinical success at a given timepoint (EOT, TOC and FV) if the following criteria are met (programmatically, based on the data on the eCRF):

- The patient is alive
- The patient has received no non-study antibacterial therapy for uUTI. (Note: If an antibiotic is started after a visit, then for that visit's assessment the patient will be considered as not having received antibiotic therapy)
    - If an antibiotic active against the urinary tract pathogen is given for non-uUTI reasons and the baseline pathogen is susceptible to the antibiotic, then the patient will be considered indeterminate
- The patient has resolution of the symptoms of uUTI present at trial entry and no new uUTI symptoms (based on the Patient Symptom Assessment Questionnaire). Missing answers to PSAQ severity questions are treated as missing thus the outcome will be indeterminate.
    - Baseline symptoms associated with another known condition (e.g., overactive bladder) do not need to be resolved.

All other patients will be considered as failures unless data are unavailable to determine if the patient is a success or failure. In this case, the patient will be considered as having an indeterminate response. Patients who died due to reasons other than the uUTI will have an

indeterminate outcome. If an antibiotic active against the urinary tract pathogen is given for non-uUTI reasons and the baseline pathogen is susceptible to the antibiotic, then the patient will be considered indeterminate. Patients with missing answers to PSAQ severity questions will be treated as indeterminate.

5.4 Asymptomatic Bacteriuria

A patient will be defined to have asymptomatic bacteriuria at a given timepoint (EOT, TOC and FV) if both of the following criteria are met:

- The patient is a clinical success (as defined in Section 5.3)
- The patient is a microbiologic failure (as defined in Section 5.2.1)

5.5 Investigator-Determined Clinical Response

Investigators will use the definitions below to document clinical response, irrespective of microbiologic findings, at EOT, TOC, FV or premature discontinuation:

Clinical response	**Definition**
Clinical success	All pre-therapy signs and symptoms of the index infection had resolved such that no additional antibiotics were required
Clinical failure	Patients who met any one of the criteria below are considered as failures: • Death related to uUTI prior to EOT, TOC and FV, respectively • Persistence or progression of any pre-therapy uUTI signs and symptoms or use of additional antibiotics for the current infection • Patient previously met criteria for failure and received rescue antibiotics
Indeterminate	Data not available for evaluation of efficacy for any reason, including but not limited to: • Patient lost to follow-up or assessment not undertaken such that a determination of clinical response could not be made at either the EOT, TOC or FV, respectively • Death prior to EOT, TOC or FV, respectively, where uUTI was clearly non-contributory

5.6 Patient Symptom Assessment Questionnaire (PSAQ)

Patients will report their UTI symptoms as no symptom, mild, moderate or severe and this will be recorded on the Patient Symptom Assessment Questionnaire (PSAQ). The symptoms are:

- Pain (uncomfortable pressure) in the lower abdomen/pelvic area
- Burning (dysuria) when passing urine

- Frequency of urination or going to the toilet very often
- Urgency of urination or a strong and uncontrollable urge to pass urine

If a symptom is mild, moderate or severe then patients will report the impact of the symptom on daily activities as: not at all, not significantly bothersome, moderately bothersome or severely bothersome.

5.7 Safety Endpoints

The safety parameters include AEs, clinical laboratory evaluations and vital signs. Adverse Events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) Version 24.1 or higher to the System Organ Class and Preferred Term levels.

6. ESTIMANDS

Estimands are defined for the primary objective of the study.

- Target population: There are 3 populations in which the primary objective will be assessed: the micro-MITT, micro-MITTS and micro-MITTR populations.
- Endpoint of interest: Overall success at TOC
- Intercurrent events: The following intercurrent events could impact the assessment of overall response in each of the target populations:
    - Patient receives non-study antibacterial therapy for uUTI (ie, rescue therapy). This is handled as a composite variable and is incorporated into the definition of the endpoint.
    - Patient receives anti-bacterial therapy that is active against the urinary tract pathogen for non-uUTI reasons. This is handled as a composite variable and is incorporated into the definition of the endpoint.
    - Missing or incomplete assessment of uUTI symptoms at TOC for any reason including study discontinuation. This is handled as a composite variable and is incorporated into the definition of the endpoint.
    - No urine culture was obtained or culture results could not be interpreted at TOC. This is handled as a composite variable and is incorporated into the definition of the endpoint.
    - Death due to reasons other than uUTI. This is handled as a composite variable and is incorporated into the definition of the endpoint.
- Population-level summary: Difference in rates of overall response between oral sulopenem etzadroxil/probenecid and oral amoxicillin/clavulanate

7. STATISTICAL METHODS

7.1 Sample Size

The study is designed to determine whether oral sulopenem etzadroxil/probenecid is non-inferior

(NI) to oral amoxicillin/clavulanate for the outcome measure of overall success (combined clinical and microbiologic success) at Day 12 (± 1 day)/TOC in both the micro-MITT and micro-MITTS populations and whether oral sulopenem is superior to oral amoxicillin/clavulanate for overall success at Day 12 (± 1 day)/TOC in the micro-MITTR population. The primary outcome measure of overall success (combined clinical and microbiologic success) is defined as resolution of the symptoms of uUTI present at trial entry (and no new symptoms), and the demonstration that the bacterial pathogen found at trial entry is reduced to $<10^3$ CFU/mL on urine culture (microbiological success [eradication]).

The proposed sample size in the micro-MITTS population is 505 patients per arm (total of 1010 patients) based on the method of Farrington and Manning. This assumes a non-inferiority margin of 10.0%, a power of 90%, a one-sided alpha level of 0.025, 60% overall success rate with amoxicillin/clavulanate and 60% overall success rate with sulopenem etzadroxil/probenecid. Assuming that 21% of the patients will have non-susceptible pathogens and assuming 85% power to show superiority in the micro-MITTR population (micro-MITT=1278 patients), 67% of the randomized patients will meet criteria for inclusion into the micro-MITT population (MITT=1907 patients) and allowing for a dropout rate of 3%, the sample size for the ITT population is 1966. With 134 patients per treatment group in the micro-MITTR population, there is at least 85% power to show superiority at the one-sided 2.5% alpha level given a 51% and 33% overall success rate in the oral sulopenem and amoxicillin/clavulanate groups, respectively. With 1278 patients in the micro-MITT population, there is at least 95% power to show non-inferiority (non-inferiority margin of 10.0%) at the one-sided alpha level of 0.025 with the treatment success rates of the oral sulopenem etzadroxil/probenecid and amoxicillin/clavulanate groups assumed to be 58% in this population.

One blinded interim analysis for sample size re-estimation is planned (See Section 8.8).

7.2 Randomization

Patients will be randomized in a 1:1 ratio to sulopenem etzadroxil/probenecid versus amoxicillin/clavulanate using an Interactive Web Randomization System (IWRS), provided they have satisfied all patient selection criteria. Once IWRS provides a randomization number, the patient is officially randomized.

7.3 Visit Windows

Visit windows are used in determining whether a patient will be included in the CE and ME populations at EOT, TOC or FV. If their assessments are out of window, they will not be included in that population. If the data for a visit is collected on 2 separate days (i.e., partly on a scheduled visit and partly on an unscheduled visit), then the data from both days will be considered provided the days are within the prescribed window for that visit.

For safety laboratory and vital signs by-visit analyses, the value closest to the target date for the visit will be used in the analyses if more than one assessment was within the visit window (i.e., unscheduled assessments were obtained). If two values are equidistant from the planned visit date, then the first value will be used.

The following visit windows will be used for analysis conducted using CE and ME populations and safety data described above. The date of PSAQ assessment and the date of urine specimen sample collection will be used to determine CE and ME populations.

Visit	Window
Day 5 – End of Treatment (EOT)	+ 1 day
Day 12 – Test of Cure (TOC)	± 1 day
Day 28 – Final Visit (FV)	± 2 days

For the ITT populations, patients are not dropped from the populations for assessments out of window. The nominal visit from the eCRF is used to assign assessments to the appropriate time point. If the data for a visit is collected on 2 separate days (i.e., partly on a scheduled visit and partly on an unscheduled visit), then the data from the unscheduled visit will be considered provided the days are within the prescribed broader windows for that visit as below. For missed nominal visits or missed assessments at nominal visits, data from the closest unscheduled/early termination visits will be used provided unscheduled /early termination assessment day falls in the window provided below.

Window for unscheduled visits for ITT analysis:

Visit	Time interval (Days)*
Day 5 – End of Treatment (EOT)	5 - 7
Day 12 – Test of Cure (TOC)	8 - 20
Day 28 – Final Visit (FV)	21 - 35

***** The one closest to the target date for the visit will be used in the analyses if more than one unscheduled assessments are within the window. If two visits are equidistant from the target visit date, then the first one will be used

7.4 Microbiology Data

The following organisms will be considered a uropathogen for this study:

- Monomicrobial or polymicrobial infections caused by:
  - Enterobacterales
  - Enterococci
  - *Pseudomonas aeruginosa*
  - *S. saprophyticus*
- The micro-MITT population will only include patients with uUTIs caused by the following (study pathogens): Enterobacterales.

The following normal flora are never a pathogen:

- Corynebacterium spp.
- *Staphylcoccus epidermidis*
- *Stayplococcus aureus*

- Bacillus *spp.*
- Diphtheroids
- Micrococcus spp.
- Lactobacillus spp.
- Viridans Streptococci
- Group B Streptococci
- *Gardnerella vaginalis*
- *Neisseria gonorrhoeae*
- Yeasts

All isolates will be assessed on a case-by-case basis via manual review by the Sponsor. This could include isolates not listed above. If needed, patient's clinical and microbiological information will be used to assist in determining if the isolate is a pathogen. Appendix D provides the microbiology rules for determination of final pathogen.

7.5 Handling of Missing Data

Missing data will be handled as outlined below:

- All missing and partial dates for events and assessments occurring after randomization or for medications received after randomization will be queried for a value. If no value can be obtained, missing dates or partial dates will remain missing, but the following actions will take place:
  - Adverse Events
    - If an adverse event is missing a start date, the adverse event will be treated as treatment-emergent.
    - If the start date only contains the year, and if the year is prior to the year of first dose then the adverse event will not be treatment-emergent. Otherwise, it will be treatment-emergent unless it is possible to conclude that the stop date is prior to first dose (based on the available parts of stop date if it is partial).
    - If the start date only contains the year and month, and if the year/month combination is prior to the year/month combination of first dose then the adverse event will not be treatment-emergent. Otherwise, it will be treatment-emergent unless it is possible to conclude that the stop date is prior to first dose (based on the available parts of stop date if it is partial).
    - Other partial start dates will be treated as treatment-emergent unless it is possible to conclude that the stop date is prior to first dose (based on the available parts of stop date if it is partial).
    - If an AE starts on the same day that dosing is initiated and the start time of the AE is missing, then the AE is considered treatment-emergent AE (TEAE).
  - Prior/Concomitant Medications and Prior/Concomitant Antibiotic Therapy

- If a concomitant drug is missing a start date and stop date, then the concomitant drug should be reported both as a prior and concomitant drug.
- If the start date only contains the year, and if the year is prior to the year of first dose then the drug should be reported as prior. Otherwise, it should be reported as concomitant unless it is possible to conclude that the stop date is prior to first dose (based on the available parts of stop date if it is partial).
- If the start date only contains the year and month, and if the year/month combination is after the year/month combination of first dose then the drug should be reported as concomitant only. Otherwise, it should be reported as both prior and concomitant unless it is possible to conclude that the stop date is prior to first dose (based on the available parts of stop date if it is partial). In this case it should be reported as prior only.
- Other partial start dates will be treated as both prior and concomitant unless it is possible to conclude that the stop date is prior to first dose (based on the available parts of stop date if it is partial). In this case it should be reported as prior only.

- The severity and causality assessment for an AE cannot be missing. Missing data will be queried for a value.
- For overall response, patients will be defined as an indeterminate if any data needed to determine whether a patient is a success or failure are missing, unless, since this is a composite endpoint, the data that is present shows the patient is a failure.
- For overall response, sensitivity analyses will be performed considering different imputations techniques for missing response data. These are described in Section 8.7.2.
- Except as specifically noted for pre-planned imputation analyses, missing values for other individual data points (not described above) will remain as missing. Missing values will not be imputed and only observed values will be used in data analyses and presentations.
- Where individual data points are missing, categorical data will be summarized based on reduced denominators (i.e., only patients with available data will be included in the denominators).

7.6 Comments on Statistical Analysis

The following general comments apply to all statistical analyses and data presentations:

- Summaries will include frequency and percentages for categorical data; frequency and median for ordinal data; and number, mean, standard deviation, median, minimum, maximum and quartiles for quantitative data.
- Duration variables will be calculated using the general formula: (end date - start date) +1 for end dates after first dose and (end date - start date) for end dates before first dose.
- If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table (e.g., a character string is reported for a parameter of the numerical type), a coded value must be appropriately determined and used in the statistical analyses. In general, a value or lower and upper limit of normal range such as ‘<10’ or ‘≤ 5’ will be

treated as '10' or '5' respectively, and a value such as '>100' will be treated as '100'. However, the actual values as reported in the database will be presented in data listings.

- Individual patient listings of all data represented on the eCRFs will be provided to facilitate the investigation of tabulated values and to allow for the clinical review of all efficacy and safety parameters.
- Version 9.4 (or higher) of SAS® statistical software package will be used to provide all summaries, listings, graphs, and statistical analyses.

8. STATISTICAL ANALYSES

The tables to be presented for each population are specified in the subsections below. All tables specified for the micro-MITT population will also be presented for the micro-MITTS and micro-MITTR populations. All tables specified for the ME population will also be presented for the ME-S and ME-R populations.

8.1 Patient Disposition

The number of patients included in each of the study populations (i.e., ITT, Safety, MITT, micro-MITT, micro-MITTS, micro-MITTR, CE-EOT, CE-TOC, CE-FV, ME-EOT, ME-TOC and ME-FV) will be summarized by treatment group. A table and listing will be provided that details the reasons the patient is excluded from each population.

A listing will be provided of randomized patients who did not meet all inclusion/exclusion criteria.

The frequency and percentage of patients completing the study, prematurely discontinuing from study drug, and prematurely discontinuing from the study will be presented for each treatment group and overall, for the ITT, MITT, micro-MITT, micro-MITTS, micro-MITTR and Safety populations.

Reasons for premature discontinuation of study drug and/or withdrawal from the study as recorded on the e-CRF will be summarized (frequency and percentage) by treatment group. A listing of all patients who prematurely discontinued from study drug or withdrew from the study will be presented, and the primary reason for premature discontinuation of study drug or withdrawal from the study will be provided.

A listing of deaths will be presented separately.

8.2 Demographics and Baseline Characteristics

Demographic data and baseline characteristics will be presented by treatment group for the ITT, MITT and micro-MITT populations. A table will present the patient demographics (e.g., sex, age, age group [<65, ≥65 years], ethnicity, race) and baseline characteristics (height, weight, BMI as both a continuous variable and categorized BMI [<25, 25-30, >30], diabetes status [present/absent] and creatinine clearance as both a continuous variable and categorized creatinine clearance [<60 mL/min, ≥60 mL/min]).

Differences between treatment groups will be analyzed using Fisher's exact test for dichotomous variables (sex, age group, ethnicity, race, categorized BMI, diabetes status and categorized creatinine clearance) and the Wilcoxon Rank Sum test for continuous variables (age, height,

weight and BMI).

Medical history will be summarized based on System Organ Class/Preferred term and treatment group for the ITT population.

Patient-determined symptoms and bothersome symptoms as captured on the PSAQ at baseline will be summarized by treatment and compared using Fisher's exact test.

Note: The p-values from the tests at baseline are provided to assess overall baseline comparability and should be interpreted with caution.

8.3 Baseline Microbiology

A frequency distribution of the result of the urine cultures, including organism characteristics will be presented for the ITT, MITT and micro-MITT populations. The number and percentage of patients with no growth, contaminant and positive for a pathogen will also be presented.

The bacterial pathogens identified from the baseline urine culture will be presented. The number and percentage of patients with isolated pathogens will be presented by genus and species for the MITT, micro-MITT and ME populations. In addition, the number and percentage of patients with mono-microbial and poly-microbial infections as well as ESBL positive and negative infections will be provided.

Tables will be provided for a summary of pathogens at baseline and the distribution of pathogens by culture concentration at baseline for the micro-MITT populations.

A listing will be provided that includes all baseline and post-baseline isolates obtained from the urine specimens, and whether or not the isolate is considered the pathogenic organism.

Several tables providing the frequency distribution of the minimum inhibitory concentrations (MIC) by treatment group and both treatment groups combined will be provided for the micro-MITT and the ME populations. These include the following:

- The distribution of MIC to sulopenem etzadroxil/probenecid, amoxicillin/clavulanate, meropenem, ciprofloxacin, ertapenem, nitrofurantoin, trimethoprim-sulfamethoxazole, cefazolin, ceftriaxone and fosfomycin for the baseline pathogens
- MIC summary statistics (i.e., range, MIC_{50} and MIC_{90} for pathogens that have 10 or more occurrences) for the study pathogens: Enterobacterales

8.4 Prior and Concomitant Procedures

All non-drug interventions received prior to randomization as well as those received during the study (up through FV) will be recorded on the e-CRF. The percentage of patients who received prior and concomitant non-drug interventions will be presented by treatment group for the ITT and micro-MITT populations.

A listing will be provided of all prior and concomitant non-drug interventions.

8.5 Prior and Concomitant Medications

All medications taken within 30 days prior to the first dose of the study drug and through the FV visit will be recorded on the e-CRF. Medications will be summarized by WHODRUG (March 2022 version or higher) highest ATC level and generic medication name for the ITT and micro-MITT populations. Patients will be counted only once for an ATC class and generic medication

name.

Medications are considered prior if taken prior to the first dose of study drug. Medications are considered concomitant if taken on or after the first dose of study drug or if marked as continuing. For missing or incomplete start or stop dates, refer to rules in Section 7.5.

Tables will be provided for prior medications, all concomitant medications, concomitant anti-inflammatory and analgesic medications and concomitant antibacterial medications. Concomitant medications and concomitant antibacterial medications will be presented in several tables of medications taken from study start to each visit (e.g., medications taken from study start through EOT visit). If a medication was taken during this interval, regardless if it was started in that interval, it will be counted.

A listing will be provided of all prior and concomitant medications.

8.6 Study Drug Exposure

A dosing summary by treatment group will be presented for all study populations. The distribution of patients by the number of days on study drug therapy in each treatment group will be presented. Each tablet or capsule taken is considered a half day of therapy.

8.7 Efficacy Analyses

For all efficacy analyses, patients will be analyzed in the treatment group to which they were randomized. By definition, patients who receive the study drug regimen other than the regimen to which they were randomized are not included in the CE and ME populations.

For the ITT, MITT and micro-MITT populations, patients with an indeterminate response are included in the denominator for computing the proportion of success. The proportion of success is defined using the formula:

$$(\text{Number of successes})/(\text{Number of successes} + \text{Number of failures} + \text{Number of indeterminates})$$

For the CE and ME populations, patients must have sufficient information for determining success or failure. The proportion of success is defined using the formula:

$$(\text{Number of successes})/(\text{Number of successes} + \text{Number of failures})$$

8.7.1 Primary Efficacy Analysis

The primary efficacy endpoint is the outcome of overall success (combined clinical and microbiologic success) at TOC in each of the micro-MITT, micro-MITTS and micro-MITTR populations.

Patients will be programmatically categorized as a success, failure or indeterminate based on the data in the e-CRF and from the microbiology lab. The number and percentage of patients with success, failure and indeterminate response will be determined in each treatment group in the micro-MITT, micro-MITTS and micro-MITTR populations.

The primary comparison of the study is in the micro-MITT population (the combined population

of patients with a positive baseline culture and without regard to amoxicillin/clavulanate susceptibility). These outcomes are most relevant to the practicing clinician who must choose empiric treatment of uUTI before culture results become available, hence these results will help put into context the outcomes in the culture and susceptibility-driven sub-populations.

To control for the inflation of the overall type I error rate, the hierarchical testing procedure of Westfall and Krishen (Westfall 2001) will be used to test the hypotheses of the primary efficacy outcome in these populations in the sequential order described below. Testing will proceed to the next comparison, only in the case where the null hypothesis in the previous comparison was rejected. When testing in a sequential manner with pre-planned hierarchy, no adjustment to the alpha level is required.

(1) NI in the micro-MITT population:

For this population, a NI test of the overall success rate will be conducted. The null and alternative hypotheses are the following:

$$H_0 : p_1 - p_2 \leq -\Delta \text{ and } H_1 : p_1 - p_2 > -\Delta ,$$

where p_1 is the overall success rate in the sulopenem etzadroxil/probenecid treatment group, p_2 is the overall success rate in the amoxicillin/clavulanate group, and Δ is the non-inferiority margin of 10%.

The NI hypothesis test is a 1-sided hypothesis test performed at the 2.5% level of significance. This is based on the lower limit of the 2-sided 95% CI for the observed difference in the overall success rates (oral sulopenem etzadroxil/probenecid group minus amoxicillin/clavulanate group). The primary analysis is based on the CI computed using the method proposed without stratification by Miettinen and Nurminen, which corresponds to the p-value approach of the Farrington-Manning test. If the lower limit of the 95% CI for difference in success rates in the micro-MITT population is greater than -10%, the null hypothesis will be rejected and the NI of oral sulopenem etzadroxil/probenecid to amoxicillin/clavulanate will be concluded and testing will proceed to the next step.

(2) NI in the micro-MITTS population OR superiority in the micro-MITTR population as described below:

Micro-MITTS population: For this population, a NI test of the overall success rate will be conducted. The null and alternative hypotheses are the following:

$$H_0 : p_1 - p_2 \leq -\Delta \text{ and } H_1 : p_1 - p_2 > -\Delta ,$$

where p_1 is the overall success rate in the sulopenem etzadroxil/probenecid treatment group, p_2 is the overall success rate in the amoxicillin/clavulanate group, and Δ is the non-inferiority margin of 10%. The NI hypothesis test is a 1-sided hypothesis test performed at the 2.5% level of significance. A 2-sided 95% CI for the observed treatment difference in success rates will be determined using the method without stratification of Miettinen and Nurminen. If the lower bound of the 95% CI is greater than -10%, the null hypothesis will be rejected and the NI of oral sulopenem etzadroxil/probenecid to amoxicillin/clavulanate in the micro-MITTS population will be concluded.

Micro-MITTR population: For this population, a superiority test will be conducted. The null and alternative hypotheses are the following:

$$H_0: p_1 = p_2 \text{ and } H_1: p_1 \neq p_2$$

A 2-sided 95% CI for the observed treatment difference in success rates will be determined using the method without stratification of Miettinen and Nurminen. The 1-sided p-value corresponding to the lower bound of the 95% CI will be reported. If the lower bound of the 95% CI is greater than 0%, the null hypothesis will be rejected and superiority of oral sulopenem etzadroxil/probenecid to amoxicillin/clavulanate will be concluded in the micro-MITTR population.

If either of these 2 null hypotheses is rejected, then testing will proceed to the next step.

(3) Superiority in the micro-MITT population

The null and alternative hypotheses are: $H_0: p_1 = p_2$ and $H_1: p_1 \neq p_2$.

The 1-sided p-value corresponding to the lower bound of the 95% CI calculated for the hypothesis test in (1) will be reported. If the lower bound of the 95% CI (for the hypothesis test in (1)) is greater than 0%, the null hypothesis will be rejected and the superiority of oral sulopenem etzadroxil/probenecid to amoxicillin/clavulanate in the micro-MITT population will be concluded.

For regulatory approval, the primary comparisons are in two mutually exclusive sub-populations of the micro-MITT population defined by a baseline characteristic, the micro-MITTS and micro-MITTR populations. To control for the inflation of the overall type I error rate, the following hierarchical testing procedure will be used to test the hypotheses of the primary efficacy outcome in these populations in the sequential order described below. Testing will proceed to the next comparison, only in the case where the null hypothesis in the previous comparison was rejected. When testing in a sequential manner with pre-planned hierarchy, no adjustment to the alpha level is required.

(1) NI in the micro-MITTS population OR superiority in the micro-MITTR population as described below:

Micro-MITTS population: For this population, a NI test of the overall success rate will be conducted. The null and alternative hypotheses are the following:

$$H_0: p_1 - p_2 \leq -\Delta \text{ and } H_1: p_1 - p_2 > -\Delta ,$$

where p_1 is the overall success rate in the sulopenem etzadroxil/probenecid treatment group, p_2 is the overall success rate in the amoxicillin/clavulanate group, and Δ is the non-inferiority margin of 10%. The NI hypothesis test is a 1-sided hypothesis test performed at the 2.5% level of significance. A 2-sided 95% CI for the observed treatment difference in success rates will be determined using the method without stratification of Miettinen and Nurminen. If the lower bound of the 95% CI is greater than -10%, the null hypothesis will be rejected and the NI of oral sulopenem etzadroxil/probenecid to amoxicillin/clavulanate in the micro-MITTS population will be concluded.

Micro-MITTR population: For this population, a superiority test will be conducted. The null and alternative hypotheses are the following:

$$H_0: p_1 = p_2 \text{ and } H_1: p_1 \neq p_2$$

A 2-sided 95% CI for the observed treatment difference in success rates will be determined using the method without stratification of Miettinen and Nurminen. The 1-sided p-value corresponding to the lower bound of the 95% CI will be reported. If the lower bound of the 95% CI is greater than 0%, the null hypothesis will be rejected and superiority of oral sulopenem etzadroxil/probenecid to amoxicillin/clavulanate will be concluded in the micro-MITTR population.

If either of these 2 null hypotheses is rejected, then testing will proceed to the next step.

(2) Superiority in the micro-MITT population

The null and alternative hypotheses are: $H_0 : p_1 = p_2$ and $H_1 : p_1 \neq p_2$.

A 2-sided 95% CI for the observed treatment difference in success rates will be determined using the method without stratification of Miettinen and Nurminen. The 1-sided p-value corresponding to the lower bound of the 95% CI will be reported. If the lower bound of the 95% CI is greater than 0%, the null hypothesis will be rejected and the superiority of oral sulopenem etzadroxil/probenecid to amoxicillin/clavulanate in the micro-MITT population will be concluded.

The reasons for failure and indeterminate will be tabulated for the primary efficacy endpoint at TOC in each of the micro-MITT, micro-MITTS and micro-MITTR populations.

8.7.2 Additional Analysis of the Primary Efficacy Endpoint

The following sensitivity analyses of the primary endpoint at TOC will be conducted and a 2-sided 95% unstratified CI will be computed for the difference in success rates between the treatment groups in the micro-MITT population:

- A sensitivity analysis will consider all patients who have missing data for the primary endpoint (i.e., an indeterminate response) as successes.
- A sensitivity analysis applying multiple imputation methods for missing data will be conducted. The multiple imputation analysis assuming a monotone missing data pattern will be used to define the missing data (indeterminate response). 100 datasets will be created using a logistic regression model with treatment, clinical response and microbiologic response at EOT as predictors.
- An analysis will consider the primary endpoint at TOC defined in Section 5.1 except, improvement of symptoms (instead of resolution) from baseline and no worse than mild and no new uUTI symptoms.
- An analysis will consider the primary endpoint at TOC defined in Section 5.1 except, urgency and frequency are improved and no worse than mild and all symptoms are resolved and no new uUTI symptoms.
- An analysis will consider the primary endpoint at TOC where microbiologic response is determined by molecular testing by PFGE, PCR or whole genome sequencing (WGS)
- An analysis will consider the primary endpoint at TOC with varying thresholds of urine culture concentration at TOC

- An optional covariate exploratory analysis using logistic regression will be performed using baseline variables such as study drug, age, race, *E. coli* at baseline, creatinine clearance, albumin, comorbidities (such as diabetes), and other variables, if imbalances exist at baseline. For the latter, baseline tables will be reviewed by Iterum prior to the covariate analysis. Once the covariates are determined, a univariate logistic regression will be run for each covariate. Covariates with a p-value ≤0.10 will be used in a multivariate analysis with a stepwise selection method. The alpha level for both entering and removing a covariate will be 0.10.

A subgroup analysis of the primary efficacy endpoint by fed/fasted state will be conducted. A patient will be considered fed if she took 100% of her doses in a fed state (took either snack or meal 2 hours before or 30 minutes after the dose), otherwise fasted. Different proportions of doses taken in a fed state may be explored if the analysis suggests that the fed state makes a difference.

8.7.3 Secondary Efficacy Analysis

The following analyses will be performed for the secondary efficacy endpoints in the populations as defined below. Tables specified for the micro-MITT population will also be presented for the micro-MITTS and micro-MITTR populations.

- The number and percentage of patients in each treatment group with a (patient-determined) clinical response of success, failure and indeterminate at TOC will be presented for the ITT, MITT and micro-MITT populations. The number and percentage of patients in each treatment group with a clinical response of success and failure at TOC will be presented for the CE and ME populations. Two-sided 95% unstratified CIs will be constructed for the observed difference in the clinical success rates between the treatment groups.

- The number and percentage of patients in each treatment group with a per patient microbiologic response of success (eradication), failure (persistence or persistence with increasing MIC) and indeterminate at TOC will be presented for the micro-MITT population. The number and percentage of patients in each treatment group with a per patient microbiologic response of success and failure at TOC will be presented for the ME population. Two-sided 95% unstratified CIs will be constructed for the observed difference in the microbiologic success rates between the treatment groups for descriptive purposes, no conclusion of NI will be made.

8.7.4 Additional Efficacy Analyses

All efficacy tables below will be presented for the specified populations. Tables specified for the micro-MITT population will also be presented for the micro-MITTS and micro-MITTR populations. Tables specified for the ME population will also be presented for the ME-S and ME-R populations.

Analysis	**EOT (Day 5)**	**TOC (Day 12)**	**FV (Day 28)**
Overall response	Micro-MITT ME	Micro-MITT[1] ME	Micro-MITT ME

Overall response by baseline pathogen	Micro-MITT ME	Micro-MITT ME	Micro-MITT ME
Overall response by MIC		Micro-MITT ME	
Overall response by combination of antibiotic resistance classes	Micro-MITT ME	Micro-MITT ME	Micro-MITT ME
Overall response by study day*			
Overall response with failure requiring both clinical and microbiological failure		Micro-MITT ME	
Patient determined clinical response	ITT MITT Micro-MITT CE ME	ITT[2] MITT[2] Micro-MITT[2] CE[2] ME[2]	ITT MITT Micro-MITT CE ME
Patient determined clinical response by baseline pathogen	Micro-MITT ME	Micro-MITT ME	Micro-MITT ME
Patient determined clinical response by ESBL positive and ESBL negative	Micro-MITT ME	Micro-MITT ME	Micro-MITT ME
Patient determined clinical response by baseline culture density	MITT	MITT	MITT
Patient determined clinical response defined by improvement of symptoms (instead of resolution) from baseline and no worse than mild and no new uUTI symptoms		ITT MITT Micro-MITT CE ME	
Patient determined clinical response defined by urgency and frequency are improved and no worse than mild and all other symptoms are resolved and no new uUTI symptoms		ITT MITT Micro-MITT CE ME	
Patient determined clinical response failure by symptoms and bothersome questions	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME
Microbiologic response	Micro-MITT ME	Micro-MITT[2] ME[2]	Micro-MITT ME
Per pathogen microbiologic response	Micro-MITT ME	Micro-MITT ME	Micro-MITT ME
Microbiologic response by ESBL positive and ESBL negative	Micro-MITT ME	Micro-MITT ME	Micro-MITT ME
Per pathogen microbiologic response by MIC		Micro-MITT ME	
Asymptomatic bacteriuria	Micro-MITT ME	Micro-MITT ME	Micro-MITT ME
Investigator determined clinical response	ITT	ITT	ITT

	MITT Micro-MITT CE ME	MITT Micro-MITT CE ME	MITT Micro-MITT CE ME
PSAQ – by each symptom and severity	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME
PSAQ – Shift table of severity	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME
PSAQ – Kaplan-Meier plot of time to resolution of all symptoms*			
PSAQ – Severity by bothersome questions	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME
PSAQ – Sensitivity analysis using bothersome questions	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME

1 Primary efficacy endpoint
2 Secondary efficacy endpoint
* Overall response by study day (not grouped by visit) and Kaplan-Meier plot of time to resolution of all PSAQ symptoms are not done at individual visits and will be done in the micro-MITT populations

Overall Response

The number and percentage of patients in each treatment group with an overall response of success, failure and indeterminate at EOT and FV will be presented for the micro-MITT populations. The number and percentage of patients in each treatment group with an overall response of success and failure at EOT, TOC and FV will be presented for the ME populations. Two-sided 95% unstratified CIs will be constructed for the observed difference in the overall success rates between the treatment groups for descriptive purposes; no conclusion of NI will be made. Note, overall response is not analyzed in the ITT, MITT and CE populations because these populations do not require a baseline pathogen.

Overall response at EOT, TOC and FV by baseline pathogen (key pathogens and species such as *E. coli*, *Klebsiella* species and *Proteus* species) will be summarized by treatment group in the micro-MITT and ME populations. Confidence intervals at the genus level will be provided.

Overall response by amoxicillin/clavulanate MIC and sulopenem MIC for baseline pathogens will be provided for TOC visit in the micro-MITT and ME populations.

Overall response by combination of antibiotic resistance classes will be provided. The classes

will be

- ESBL status,
- quinolone non-susceptible (QNS),
- TMP-SMX non-susceptible,
- nitrofurantoin (NTF) non-susceptible,
- non-susceptible to at least 3 classes of antibacterials (MDR) (e.g., -quinolones, TMP-SMX and beta-lactams),
- resistance to all four classes (quinolones, TMP-SMX, nitrofurantoin and beta-lactams) and combinations of these resistant classes.

Ceftriaxone will serve as the reference drug for ESBL status, ciprofloxacin will serve as the reference drug for the quinolone class, and cefazolin will serve as the reference drug for the beta-lactam class. Resistance to a class means resistance to the reference drug in that class. A second table will be provided for resistance to oral drugs (ciprofloxacin, TMP-SMX, nitrofurantoin, amoxicillin/clavulanate, tetracycline and fosfomycin). Multi-drug resistance will not be included in this table. However, multi-drug resistance will be explored for the primary endpoint in other ways.

Summary tables will be provided by the treatment group and by day the overall assessment was made. For example, if a patient's EOT assessment was conducted on Day 6 then she would be analyzed in the Day 6 table. A figure of overall response by day of assessment will be provided.

Overall response with failure defined as both clinical and microbiological failure will be presented for micro-MITT and ME populations.

The reasons for overall non-response at EOT, TOC and FV and overall indeterminate at TOC will be summarized for the micro-MITT and ME populations. The uUTI signs and symptoms in patients who were clinical failures at TOC will be summarized for the micro-MITT populations.

Patient-Determined Clinical Response

The number and percentage of patients in each treatment group with a patient-determined clinical response of success, failure and indeterminate at EOT and FV will be presented for the micro-MITT, MITT and ITT populations. The number and percentage of patients in each treatment group with a patient-determined clinical response of success and failure at EOT and FV will be presented for the CE and ME populations. Two-sided 95% unstratified CIs will be constructed for the observed difference in the overall success rates between the treatment groups for descriptive purposes; no conclusion of NI will be made.

Patient-determined clinical response will also be presented by baseline pathogen and by ESBL positive/negative at EOT, TOC and FV in each treatment group for all populations. Confidence intervals at the genus level will be provided.

Patient-determined clinical response defined by improvement of symptoms (instead of resolution) from baseline and no worse than mild and no new uUTI symptoms will be presented at TOC in each treatment group for all populations.

Patient-determined clinical response defined by urgency and frequency are improved and no worse than mild and all other symptoms are resolved and no new uUTI symptoms will be presented at TOC in each treatment group for all populations.

Patient-determined clinical response failure by symptoms and bothersome questions will be presented at EOT, TOC and FV in each treatment group for all populations.

The reasons for clinical non-response at EOT, TOC and FV will be summarized for all the populations.

Microbiologic Response

The number and percentage of patients in each treatment group with a per patient microbiologic response of success, failure (persistence and persistence with increasing MIC) and indeterminate at EOT and FV will be presented for the micro-MITT populations. The number and percentage of patients in each treatment group with a per patient microbiologic response of success and failure at EOT and FV will be presented for the ME population. The microbiologic response per patient with definition of success varying by threshold of CFU/ml at TOC will be presented for the ME population. Two-sided 95% unstratified CIs will be constructed for the observed difference in the microbiologic success rates between the treatment groups for descriptive purposes; no conclusion of NI will be made.

Per pathogen microbiologic response at EOT, TOC and FV by baseline pathogen will be summarized by treatment group in the micro-MITT and ME populations. Confidence intervals at the genus level will be provided.

Per pathogen microbiologic response by amoxicillin/clavulanate MIC and sulopenem MIC for individual pathogens will be provided for TOC visit in the micro-MITT population.

Microbiological categories for pathogens identified after baseline assessment are superinfection, colonization, new infection and relapse/recurrence. The number and percentage of patients with a superinfection, colonization, new infection and recurrence will be presented by treatment group. A listing will be provided that presents the patients with a superinfection, colonization, new infection and recurrence including the pathogen.

The impact of antibiotic therapy on the *in vitro* susceptibility of study uropathogens identified at baseline will be assessed at TOC. The distribution of MICs to sulopenem will be plotted at screening and TOC for the micro-MITT population. The distribution of MICs to amoxicillin/clavulanate will be plotted at screening and TOC for the micro-MITT, micro-MITTS and micro-MITTR populations.

Asymptomatic Bacteriuria

The number and percentage of patients in each treatment group with asymptomatic bacteriuria at EOT, TOC and FV will be presented for the micro-MITT and ME populations. Two-sided 95%

unstratified CIs will be constructed for the observed difference in the rate of asymptomatic bacteriuria between the treatment groups for descriptive purposes; no conclusion of NI will be made.

Investigator-Determined Clinical Response

Investigator-determined clinical response (clinical success, failure and indeterminate) at the EOT, TOC and FV visits will be presented by treatment group for the ITT, MITT, micro-MITT, CE and ME populations. Two-sided 95% unstratified CIs will be constructed for the observed difference in the clinical cure rates between the treatment groups for descriptive purposes.

Investigator-determined clinical response rates will be presented by treatment group for key targeted baseline pathogens at EOT, TOC and FV visits for the micro-MITT and ME populations.

The reasons for investigator non-response at EOT, TOC and FV will be summarized for all the populations.

Patient Symptom Assessment Questionnaire

A table of the severity of each uUTI symptom based on the PSAQ from baseline to EOT, TOC and FV will be provided by treatment group for all populations.

A shift table of the severity of each uUTI symptom based on the PSAQ from baseline to EOT, TOC and FV will be provided by treatment group for all populations.

Kaplan-Meier plots for time to resolution of all PSAQ symptoms will be provided for the micro-MITT population, where patients will be censored at time of death and taking non-study antibacterial therapy for uUTI. Plots for time to resolution of all PSAQ symptoms will also be provided where deaths and use of non-study antibacterial therapy are considered as failure.

A two-way table for each symptom will be provided by treatment group with severity of the symptom as rows and the bothersome responses as columns for EOT, TOC and FV in all populations.

An additional analysis will then be performed in which “negative symptoms” will be defined as not at all or not significantly bothersome for mild symptoms for all visits and populations. The negative symptoms will be counted as no symptom.

8.8 Interim Analysis

To ensure that the point estimate of overall success (combined clinical and microbiologic success) used in the estimation of sample size, the estimated eligibility rate, susceptibility rate, and rate of post-treatment asymptomatic bacteriuria is valid for this study, an interim analysis for sample size re-estimation will be performed when clinical and microbiologic response data at TOC are available for 50% of the patients (approximately 983 patients). The FDA Guidance “Non-inferiority Clinical Trials to Establish Effectiveness” [FDA Guidance 2016] notes that such a sample size re-estimation if based on the blinded overall response rates is not only acceptable but is advisable. The interim analysis will involve a sample size re-estimation to either confirm the initial sample size estimate is adequate or increase the sample size (number of randomized

patients) to ensure the study has adequate power for determining whether oral sulopenem etzadroxil/probenecid is NI to oral amoxicillin/clavulanate for the primary outcome measure in the micro-MITTS population. This will ensure that the study is sufficiently powered to test the primary endpoint in the micro-MITT. The sample size will not be decreased. In addition, the sample size may be increased based on a lower-than-expected evaluability rate (i.e., percentage of the micro-MITT population in the ITT population), lower-than-expected percentage of patients with a susceptible pathogen and a lower-than-expected overall success rate. The sample size re-estimation will be based on the blinded overall (not by treatment group) pooled data.

The blinded interim analysis will proceed as follows:

(1) Determine the percentage of patients with a baseline pathogen $\geq 10^5$ CFU/mL (micro-MITT population), which is the micro-MITT eligibility rate

(2) Determine the percentage of patients with a susceptible (to comparator study drug, amoxicillin/clavulanate) pathogen (micro-MITTS population) and a non-susceptible (to amoxicillin/clavulanate) pathogen (micro-MITTR population) at baseline

(3) Determine the overall success rate and overall rate of asymptomatic bacteriuria at TOC aggregated across treatment groups in the micro-MITTS population

(4) Determine if there is sufficient power (80-90%) in the micro-MITTS to show NI with the planned sample size based on the observed aggregated (across treatment groups) overall success rate

    a. If NO, then increase the sample size in the micro-MITTS population to have sufficient power.

(5) If the aggregated overall success rate in the micro-MITTS population is higher than 70%, or if the aggregated rate of asymptomatic bacteriuria is significantly lower than anticipated, then a futility analysis may be conducted to assess if the study should continue. The futility analysis will be done by computing the conditional power at the interim analysis, given the observed overall success rates in each treatment group in the micro-MITTS population.

The (blinded) sample size re-estimation will be conducted by a blinded statistician and the (unblinded) futility analysis will be conducted by an independent, unblinded statistician. A Data Monitoring Committee (DMC) will be provided the results of the interim analysis to make a recommendation regarding changes to the sample size and if the study should continue. A detailed DMC charter will be developed to outline the analyses to be completed, statistical rules, potential changes to the sample size and the recommendations that can be made to the sponsor.

8.9 Safety Analyses

All safety analyses will be conducted in the Safety population. Patients who receive the wrong regimen of study drug for their entire course of treatment will be analyzed in the group based on the regimen received. Safety parameters include AEs, clinical laboratory parameters and vital signs. For each safety parameter, the last assessment made before the first dose of study drug will be used as the baseline for all analyses.

8.9.1 Adverse Events

Verbatim descriptions of AEs will be coded using Version 24.1 or higher of MedDRA. Summary tables will be provided for all treatment-emergent AEs (TEAEs). A TEAE is defined as any AE that newly appeared or worsened in severity following initiation of study drug (on or after start date and time of first dose). All AEs (including non-TEAEs), serious TEAEs, and TEAEs leading to study drug discontinuation will be provided in listings by treatment group, site, patient, verbatim term, MedDRA system organ class and preferred terms, onset and resolution date, seriousness flag, intensity, relationship to study drug, action taken and outcome.

An overall summary of AEs will include number of patients who experienced at least one AE of the following categories: any AE, any TEAE, any drug-related TEAE (drug-related defined as possibly or probably related to study drug), any serious TEAE, any drug-related SAE, any SAE leading to death, any TEAE leading to premature discontinuation of study drug, any TEAE leading to discontinuation from the study, and any SAE leading to premature study drug discontinuation.

The number and percentage of patients reporting a TEAE in each treatment group will be tabulated by system organ class and preferred term for all TEAEs. TEAEs will also be summarized separately by system organ class, preferred term, and intensity (mild, moderate, and severe); and by system organ class, preferred term, and relationship (unrelated (unrelated or unlikely) or related (possibly or probably)) to the study drug. The incidence of all TEAEs that occur in at least 1% and 2% of patients in either treatment group will be summarized separately by preferred term and treatment group, sorted by decreasing frequency in the sulopenem etzadroxil/probenecid group. A table will provide all SAEs (through FV) by system organ class and preferred term. For all analyses of TEAEs, if the same AE (based on preferred term) is reported for the same patient more than once, the patient is counted only once for that preferred term and at the highest intensity and strongest relationship to study drug.

Incidence of TEAEs by system organ class, preferred term will also be presented by race and age.

Analysis of the distribution of the duration of select adverse events as well as an overall mean adverse event duration in days for each treatment regimen will be presented. If the AE is still ongoing at the last visit, it will be censored at the last visit.

8.9.2 Laboratory Values

Several analyses of the laboratory data will be presented. Central labs were used in the study. A listing will be provided containing all lab data.

For descriptive statistics of actual values and the change from baseline, values obtained from local laboratories will be normalized against the central laboratory normal ranges according to the following formula (Karvanen):

$$s = x\ \ U\_s/U\_x$$

where s = the individual local laboratory value normalized against the central laboratory normal range; x = the original individual local laboratory value; U_x is the upper limit of the normal range for an individual laboratory parameter; $-\ U\_s$ is the upper limit of the laboratory normal range for that laboratory parameter from the common source.

Descriptive statistics for chemistry and hematology values and the change from baseline will be

summarized for all study visits. The change from baseline will be calculated for each patient at the specified visit as the value at the specified visit minus the baseline value.

Laboratory values will also be classified as of potential clinical concern. The number and percentage of patients with a laboratory value of potential clinical concern will be summarized by visit and treatment group and broken out by patients with normal and abnormal at baseline. Worst overall value for each test will be used for this table. For a few tests, worst value can have both a low and a high value. When calculating the worst overall value, use the highest value when dealing with ULN or a > sign or a ≥ sign and use the lowest value when dealing with LLN or a < sign or a ≤ sign. If a patient has a value below the lower limit and a value above the upper limit, then the worst value will be the one that is furthest away from its corresponding limit. See Appendix B.

The number and percentage of patients in each treatment group with an elevated alanine aminotransferase (ALT) level (>3 x ULN, >5 x ULN, and >10 x ULN), an elevated aspartate transaminase (AST) level (>3 x ULN, >5 x ULN, and >10 x ULN) and an elevated bilirubin level (>1.5 x ULN and >2 x ULN) will be presented by study visit and any visit post-baseline. The denominator will be number of patients within normal limits at baseline.

Tables will be provided for elevated ALT and AST levels (>ULN, >ULN to 3 x ULN, >3 x ULN to 5 x ULN, >5 x ULN to 10 x ULN, >10 x ULN to 20 x ULN, >20 x ULN) and elevated ALT and AST levels by normal and abnormal at baseline. Additionally, shift tables will be provided for elevated ALT and AST levels (shift from baseline to each study visit for each of the cutoffs).

A listing of patients who meet the laboratory screening criteria for potential Hy's law cases will also be provided. The laboratory screening criteria for identification of potential Hy's law cases for further review are defined as any elevated ALT and/or AST of >3 x ULN that is associated with both an ALP <2 x ULN and an increase in bilirubin ≥ 2 x ULN.

For "worst overall value" post-baseline analyses, all laboratory assessments including those obtained from unscheduled visits will be included.

Detailed patient listings of all laboratory data collected during the study will be provided. Laboratory values outside normal limits will be identified in the patient data listings with flags for low (L) and high (H).

8.9.3 Physical Examinations

Detailed patient listings of all physical examination results will be provided.

8.9.4 Vital Signs

Blood pressure (systolic and diastolic), respiration rate, pulse rate, and temperature will be summarized using descriptive statistics at each study visit by treatment group. Descriptive statistics of the change from baseline will also be provided. Change from baseline will be calculated for each patient at the specified visit as the value at the specified visit minus the baseline value.

Vital signs will also be classified as of potential clinical concern (Appendix B). The number and percentage of patients with a vital sign measurement of potential clinical concern will be summarized by treatment group and broken out by patients with normal and abnormal at baseline.

8.10 Protocol Deviations

A listing of all protocol deviations will be provided. Deviations will also be reviewed by the sponsor concurrent with the conduct of the study and categorized into general categories such as: inclusion/exclusion criteria, study drug administration, informed consent, visit schedule, test and procedures, randomization error, other, etc. The deviations will be adjudicated as major or minor as per Iterum process. Major deviations are defined as departures from the protocol that impact subject safety or data integrity. The number of patients with at least one protocol deviation and the number of patients with at least one deviation in each category will be presented by treatment group for the ITT population. They will also be presented by major / minor classification.

Protocol deviations that impact the analyses, typically major deviations, will be noted by the clinical team so that the identified patients can be excluded from the appropriate CE population. Most, if not all, protocol deviations impacting the analyses and requiring exclusion will be excluded automatically through programming of other CE criteria (e.g., outcome assessment done within window or concomitant antibiotic use).

9. CHANGES FROM ANALYSES SPECIFIED IN THE PROTOCOL

The following is the list of changes in the analyses from what was planned in the protocol:

- The following are additions or changes to the clinical evaluable definition:
    - The patient must meet certain inclusion and exclusion criteria
    - The patient must have received appropriate adjunctive antibacterial coverage if the patient had a culture-documented Enterococcus spp. or other gram-positive resistant pathogens at baseline and symptoms at the post-baseline visit
    - Site personnel involved in the assessment of efficacy parameters must have remained blinded to study treatment up to the time of the efficacy assessment
    - Patients who receive study drug therapy beyond the protocol treatment period as a result of the investigator's assessment that additional drug therapy is needed for treatment of the underlying infection will be defined as failures for patient determined clinical response at TOC. Thus, these patients will be included in the CE populations, if all other criteria are met.
- Only one micro-evaluable population is defined in the protocol. The SAP defines two: ME-S for micro-evaluable amoxicillin/clavulanate susceptible patients and ME-R for micro-evaluable amoxicillin/clavulanate resistant patients.
- For microbiologic response, post baseline responses of superinfection, new infection, recurrence and colonization were added.
- The following sensitivity analyses of the primary endpoint have been added:
    - Overall response defined by improvement of symptoms (instead of resolution) from baseline and no worse than mild and no new uUTI symptoms
    - Overall response defined by urgency and frequency are improved and no worse than mild and all symptoms are resolved and no new uUTI symptoms
    - Overall response with varying thresholds of urine culture concentration at TOC
    - Covariate analysis
- Based on feedback received from the FDA on 30 October 2023, *Staphylococcus saprophyticus* has been excluded from the list of qualifying uropathogens in the micro-MITT population.

- Based on feedback received from the FDA on 30 October 2023, asymptomatic bacteriuria will be assessed as an additional or exploratory endpoint instead of a secondary endpoint in the study.

10. REFERENCES

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(3) Guidance for Industry: Non-Inferiority Clinical Trials to Establish Effectiveness. November 2016.

(4) Guidance for Industry: Uncomplicated Urinary Tract Infections: Developing Drugs for Treatment. August 2019.

(5) Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics. December 2019.

(6) Guidance for Industry: E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials. May 2021.

(7) Karvanen J. The Statistical Basis of Laboratory Data Normalization. *Drug Information Journal 2003*; 37: 101–107.

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11. APPENDICES

APPENDIX A: SCHEDULE OF ACTIVITIES

	SCREENING	TREATMENT PERIOD		FOLLOW-UP PERIOD		
Protocol Activity	**D-1 to D1** **Baseline**	**D1**[3]	**D5** **(+ 1 day)** **EOT**	**D12** **(± 1 day)** **TOC**	**D28** **(± 2 days)** **FV**	**Premature Study Discontinuation**
Informed Consent	X					
Medical History and Demographics	X					
Targeted Physical Examination	X		X[1]	X[1]	X[1]	X[1]
Vital Signs	X		X	X		X
Hematology	X			X		X
Serum Chemistry	X			X		X
Pregnancy testing[2]	X				X	X
Banked serum sample	X			X		
Banked urine sample	X		X	X		
Urinalysis	X		X	X	X	X
Urine Culture and sensitivity	X		X	X	X	X
Previous Drug and Non-drug Treatments	X					
Concomitant Medications		X	X	X	X	X
Provide daily dosing diary		X				
Collect daily dosing diary			X			X
Study Drug Treatment		X (BID x 10 doses total)				
Study Drug Compliance Check			X			X
Adverse Events	X	X	X	X	X	X
Patient Symptom Assessment Questionnaire (PSAQ)		X	X	X	X	X
Investigator Assessment of Clinical Response			X	X	X	X

Schedule of Activities Footnotes:

[1] If needed, based on symptoms, as determined by the investigator
[2] Baseline and Day 28 (±2 days) or Premature Discontinuation: Pregnancy test (women of childbearing potential and peri-menopausal women, defined as women < 50 years of age or those ≥ 50 years of age who have been post-menopausal for < 2 years) should be performed as required by the protocol
[3] Day 1 and Screening are generally on the same day

APPENDIX B: CRITERIA FOR SAFETY VALUES OF POTENTIAL CLINICAL CONCERN

Hematology	
Hemoglobin	<0.8 times the lower limit of the reference range
Leukocytes	<1.5 or >20 x $10^3/mm^3$
Platelets	<75 or >700 x $10^3/mm^3$
Chemistry	
Total bilirubin	>2 times the upper limit of the reference range
Direct bilirubin	>2 times the upper limit of the reference range
AST	>3 times upper limit of the reference range
ALT	>3 times upper limit of the reference range
GGT	>3 times upper limit of the reference range
Alkaline phosphatase	>3 times upper limit of the reference range
Creatinine	>1.5 times upper limit of the reference range
BUN/Urea	>1.3 times upper limit of the reference range
Sodium	<0.95 or >1.05 times the limits of the reference range
Potassium	<0.9 or >1.1 times the limits of the reference range
Albumin	<0.8 times the lower limit of the reference range
Urinalysis	
Urine WBC	≥10/HPF
Urine RBC	≥50/HPF
Vital Signs	
Pulse Rate	<40 or >130 bpm, when baseline resting heart rate is 60-120 bpm
Blood Pressure	Systolic ≥30 mm Hg change from baseline in same posture Systolic <80 mm Hg Diastolic ≥20 mm Hg change from baseline in same posture Diastolic <50 mm Hg

APPENDIX C: METHOD FOR DETERMINATION OF CREATININE CLEARANCE

Creatinine clearance should be determined by the method of Cockroft-Gault based on serum creatinine concentrations, using ideal body weight instead of actual weight. It will be computed programmatically as below.

For females:

GFR = [(140-age) * (Ideal body weight in kg) * 0.85] / (72 * Cr), for serum Cr reported as mg/dL

GFR = [(140-age) * (Ideal body weight in kg) * 1.0455] / (Cr), for serum Cr reported as micromol/L

Ideal body weight is calculated as:
For females:

If Height > 152.5 cm

Ideal body weight (kg) = 45.4 + [(Height - 152.4) * 0.89]

If Height < 152.5 cm

Ideal body weight (kg) = 45.4 – [(152.4 – Height) * 0.89]

Reference: Gault MH, Longerich LL, Harnett JD, Wesolowski C (1992). "Predicting glomerular function from adjusted serum creatinine". Nephron. 62 (3): 249–56

APPENDIX D: IT001-310 MICROBIOLOGY RULES FOR DETERMINATION OF FINAL PATHOGEN

Baseline Visit

1. Baseline urine sample is submitted for culture to Central laboratory (IHMA)
2. Quantitative urine culture using a 1 µL loop is performed on baseline urine sample by IHMA
3. Baseline urine culture is reported as:
    a. No growth,
    b. Uropathogen present ('uropathogen' is defined in section 7.4 of the Statistical Analysis Plan),
    c. Urogenital flora present, or
    d. ≥3 organisms present (uropathogen, if present, non-predominant), indicating contamination at collection
4. For the one or two uropathogen(s) identified in the baseline urine culture specimen [final pathogen(s)], IHMA will perform susceptibility testing using the susceptibility panel outlined in IHMA's Study Specifications Document (SSD)

Post-Baseline Visits

1. Post-baseline urine sample is submitted for culture to Central laboratory (IHMA)
2. Quantitative urine culture using both a 1 µL and a 10 µL loop is performed on post-baseline urine sample by IHMA
3. Post-baseline urine culture is reported as:
    a. No growth,
    b. Uropathogen present ('uropathogen' is defined in section 7.4 of the Statistical Analysis Plan),
    c. Urogenital flora present, or
    d. ≥3 organisms present (uropathogen, if present, non-predominant), indicating contamination at collection
4. For the one or two uropathogen(s) identified in the post-baseline urine culture specimen [final pathogen(s)], IHMA will perform susceptibility testing using the susceptibility panel outlined in IHMA's Study Specifications Document (SSD)