Clinical Trial Protocol: 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)
IND Number:	129,849
EudraCT Number	2017-003771-57
Indication:	Uncomplicated urinary tract infection
Investigators:	Multicenter
Sponsor:	Iterum Therapeutics International Limited Fitzwilliam Court, 1st Floor, Leeson Close Dublin 2, D02 YW24 Ireland
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	Date
Original Draft Protocol	May 31, 2022
Final Protocol	July 7, 2022
Amendment 1	December 5, 2022

SYNOPSIS

Sponsor:

Iterum Therapeutics International Limited

Name of Finished Product:

Sulopenem etzadroxil/probenecid tablets (500 mg/500 mg)

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

Objective(s):

Non-inferiority Trial:	
Objective	**Estimand/Endpoint**
Primary: To compare the overall response (clinical and microbiologic combined response) at Day 12 (±1 day)/test of cure (TOC) of oral sulopenem etzadroxil/probenecid tablets (500 mg/500 mg) versus oral amoxicillin/clavulanate (875 mg/125 mg) tablets for the treatment of uncomplicated urinary tract infection in adult women.	**Primary Estimand:** Endpoint of interest: Overall success at Day 12 (±1 day)/TOC (clinical and microbiologic combined) Intercurrent events: non-susceptibility or resistance to amoxicillin/clavulanate, use of rescue antibiotic, study discontinuation Population level summary of variable: Comparison of overall success rates between treatment groups
Secondary:	**Secondary Endpoints:**
To evaluate the clinical efficacy at Day 12 (±1 day)/TOC.	Clinical cure (resolution of the symptoms of uUTI present at trial entry and no new uUTI symptoms) at Day 12 (±1 day)/TOC.
To evaluate the rate of post-treatment asymptomatic bacteriuria at Day 12 (±1 day)/TOC.	Clinical cure (resolution of the symptoms of uUTI present at trial entry and no new uUTI symptoms) and microbiologic persistence ($\geq 10^3$ CFU/mL of the baseline uropathogen) at Day 12 (±1 day)/TOC
To evaluate the microbiologic efficacy at Day 12 (±1 day)/TOC.	Microbiologic eradication ($<10^3$ CFU/mL of the baseline uropathogen) at Day 12 (±1 day)/TOC
To further evaluate the safety profile of oral sulopenem etzadroxil/probenecid tablets (500 mg/500 mg) when used for treatment of uUTI in adult women.	Incidence of TEAEs through Day 28 (±2 days); Changes from baseline in clinical laboratory tests at the Day 12 (±1 day)/TOC visit; Changes from baseline in vital signs at the Day 5 (+1 day)/EOT, and Day 12 (±1 day)/TOC visits
Additional:	**Additional Endpoints:**
To evaluate the clinical efficacy at Day 5 (+1 day) and Day 28 (±2 days).	Clinical cure (resolution of the symptoms of uUTI present at trial entry and no new uUTI symptoms) at Day 5 (+1day) and Day 28 (±2 days).
To evaluate the rate of post-treatment asymptomatic bacteriuria at Day 5 (+1 day) and Day 28 (±2 days).	Clinical cure (resolution of the symptoms of uUTI present at trial entry and no new uUTI symptoms) and microbiologic persistence ($\geq 10^3$ CFU/mL of the baseline uropathogen)

	at Day 5 (+1 day) and Day 28 (±2 days).
To evaluate the microbiologic efficacy at Day 5 (+1 day) and Day 28 (±2 days).	Microbiologic eradication ($<10^3$ CFU/mL of the baseline uropathogen) at Day 5 (+1 day) and Day 28 (±2 days).
To evaluate overall response at other relevant timepoints	Overall success (clinical and microbiologic combined response) at Day 5 (+1 day) and Day 28 (±2 days) visits
To evaluate the investigator determined clinical response	Investigator determined clinical response (clinical success, failure, and indeterminate) at Day 5 (+1 day), Day 12 (±1 day)/TOC, and Day 28 (±2 days)
To evaluate overall success, clinical success, and microbiologic success by key baseline pathogens	Overall success, clinical success, and microbiologic success at Day 5 (+1 day), Day 12 (±1 day)/TOC, and Day 28 (±2 days) by key baseline pathogen

Study Design:

Sulopenem is an investigational thiopenem antibiotic being developed for treatment of uUTI, complicated urinary tract infections (cUTI), and complicated intra-abdominal infections (cIAI). Sulopenem etzadroxil is an oral pro-drug of sulopenem. Upon oral absorption, sulopenem etzadroxil is expected to be rapidly hydrolyzed to yield sulopenem, the active moiety.

Sulopenem possesses potent activity against species of the Enterobacterales including those that encode Extended Spectrum β-lactamase (ESBL) or AmpC-type β-lactamases that confer resistance to third generation cephalosporins. Sulopenem etzadroxil is expected to be the first oral penem for uUTI on the market in the United States and Europe and will offer the option of treatment in the outpatient setting as well as intravenous (IV) to oral switch therapy for early discharge of patients hospitalized with serious, complicated infections. Probenecid, co-administered with the oral prodrug, in a bilayer tablet formulation, will reduce renal clearance and increase systemic exposure of the active moiety, sulopenem (CP-70,429).

This trial is a prospective Phase 3, randomized, multicenter, double-blind, double dummy, controlled study to compare oral sulopenem etzadroxil/probenecid (oral sulopenem) to oral amoxicillin/clavulanate for the treatment of patients with uUTI. Approximately 1966 adult women with uUTI will be randomized in a 1:1 fashion to receive either a 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.

The primary outcome measure for efficacy evaluation will be the overall success (combined clinical and microbiologic success) on Day 12 (± 1 day)/TOC in the micro-MITT, micro-MITTS and micro-MITTR populations.

The micro-MITT population will be comprised of all randomized patients who received at least one dose of study drug and had $\geq 10^5$ CFU/mL of a baseline pathogen (Enterobacterales or *Staphylococcus saprophyticus* only) isolated from a urine culture specimen taken at baseline, prior to initiation of study drug therapy.

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. From a regulatory perspective, these results will help put into context the outcomes in the culture and susceptibility- driven subpopulations.

The primary comparisons for regulatory approval are in two mutually exclusive sub-populations of the micro-MITT population defined by a baseline characteristic, the micro-MITTS and micro-MITTR populations:

- **The micro-MITTS population**: the subset of patients whose baseline pathogens are determined to be susceptible (MIC ≤ 8/4 mg/L) to the comparator study drug, amoxicillin/clavulanate.
- **The micro-MITTR population**: the subset of patients whose baseline pathogen is determined to be non-susceptible [intermediate (MIC 16/8 mg/L) or resistant (MIC ≥ 32/16 mg/L)] to the comparator study drug, amoxicillin/clavulanate.

Amoxicillin/clavulanate breakpoints as per Clinical Laboratory Standards Institute (CLSI) (M100 Performance Standards for Antimicrobial Susceptibility Testing, 32nd edition).

Study Population:

A total enrollment of approximately 1966 patients is planned.

Patients will be randomized using an Interactive Web Randomization System (IWRS) into the study, provided they have satisfied all patient selection criteria.

Inclusion Criteria:

1. Female patients ≥18 years of age with ≥24 hours and ≤96 hours of urinary symptoms attributable to a UTI
2. Two of the following signs and symptoms of uUTI: urinary frequency, urinary urgency, pain or burning on micturition, suprapubic pain
3. A mid-stream urine specimen with:

a. a machine-read dipstick positive for nitrite AND any positive leukocyte esterase

OR,

b. evidence of pyuria alone as defined by either:

i. a machine-read dipstick positive for large leukocyte 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

4. Has given written informed consent to participate in the study

Exclusion Criteria:

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
2. Receipt of antibacterial drug therapy potentially effective as treatment of uUTI within the prior 7 days
3. 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. Note: Patients can be included if these medications were previously taken and have ceased at the time of Screening onward.
4. Any anatomical abnormality of the urinary tract, including surgically modified urinary tract anatomy, and obstructive uropathy due to nephrolithiasis, stricture, tumor, or fibrosis
5. Ongoing urinary retention
6. Neurogenic bladder
7. Current resident of a long-term care facility
8. Instrumentation of urinary tract in the previous 30 days
9. An indwelling urinary catheter, ureteral stent or other foreign material in the urinary tract
10. Any history of trauma to the pelvis or urinary tract
11. Current urine culture, if available while evaluating eligibility, that is positive for more than 2 microorganisms regardless of colony count (contaminated), or confirms a fungal UTI
12. Receiving hemodialysis, hemofiltration, peritoneal dialysis, or had a renal transplant
13. Immunocompromised as evidenced by any of the following:

- Known HIV positive, with either a recent (in the past 6 months) AIDS-defining condition or a CD4 + T lymphocyte count <200/mm^3
- Known neutropenia (defined as absolute neutrophil count <1000 cells/mm^3)
- Systemic or hematological malignancy requiring chemotherapeutic or radiation/immunologic interventions within 6 weeks prior to randomization or anticipated to begin prior to completion of study
- Immunosuppressive therapy, including maintenance corticosteroid therapy (>40 mg/day equivalent prednisolone for 5 days or more in the 30 days prior to randomization)

14. Known liver function abnormalities as defined by the following laboratory criteria:
    - ALT or AST > 3x upper limit of normal, and/or
    - Total bilirubin > 2x upper limit of normal
15. Females of child-bearing potential who are unable to take adequate contraceptive precautions (refer to Sections 4.4 and 4.5), have a positive pregnancy test result within 24 hours of study entry, are otherwise known to be pregnant, or are currently breastfeeding
16. Poorly controlled Diabetes mellitus, including the presence of ketoacidosis and hyperosmolar hyperglycemia
17. History of seizures
18. History of blood dyscrasias
19. History of uric acid kidney stones
20. Acute (current) gouty arthritis
21. Concomitant administration of valproic acid
22. History of allergy or hypersensitivity to carbapenems, β-lactams or probenecid, as formulated with their excipients
23. Unlikely to survive the 4-week study period or has a rapidly progressive or terminal illness, including septic shock, associated with a high risk of mortality
24. The use of any other investigational drug in the 30 days prior to the first dose of study drug, or prior participation in any sulopenem clinical trial

Urine samples, including results from urine tests, collected as part of routine standard of care, prior to obtaining informed consent, may be used to assess eligibility for enrollment into study and/or for baseline urine culture.

Test Product, Dose, and Mode of Administration:

Patients will be randomized to receive either an oral bilayer tablet with sulopenem etzadroxil/probenecid 500 mg/500 mg PO twice daily for 5 days or oral amoxicillin/clavulanate 875 mg/125 mg PO twice daily for 5 days.

Patients found to have pathogens isolated from urine cultures that are resistant to amoxicillin/clavulanate or carbapenems may be allowed to continue on study drug therapy to complete the 5-day duration of treatment based on clinical response and investigator judgement and are not required to receive alternative antibiotic therapy.

Adjunctive Systemic Antibiotics (Rescue Therapy)

In general, adjunctive systemic antibiotics are not allowed for patients enrolled in the study. At any time during the study period, and at the discretion of the principal investigator (PI), additional antibiotics—oral or IV, as appropriate—can be prescribed as rescue therapy, e.g., in the event of worsening signs and symptoms of uUTI, or if the patient develops fever and/or flank pain suggestive of upper urinary tract involvement. In the event that rescue therapy is prescribed, patient symptoms will be collected as an unscheduled event; such patients will be considered as treatment failures and will be asked to still complete all protocol-specified assessments through the Final Visit. Use of adjunctive antibiotics without clinical symptoms is strongly discouraged.

Other Systemic Antibiotics:

For *Clostridioides difficile* infections, metronidazole (IV or oral), vancomycin (oral or rectal), or fidaxomicin (oral) may be used in both treatment groups. Patients with a co-infection with a gram-positive uropathogen known or suspected to be resistant to study drugs are allowed to receive agents with narrow spectrum gram-positive coverage (such as oral linezolid**)** at the discretion of the investigator.

Formulation and Packaging:

Sulopenem etzadroxil treatment group: The study drug will be supplied as a study kit containing one bottle with 10 bilayer tablets containing sulopenem etzadroxil/probenecid 500 mg/500 mg and one blister wallet containing10 amoxicillin/clavulanate placebo capsules.

Comparator treatment group: The study drug will be supplied as a study kit containing one blister wallet containing 10 over-encapsulated amoxicillin/clavulanate 875 mg/125 mg tablets, and one bottle with 10 placebo tablets to match sulopenem etzadroxil/probenecid tablets.

Preparation and Dispensing:

Each patient will receive a treatment kit containing one 5-day treatment course of either sulopenem etzadroxil/probenecid and placebo amoxicillin/clavulanate or placebo sulopenem etzadroxil/probenecid and amoxicillin/clavulanate.

Administration:

Patients randomized to the sulopenem treatment group will take one sulopenem etzadroxil/probenecid tablet and one placebo capsule twice daily for 5 days and those randomized to the amoxicillin/clavulanate treatment group will take one over-encapsulated amoxicillin/clavulanate tablet and one placebo tablet twice daily for 5 days (10 doses total over a 5-day period; if Dose 1 is taken in the evening of Day 1, Dose 10 will be taken in the morning of Day 6). The first dose of each medication will be administered under the supervision of study site personnel to help ensure compliance with dosing directions.

Dosing with food:

Food significantly increases bioavailability of sulopenem and consequently results in decreased rates of diarrhea. Therefore, dosing of oral sulopenem with food whenever possible is recommended. Since adequate target attainment appears to be achieved in the fasted state, an inability to administer the dose with food should not preclude dosing.

Amoxicillin and clavulanate are well absorbed from the gastrointestinal tract after oral administration. Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. While amoxicillin/clavulanate can be given without regard to meals, absorption of clavulanate when taken with food is greater relative to the fasted state. Therefore, dosing of oral amoxicillin/clavulanate with food whenever possible is also recommended.

Efficacy Assessments:

The assessment of clinical response includes a review of the following symptoms at the Baseline, Day 5 (+1 day)/End of Treatment (EOT) visits, and the Day 12 (± 1 day)/TOC, and Day 28 (± 2 days) visits or at Premature Discontinuation: urinary frequency, urinary urgency, pain or burning on micturition, and suprapubic pain.

Microbiologic response assessments will be made based on quantitative cultures performed on collected urine specimens at the Baseline, Day 5 (+1 day), Day 12 (± 1 day)/TOC, and Day 28 (± 2 days) visits or at Premature Discontinuation.

Results of susceptibility testing to differentiate between pathogens isolated at baseline and follow-up visits will be used in a sensitivity analysis to be specified in the statistical analysis plan (SAP); whole genome sequencing (WGS) may be performed if needed and results will be used in a sensitivity analysis to be specified in the SAP.

Safety Assessments:

Safety will be assessed by means of vital signs, collection of adverse events and clinical laboratory tests.

A targeted physical examination will be performed at the Baseline visit, and a targeted exam will be conducted if needed (as determined by the investigator) at Day 5 (+1 day), Day 12 (± 1 day)/TOC, Day 28 (± 2 days) visits or at Premature Discontinuation; vital signs will be collected at the Baseline visit, and at Day 5 (+1 day), and Day 12 (± 1 day)/TOC or Premature Discontinuation. Adverse events will be collected at every visit, beginning from the signing of Informed Consent. Clinical laboratory tests will be obtained at the Baseline visit, the Day 12 (± 1 day)/TOC visit, in follow-up of any clinically significant laboratory findings, as well as at Premature Discontinuation.

Statistical Methods:

Sample Size Considerations:

Study IT001-310 is designed to determine whether oral sulopenem is non-inferior 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 with no new symptoms, and the demonstration that the bacterial pathogen found at trial entry is reduced to $<10^3$ CFU/mL on urine culture.

The proposed sample size in the micro-MITTS population is 505 patients per arm (total sample size 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 to amoxicillin/clavulanate 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 and amoxicillin/clavulanate groups assumed to be 58% in this population.

To ensure that the point estimate of overall success (combined clinical and microbiologic success) used in the estimation of sample size, and 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 Day 12 (± 1 day)/TOC are available for approximately 50% of the patients (approximately 983 patients) (see Section 9.7). The FDA Guidance "Non-

inferiority Clinical Trials" [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. The sample size of the study will be computed to ensure that there is sufficient power for determining whether oral sulopenem 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 and micro-MITTR populations as well. The sample size will not be decreased after the interim analysis. In addition, the sample size may be increased based on a lower-than-expected evaluability rate (i.e., percentage of the ITT population in the micro-MITT population), higher- than-expected rate of asymptomatic bacteriuria or lower than expected percentage of patients with a susceptible pathogen. The sample size re-estimation will be based on the blinded overall (not by treatment group) pooled data. 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 by the DMC to assess if the study should continue. Further details of how the DMC will decide to do the futility analysis, how the sponsor will be involved and how the analysis will be conducted will be provided in the SAP and the DMC charter.

General Statistical Considerations:

Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided. All comparisons will be for oral sulopenem versus oral amoxicillin/clavulanate. Exploratory analyses may also be performed. Listings of individual patient's data will be produced.

A comprehensive Statistical Analysis Plan (SAP) will be finalized and submitted to the FDA prior to the interim analysis.

Efficacy Analyses:

Analysis of Primary Outcome Measure:

The study is designed to determine whether oral sulopenem is NI to oral amoxicillin/clavulanate for the outcome measure of overall success (combined clinical and microbiologic success) at Day 12 (± 1 day)/TOC in 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.

A patient will be defined as an overall success if the following criteria are met:

- The patient is alive
- The patient has received no rescue therapy for uUTI
  - If an antibiotic active against the urinary tract pathogen is given for other reasons, 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)
- Urine culture taken on Day 12 (± 1 day)/TOC demonstrates $<10^3$ CFU/mL of the baseline uropathogen based on results of quantitative cultures performed on collected urine specimens.

All other patients will be considered as failures unless data are unavailable to determine if the patient is a success or a failure. In this case, the patient will be considered as having an indeterminate response. Patients with an indeterminate response are included in the denominator for determination of the overall success rate.

The number and percentage of patients with success, failure and indeterminate outcomes will be determined in each treatment group in the micro-MITT, micro-MITTS and micro-MITTR populations. For each analysis population, the observed difference in the percentage of patients with success at Day 12 (± 1 day)/TOC (oral sulopenem group minus the amoxicillin/clavulanate group) will be determined and a two-sided 95% confidence interval (CI) for the observed difference will be computed using the method proposed without stratification by Miettinen and Nurminen.

The framework for the statistical hypothesis testing of the primary efficacy outcome, overall success (combined clinical and microbiological success) at Day 12 (± 1 day)/TOC, is defined below.

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. From a regulatory perspective, these results will help put into context the outcomes in the culture and susceptibility- driven subpopulations.

The primary comparisons for regulatory approval are in two mutually exclusive sub-populations of the micro-MITT population defined by a baseline characteristic: 1) the micro-

MITTS population (the subset of the micro-MITT population in which the baseline pathogen is determined to be susceptible to the comparator study drug, amoxicillin/clavulanate); and 2) the micro-MITTR population (the subset of the micro-MITT population in which the baseline pathogen is determined to be non-susceptible [intermediate (MIC 16/8 mg/L) or resistant (MIC ≥ 32/16 mg/L)] to the comparator study drug, amoxicillin/clavulanate).

To control for 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 testing, 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:

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

where p_1 is the primary efficacy outcome rate in the oral sulopenem group, p_2 is the primary efficacy outcome rate in the amoxicillin/clavulanate group, and Δ is the non-inferiority margin of 10.0%.

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 rate (oral sulopenem 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 -10.0%, the null hypothesis will be rejected and the NI of oral sulopenem to amoxicillin/clavulanate will be concluded.

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

Micro-MITTS population: the subset of the micro-MITT population in which the baseline pathogen is determined to be susceptible to the comparator study drug, amoxicillin/clavulanate. For this population, a NI test of the overall success rate will be conducted. The null and alternative hypotheses are as follows:

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

A 2-sided 95% CI for the observed treatment difference in success rates will be determined. If the lower bound of the 95% CI is greater than -10.0%, the null hypothesis will be rejected and the NI of oral sulopenem to amoxicillin/clavulanate in the micro-MITTS population will be concluded.

Micro-MITTR population: the subset of the micro-MITT population in which the baseline pathogen is determined to be non-susceptible to the comparator study drug, amoxicillin/clavulanate. For this population, a superiority test will be conducted. The null and alternative hypotheses are as follows:

$H_0 : p_1 = p_2$ and $H_A : p_1 \neq p_2$

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. If the lower bound of the 95% CI is greater than 0%, the null hypothesis will be rejected and superiority of oral sulopenem to amoxicillin/clavulanate will be concluded in the micro-MITTR population.

Each of the 2 null hypotheses in this step will be tested at the 2.5% level and if either hypothesis is rejected, then testing will proceed to the next step.

(3) Superiority test of overall success, $H_0: p_1 = p_2$ and $H_A: p_1 \neq p_2$, in the micro-MITT population. If the lower bound of the 95% CI (calculated for the hypothesis test in (1) is greater than 0%, the null hypothesis will be rejected and the superiority of oral sulopenem to amoxicillin/clavulanate in the micro-MITT population will be concluded.

Analysis of Secondary Efficacy Outcome Measure:

The number and percentage of patients in each treatment group with a clinical response of success, failure and indeterminate at Day 12 (±1 day)/TOC will be presented for the MITT, micro-MITT, micro-MITTS, and micro-MITTR populations. The number and percentage of patients in each treatment group with a clinical response of success and failure at Day 12 (±1 day)/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 for descriptive purposes; no conclusion of NI will be made.

The number and percentage of patients in each treatment group with asymptomatic bacteriuria at Day 12 (±1 day)/TOC will be presented for the micro-MITT, micro-MITTS, micro-MITTR and ME populations. The difference in rate of asymptomatic bacteriuria (oral sulopenem group minus the amoxicillin/clavulanate group) will be determined and 2-sided 95% unstratified CIs will be constructed for the observed difference between the treatment groups for descriptive purposes; no conclusion of NI will be made.

The number and percentage of patients in each treatment group with a microbiologic response of success, failure and indeterminate at Day 12 (±1 day)/TOC will be presented for the micro-MITT, micro-MITTS, and micro-MITTR populations. The number and percentage of patients in each treatment group with a microbiologic response of success and failure at Day 12 (±1 day)/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.

Safety analyses will be conducted in the Safety population (all patients who received at least one dose of study drug) and will be summarized by treatment group. Safety will be assessed through summaries of AEs, laboratory evaluations, and vital signs.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC_{0-24}	Area under the curve from zero to 24 hours
βhCG	Beta Human Chorionic Gonadotropin
BID	Twice daily
BUN	Blood Urea Nitrogen
C_{max}	Maximum concentration
CA	Community-acquired
CBC	Complete Blood Count
CE	Clinically Evaluable
CI	Confidence Interval
cIAI	Complicated Intra-Abdominal Infection
CFU	Colony Forming Unit
CLSI	Clinical and Laboratory Standards Institute
C_{max}	Maximum concentration
CRE	Carbapenem Resistant Enterobacterales
CRF	Case Report Form
CTA	Clinical Trial Application
cUTI	Complicated Urinary Tract Infection
DMC	Data Monitoring Committee
EARS-NET	European Antimicrobial Resistance Surveillance Network
ECG	Electrocardiogram
E. coli	*Escherichia coli*
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure in Utero

EOT	End of Treatment Visit
ESBL	Extended Spectrum Beta-lactamase
FDA	Food and Drug Administration
FSH	Follicle-stimulating Hormone
FV	Final Visit
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transpeptidase
GMP	Good Manufacturing Practice
hERG	Human Ether-a-go-go-Related Gene
HIV	Human Immunodeficiency Virus
HPF	High power field
hs-CRP	High-sensitivity C-reactive Protein
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IDSA	Infectious Disease Society of America
IRB/IEC	Institutional Review Board /Independent Ethics Committee
ITT	Intent-to-Treat
IUD	Intrauterine Device
IV	Intravenous
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
LTFU	Lost to Follow-Up
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary of Regulatory Activities
MIC	Minimal Inhibitory Concentration
MITT	Modified ITT
Micro-MITT	Microbiologic-MITT
Micro-MITTR	Microbiologic-MITT Resistant
Micro-MITTS	Microbiologic-MITT Susceptible

NI	Non-inferior/Non-inferiority
NOAEL	No Observed Adverse Effect Level
PBP	Penicillin-Binding Proteins
PCS	Potentially clinically significant
PK	Pharmacokinetic
PK/PD	Pharmacokinetic / Pharmacodynamic
PO	Per-oral
PSAQ	Patient symptom assessment questionnaire
PT	Preferred Term
PV	Pharmacovigilance
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA	Target Achievement
TEAE	Treatment Emergent Adverse Event
TOC	Test of Cure
T_{max}	Time to maximum concentration
USPI	United States package insert
uUTI	Uncomplicated urinary tract infection
WBC	White Blood Cell
WGS	Whole genome sequencing
2-EBA	2-Ethylbutryic Acid

1 INTRODUCTION

1.1 Indication

Sulopenem and/or sulopenem etzadroxil/probenecid (oral sulopenem) are being studied for the treatment of the following indications:

- Uncomplicated urinary tract infections
- Complicated urinary tract infections
- Complicated intra-abdominal infections

1.2 Background and Rationale

β-lactam antimicrobials are widely recognized for their efficacy and low toxicity and form the cornerstone of therapy for the treatment of infections caused by gram-positive and gram-negative bacteria. However, extensive use of β-lactams during the past 50 years has resulted in the development of microbial resistance to these agents among clinically important bacteria. This resistance commonly takes the form of β-lactamase production, expression of porins in the bacterial outer membrane or alterations in penicillin-binding proteins (PBPs). Such mechanisms have reduced the clinical utility of frequently prescribed β-lactams such as amoxicillin, amoxicillin plus clavulanate (a β-lactamase inhibitor), and cephalosporins. The issue of resistance continues to drive the search for new compounds with increased stability and efficacy against resistant pathogens.

The prevalence of infections caused by extended-spectrum β-lactamase (ESBL) producing Enterobacterales has been increasing worldwide and includes both hospital-acquired and community onset infections. An analysis of data reported from 2011 to 2014 to the National Healthcare Safety Network performed by the Centers for Disease Control in March 2016 revealed that the proportion of *E. coli* resistant to extended-spectrum cephalosporins causing hospital-acquired infection was 13.4% nationally, with rates as high as 24% reported in some Northeastern, Southern, and Western states. The same analysis also demonstrated that over a third of *E. coli* isolates in 2014 were resistant to quinolones. Data reported by the European Antimicrobial Resistance Surveillance Network (EARS-NET) in Europe demonstrate that the prevalence of quinolone resistant *E. coli* and *E. coli* resistant to third generation cephalosporins is > 25% and *E. coli* resistant to third generation cephalosporins, aminoglycosides and quinolones has increased to >10% in some southern and eastern European countries.

Oral antibiotic treatment options are extremely limited for patients with these multi-drug resistant infections, resulting in lengthy hospital stays to facilitate administration of intravenous antibiotics, even for those with uncomplicated infections. The currently available oral antibiotics with activity against ESBL producing organisms include nitrofurantoin, fosfomycin, quinolones, and trimethoprim-sulfamethoxazole. Nitrofurantoin and fosfomycin are only approved for the treatment of uncomplicated urinary tract infections in the United States, have rising rates of resistance and are associated with inferior efficacy [Munoz-Davila 2014; Schito 2009]. Resistance to trimethoprim-sulfamethoxazole is uniformly above 20% in the US. Increasing prevalence of resistance to quinolones and their propensity to cause collateral damage resulted in relegation of quinolones to second-line therapy by the Infectious Disease Society of America

(IDSA) for uUTI [Gupta 2011]. In a recent multicenter analysis of trends in resistance in >2.2 million urinary Enterobacterales isolates from ambulatory patients in the United States (2011-2020), resistance rates were 57.5%, 23.1%, 20.6%, and 20.2% for β-lactams, trimethoprim-sulfamethoxazole, fluoroquinolones, and nitrofurantoin, respectively, and 6.9% had an ESBL-producing phenotype [Dunne 2022]. Efficacy outcomes for patients treated with antibiotics for uUTI caused by non-susceptible pathogens are not known, though a recent analysis of 4,792 patients with 5,395 evaluable outpatient UTI episodes, 22% of patients received an antibiotic to which the pathogen was resistant *in vitro*, and those patients were almost twice as likely to require a second prescription (34% versus 19%) or be hospitalized (15% versus 8%) within 28 days of the initial prescription fill compared to patients who received an antibiotic to which the pathogen was susceptible [Dunne 2022].

The currently proposed study will compare the safety, tolerability, and efficacy of oral sulopenem versus oral amoxicillin/clavulanate for the treatment of uUTI in women. Sulopenem (CP-70,429) is a broad-spectrum thiopenem β-lactam antibiotic which is being developed for the treatment of infections caused by multi-drug resistant bacteria. Sulopenem possesses potent activity against species of the Enterobacterales that encode ESBLs or AmpC-type β-lactamases that confer resistance to third generation cephalosporins. The targeted gram-negative spectrum of sulopenem is balanced by its potent *in vitro* activity against anaerobic pathogens, which is similar to that of imipenem.

An *in vitro* susceptibility study of sulopenem was conducted in April 2016 utilizing contemporary clinical bacterial isolates from patients in the United States and Europe. Minimal inhibitory concentrations (MICs) of sulopenem and 18 comparators were determined against 1,122 recent (2013-2015) clinical isolates following Clinical and Laboratory Standards Institute (CLSI) guidelines. The study collection included 872 aerobes (811 gram-negative, 61 gram-positive) and 250 anaerobes. Isolates were chosen randomly from the IHMA (International Health Management Associates, Inc., Schaumburg, IL) repository, which is a global collection of single patient clinical isolates. For this study, the selection of isolates focused on infection source (IAI and UTI) and region (US and Europe) for the inclusive years. Aerobes were tested by broth microdilution and anaerobes were tested by agar dilution. Results from this study presented below demonstrate that sulopenem retains potent *in vitro* activity against common pathogens implicated in urinary tract infections and intra-abdominal infections, including those that are caused by organisms that produce ESBLs (data on file). Carbapenem resistant Enterobacterales (CRE) were excluded from the analysis shown below, but the MIC_{90} of Enterobacterales remains at 0.25 µg/mL even if CRE are included, given that their overall prevalence is low (data on file).

Table 1 Sulopenem In-Vitro Susceptibility (2013-2015)

Organism Class		N	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
Enterobacterales		636	0.03	0.25
E. coli	ESBL negative	169	0.015	0.03
	ESBL positive	20	0.03	0.06
Klebsiella spp.	ESBL negative	108	0.03	0.06
	EBSL positive	16	0.03	0.25
P. mirabilis		14	0.12	0.25
E. aerogenes		57	0.06	0.25
C. koseri		60	0.03	0.03
S. marcescens		55	0.12	0.5
Gram-negative Anaerobes		121	0.12	0.25
Staphylococcus saprophyticus		31	0.25	0.25

As in the case of most β-lactams, sulopenem is not active against methicillin-resistant Staphylococci or MDR Enterococci. Sulopenem also does not have activity against *Pseudomonas aeruginosa* and some other non-lactose fermenting gram-negative organisms, therefore its broad use for treating such cephalosporin-resistant hospital isolates should not select for resistant *P. aeruginosa* as can occur with imipenem and meropenem.

Sulopenem (CP-70,429) is available as an intravenous formulation. Intravenous sulopenem was previously evaluated in Phase 1 and Phase 2 clinical studies in Japan in approximately 1478 subjects, at doses up to 1g BID administered intravenously over 3-14 days in the early 1990s. Safety data collected from these trials regarding both adverse events as well as laboratory examinations provides support for the safety and tolerability of sulopenem in patients and its further development.

Sulopenem etzadroxil, the oral pro-drug of sulopenem, has minimal *in vitro* antibacterial activity. Upon oral absorption, sulopenem etzadroxil yields the active moiety sulopenem (CP-70,429) in addition to the non-active moieties formate and 2-ethylbutyric acid (2-EBA).

Sulopenem etzadroxil has been studied in single and multiple dose Phase 1 studies, with and without co-administration of probenecid. One small Phase 2 study in patients with community acquired pneumonia was conducted, in which 35 adult patients were randomized to one of three treatment groups to receive either: a single loading dose of intravenous (IV) sulopenem with switch to oral sulopenem etzadroxil, 4 dose minimum of IV sulopenem with switch to oral sulopenem etzadroxil, or ceftriaxone (IV) for a minimum of 2 doses, with step down to amoxicillin/clavulanate. The cure rates in the clinically evaluable patients in this study at TOC were 90%, 88% and 63% in the single IV dose sulopenem, multiple IV dose sulopenem and ceftriaxone (IV) groups, respectively. While these efficacy results were not statistically significant due to the small numbers enrolled, they provide encouraging support for further clinical testing in this indication.

Sulopenem (IV) has been studied in Phase 3 studies in patients with cUTI, and cIAI, and oral sulopenem has been studied in a Phase 3 study in patients with uUTI, as well as step-down therapy in patients in the cUTI and cIAI studies. These studies were conducted in the United States and Eastern Europe.

Study IT001-301:

Study IT001-301 was a prospective, Phase 3, randomized, multi-center, double-blind, double-dummy study of the efficacy, tolerability, and safety of oral sulopenem versus oral ciprofloxacin for treatment of uUTI in adult women. A total of 1,671 adult women with uUTI were randomized in a 1:1 fashion to receive either a bilayer tablet with sulopenem etzadroxil/probenecid 500 mg/500 mg twice daily for 5 days or oral ciprofloxacin 250 mg twice daily for 3days.

The primary efficacy endpoint for the population of patients with organisms non-susceptible to quinolones (micro-MITTR population) was overall response at the Day 12 (±1 day)/TOC Visit. Overall success was seen in 62.6% of patients in the sulopenem group and 36% of patients in the ciprofloxacin group (treatment difference 26.6%, 95% CI [15.1, 37.4]). The study demonstrated superiority of sulopenem to ciprofloxacin in the treatment of uUTI in the micro-MITTR population.

In a second population of patients with organisms susceptible to quinolones (micro-MITTS population), oral sulopenem was not noninferior to ciprofloxacin for the primary endpoint of overall response. The difference in overall success between the treatment groups in this population of patients was driven primarily by the rate of asymptomatic bacteriuria post-treatment which was lower for patients receiving ciprofloxacin relative to those receiving sulopenem etzadroxil/probenecid.

Overall response in the combined population of patients with a positive baseline culture and without regard to quinolone susceptibility, did not demonstrate a difference in treatment outcome.

Overall, the safety profile for oral sulopenem compared with ciprofloxacin was consistent across patient populations. The most common adverse event seen in patients receiving oral sulopenem was diarrhea, which was mild and self-limited. The rates of discontinuations from study drug and SAEs were low on both regimens and similar between the two groups.

Study IT001-302:

Study IT001-302 was a prospective, Phase 3, randomized, multi-center, double-blind, double-dummy study of the efficacy, tolerability and safety of sulopenem IV followed by oral sulopenem versus ertapenem IV followed by oral ciprofloxacin or amoxicillin/clavulanate for treatment of cUTI in adults. A total of 1395 patients were enrolled in the study, randomly assigned in a 1:1 ratio to sulopenem 1000 mg IV once daily for 5 days followed by oral sulopenem 500 mg/500 mg twice daily to complete 7-10 total days of treatment (N = 697) or ertapenem 1000 mg IV once daily for 5 days followed by oral ciprofloxacin 500 mg twice daily to complete 7-10 total days of treatment (N = 698). Patients with a baseline pathogen non-susceptible to ciprofloxacin, but susceptible to amoxicillin/clavulanate, and who met criteria for oral step-down took amoxicillin/clavulanate 875 mg/125 mg twice daily instead of ciprofloxacin to complete the 7-10 total days of treatment.

In Study 302, the primary efficacy endpoint was overall response at the Day 21 (TOC) Visitin the micro-MITT population. Overall success was seen in 67.8% of patients in the sulopenem group and 73.9% of patients in the ertapenem group in the micro-MITT population (treatment difference -6.1%, 95% CI [-12.0, -0.1]); because the lower bound of the CI was less than the NI margin of -10, the study did not demonstrate noninferiority of sulopenem to ertapenem in the treatment of cUTI.

Sulopenem was well-tolerated, with both the rate of discontinuations and the incidence of TEAEs similar to those of ertapenem. The rate of SAEs for patients on sulopenem was similar to that for patients on ertapenem.

Study IT001-303:

Study IT001-303 was a prospective Phase 3, double-blind, multicenter, randomized study of the efficacy and safety of sulopenem IV followed by oral sulopenem versus ertapenem followed by ciprofloxacin and metronidazole or amoxicillin/clavulanate for treatment of cIAI in adults. A total of 674 patients were enrolled in the study, randomly assigned in a 1:1 ratio to sulopenem 1000 mg IV once daily for 5 days followed by oral sulopenem 500 mg/500 mg twice daily to complete 7-10 total days of treatment (N = 338) or ertapenem 1000 mg IV once daily for 5 days followed by oral ciprofloxacin 500 mg twice daily and metronidazole 500 mg four times daily to complete 7-10 total days of treatment (N = 336). Patients with a baseline pathogen non-susceptible to ciprofloxacin, but susceptible to amoxicillin/clavulanate, and who met criteria for oral step-down took amoxicillin/clavulanate 875 mg/125 mg twice daily instead of ciprofloxacin and metronidazole to complete the 7-10 total days of treatment.

Clinical success was seen in 85.5% of patients in the sulopenem group and 90.2% of patients in the ertapenem group in the micro-MITT population (treatment difference -4.7%, 95% CI [-10.3, 1.0]); the study thus narrowly missed its stated objective of demonstrating the noninferiority of sulopenem to ertapenem in the treatment of cIAI. In all other study populations—ITT, MITT, CE, and ME—the lower limit of confidence interval was above -10.0. These findings are in the context of regulatory criteria that vary from -10 to -12.5, depending on region, for this indication.

Sulopenem was well-tolerated, with both the rate of discontinuations and the incidence of TEAEs similar to those of ertapenem. There were more SAEs on sulopenem, the difference primarily a consequence of an imbalance of SAEs related to intra-abdominal abscesses in the two treatment groups.

Given the challenges that clinicians are now facing with resistance to commonly used antibiotics for uUTI, historical protocol designs used to introduce new antibiotics may not adequately address the relevance of the new agent. This protocol employs a novel design in an attempt to understand the activity of a new compound, sulopenem, relative to a standard-of-care, amoxicillin/clavulanate, in an era of significant antibacterial resistance to multiple standard-of-care oral antibiotics. The activity of oral sulopenem will be compared to amoxicillin/clavulanate in patients with organisms susceptible to amoxicillin/clavulanate, to provide a quantitative estimate of relative activity established by non-inferiority testing as well as in patients with organisms that are resistant to amoxicillin/clavulanate through superiority testing. Further analyses examining outcomes in the as-randomized populations will attempt to define the relative activity of these two drugs without the benefit of culture results, the utility of which may be dependent on the actual findings in the different sub-populations.

Rationale for amoxicillin/clavulanate as the comparator:

Amoxicillin/clavulanate was chosen as the comparator because it is an approved antibiotic for the indication of UTI [Augmentin USPI], it is listed as a treatment option in the IDSA Treatment Guideline [Gupta 2011], and as a β-lactam antibiotic, it is likely to have a similar effect to sulopenem on the urogenital microbiome, thus allowing for a fair comparison of efficacy. The dose of amoxicillin/clavulanate (875 mg/125 mg PO twice daily) was chosen to justify the use of amoxicillin/clavulanate CLSI breakpoints for uncomplicated urinary tract infection (M100 Performance Standards for Antimicrobial Susceptibility Testing, 32nd edition). See Appendix 1 for further details on the rationale for using amoxicillin/clavulanate as the comparator.

1.2.1 Safety data

1.2.1.1 Sulopenem etzadroxil (PF-03709270; oral prodrug)

Pre-clinical data

The non-clinical program to assess toxicity of sulopenem etzadroxil consisted of acute oral and repeat-dose toxicity studies, safety pharmacology studies, genetic toxicity assessments, and reproductive development toxicity studies in rats and rabbits. Following oral administration of sulopenem etzadroxil in rats and monkeys, circulating concentrations of sulopenem etzadroxil were variable and minimal or below limits of quantitation, whereas significant levels of sulopenem and 2-EBA were present in whole blood. Effects observed in rats and monkeys from the repeat dose toxicology studies were generally consistent with those expected from the active moiety sulopenem. The No-Observed-Adverse-Effect-Level (NOAEL) in the rat is 100 mg/kg with a C_{max} of 1.90 µg/mL and AUC of 7.24 µg•h/mL for sulopenem, and the NOAEL in the monkey is 50 mg/kg with a C_{max} of 4.63 µg/mL and an AUC of 11.1 µg•h/mL for sulopenem, respectively. Sulopenem etzadroxil was negative in mutagenicity and in vivo clastogenicity tests but positive for clastogenic activity in human lymphocytes. Sulopenem etzadroxil had no effects on male and female rat fertility and early embryonic development and was not teratogenic to rats or rabbits. Developmental toxicity was observed in both rats and rabbits with the NOAEL being 100 mg/kg and 5 mg/kg, respectively, at doses where maternal toxicity was also observed.

Previous human experience

The sulopenem etzadroxil studies have investigated the pharmacokinetics, safety, and tolerability of single oral doses ranging from 400 mg to 8000 mg. The pharmacokinetics, safety and tolerability of multiple oral doses of sulopenem etzadroxil at a dose of 2000 mg BID for 10 days and 1200 mg plus 1000 mg probenecid BID for 10 days, 500 mg, 1000 mg and 1500 mg BID for 7 days have also been investigated.

Single doses of sulopenem etzadroxil of 400 mg, 600 mg, 1000 mg, and 2000 mg produced an approximately linear increase in sulopenem mean exposure. The apparent terminal half-life of sulopenem was generally dose independent and ranged from 0.76 hours to 1.10 hours.

Mean time to observed maximum concentration (T_{max}) was on average 1 hour for all doses. Neither sulopenem etzadroxil nor formic acid has been detected in either plasma or whole blood following dosing with sulopenem etzadroxil. In addition, the levels of 2-EBA were much lower (~1/20) than sulopenem concentrations. During the administration of multiple

doses of sulopenem etzadroxil for 10 days due to the short half-life of sulopenem etzadroxil there is no accumulation on Day 10 of dosing. Sulopenem etzadroxil doses of 2000 mg produced a mean sulopenem C_{max} of 4.7 μg/mL and a mean AUC_{last} of 13.1 h•μg/mL. Sulopenem systemic exposure parameters (C_{max} and AUC_{last}) following sulopenem etzadroxil single doses ranging from 400 to 2000 mg, increased in a dose-related manner.

There is a significant effect of food (high fat meal) on the PK of sulopenem, given as sulopenem etzadroxil orally. The mean AUC_{inf} and C_{max} increased 69% and 13.5% respectively, with a longer mean time above MIC of 1 μg/mL (1.91 hours). Mean $t_{1/2}$ was similar between the fed and fasted states (0.98-1.14 hr).

The concentrations of radioactivity in plasma and whole blood, the excretion of radioactivity and the metabolic pathways of [^{14}C] sulopenem etzadroxil have been determined in healthy male volunteers (N = 4) following single oral solution (2000 mg) administration. The majority of the radioactivity was excreted in the urine and feces (40.8 and 44.3% respectively). Total mean recovery of radioactivity ranged from 80.2 to 95%.

Overall sulopenem etzadroxil was well tolerated in the Phase 1 program. The most common adverse events occurring in the program were diarrhea and abnormal urine odor. Of note, the incidence of loose stools/diarrhea was significantly lower in patients dosed with food.

Oral sulopenem was safe and well-tolerated across the Phase 3 program in patients with uUTI (Study IT001-301), cUTI (Study IT001-302), and cIAI (IT001-303) (see details for individual studies above).

1.2.1.2 Sulopenem (CP-70,429; Intravenous)

Preclinical data

In non-clinical evaluations of intravenous administration of sulopenem, the NOAEL in the 2-week toxicity study in rats was 200 mg/kg with extrapolated $AUC_{(0\text{-}tlast)}$ of 50 μg•h/mL. The NOAEL was based on increases in kidney and liver weights, erythema, and salivation at 800 mg/kg.

The NOAELs in the 4-week toxicity studies in rats and monkeys were both 60 mg/kg. In rats, the NOAEL was based on a slight decrease in RBC parameters and increases in liver, kidney, and cecum weights at ≥60 mg/kg. In monkeys, the NOAEL was based on a decrease in RBC parameters and increased bilirubin at 200 mg/kg.

The NOAELs in the 3-month studies were 120 mg/kg in the rat; $AUC_{(0\text{-}tlast)}$ of 29.2 ug•hr/mL ($AUC_{(0\text{-}tlast)}$ represents 0-2 h), and 60 mg/kg in the monkey; $AUC_{(0\text{-}tlast)}$ of 49.2 ug•hr/mL; ($AUC_{(0\text{-}tlast)}$ represents 0-8 h). The NOAEL in rats was based on adverse effects on body weight and food consumption, and slight decreases in RBC parameters at 600 mg/kg. The NOAEL in monkeys was based on a positive Direct Coombs test result, decreases in RBC parameters, increased bilirubin, moribundity in 2 animals, bone marrow hyperplasia, and soft stools at 200 mg/kg.

No change in heart rate or QTc was observed in a single-dose cardiovascular safety pharmacology study in anesthetized dogs up to 300 mg/kg, yielding an average blood level of 258 μg/mL (total). Similarly, no change in heart rate or QTc was observed in the cardiovascular study in telemetry-implanted monkeys at 1000 mg/kg, yielding a blood concentration of 2270 μg/mL (total).

In a safety pharmacology study evaluating the effect on the hERG potassium channel, sulopenem inhibited the hERG current by approximately 50% at the maximum concentration of 300 µM (105 µg/mL; free). There were no changes in action potential duration in the *in vitro* Purkinje fiber assay at concentrations up to 300 µM (105 µg/mL; free).

Previous human experience

In healthy adults, intravenous sulopenem doses up to 1000 mg BID were studied in 3 small Phase 1 studies (two in Japan and one in the US) [Foulds 1991] in the early 1990's; sulopenem was well tolerated. The mean C_{max} and AUC_{inf} were 61.5 µg/mL and 51.9 µg•h/mL, respectively for a single 1000 mg dose infused over 30 minutes in the Japanese study. The mean C_{max} and AUC_{inf} were 69.8 µg/mL and 54.1 µg•h/mL, respectively, for a single 1000 mg dose infused over 10 minutes in the US study.

Doses of 400 mg, 800 mg, 1600 mg, 2400 mg and 2800 mg of IV sulopenem were evaluated in a single dose ascending study, and doses of 800 mg infused over 3 hours, 1200 mg infused over 1 hour, 1200 mg infused over 2.5 hours, 1600 mg infused over 1.5 hours for 14 days and 2000 mg infused over 1.5 hours for 7 days were evaluated in a multiple dose study in healthy volunteers (8 subjects in each dose group). There were no deaths or serious adverse events (SAEs) in either study. One subject who received 1200 mg IV BID was discontinued on Day 4 from study drug therapy due to an adverse event (AE) of mildly increased troponin (0.107 ng/mL [normal limit <0.04 ng/mL]); the AE was reported to be resolved on Day 8. The most frequently reported AEs were gastrointestinal events (nausea, vomiting). Severe AEs included nausea and vomiting and were reported only in the highest dose groups (>2000 mg), indicating that MTD had been reached. All AEs in the lower dose groups (<2000 mg) were considered mild to moderate in severity. No clinical laboratory abnormalities occurred that were considered to be clinically significant by the investigator. There were no vital signs or ECG changes (including QTc interval changes) of clinical concern.

Pharmacokinetic analysis revealed a dose proportional increase in C_{max} and AUC_{last}. The mean t ½ remained constant over the dose range. Following a 1-hour intravenous infusion, all doses higher than 400 mg produced mean concentrations above 1.0 µg/mL for > 3.3 hours, allowing for a twice daily dosing and potentially a single daily dose with a longer infusion duration.

IV sulopenem was also investigated in four Phase 2 clinical efficacy studies in Japan in the early 1990s. Over fourteen hundred patients with hospital and community acquired infections were administered primarily 250 or 500 mg BID dosing regimens of IV sulopenem for 3 to 14 days.

Complete information on oral sulopenem etzadroxil and IV sulopenem is available in the Investigator's Brochure.

1.2.2 Rationale for Study

ß-lactam antimicrobials are widely recognized for their efficacy and low toxicity and form the cornerstone of therapy for the treatment of infections caused by gram-positive and gram-negative bacteria. However, extensive use of ß-lactams during the past 50 years has resulted in the development of microbial resistance to these agents among clinically important bacteria. This resistance commonly takes the form of ß-lactamase production, development of porins or alterations in penicillin-binding proteins (PBPs). Such mechanisms have reduced the clinical utility of frequently prescribed ß-lactams such as amoxicillin, amoxicillin plus clavulanate (a ß-lactamase inhibitor), and cephalosporins. The issue of resistance continues to drive the search for

new compounds with increased stability and activity against resistant pathogens. Nowhere is the importance of resistance more evident than among agents of the ß-lactam family.

For *Escherichia coli*, ampicillin resistance has risen to ≥50% in high-risk populations, and resistance to third generation cephalosporins is now being seen in certain areas. Only through the recognition of factors associated with increasing resistance and the mechanisms responsible can strategies be designed for minimizing ß-lactam resistance. Quinolone resistance and resistance to trimethoprim-sulfamethoxazole among *Escherichia coli* is now > 20% in the United States; likewise, nitrofurantoin resistance among Enterobacterales is near or above 20%.

As antibiotic resistance leads to increased costs of treatment, increased morbidity as well as increased mortality, there is an unmet urgent medical need for antimicrobial agents that can be utilized in serious hospital and community infections, especially agents that can be delivered orally.

The penems are considered to exhibit advantages to the ß-lactam class as they possess good antibacterial activity against pneumococci and Gram-negative pathogens commonly responsible for a wide range of community and hospital infections and are stable to many ß-lactamases.

Sulopenem has *in vitro* activity against many common hospital pathogens, including extended spectrum ß-lactamase (ESBL) producing, and/or quinolone non-susceptible gram-negative pathogens (except *Pseudomonas* spp.*,* and some other non-lactose fermenting gram-negative rods), and anaerobes.

Rationale for probenecid

Probenecid is known to increase plasma levels of weak organic acids such as penicillins, cephalosporins, and other β-lactam antibiotics, including penems, by competitively inhibiting their renal tubular secretion. Probenecid has been used safely with other β-lactam antibiotics, to either reduce dose or dosing frequency of βbeta-lactams when used to treat infectious diseases in human beings.

Probenecid has been shown in an animal dog model to increase the systemic exposure of a penem CP-65,207 (sulopenem is the S-isomer of CP-65,207) by about 2-fold, suggesting a role of active renal tubular secretion in drug elimination. Findings from a previous clinical pharmacokinetic study indicate that renal clearance accounts for a significant proportion (approximately 50%) of total clearance of sulopenem in healthy volunteers suggesting that probenecid could increase exposure and thus time over MIC for sulopenem.

In a previous Phase 1 study (A8811007), the use of 500 mg and 1000 mg of probenecid was compared for its effect on the PK of sulopenem. While the sulopenem AUC was significantly higher for the 1000 mg probenecid administration, the $\%T_{free}$ >MIC was very similar, as anticipated, suggesting that the 500 mg of probenecid may provide sufficient extension of circulating sulopenem to achieve the PKPD objectives. The combination of oral sulopenem etzadroxil 500 mg and probenecid 500 mg was evaluated in a recently completed study, IT001-101. Results from this study were consistent with those observed in previous studies.

Thus, probenecid has the potential to be used as a PK booster with sulopenem etzadroxil, optimizing the time over MIC for any given sulopenem dose while minimizing the gastrointestinal exposure of the parent compound and subsequent gastrointestinal adverse events such as diarrhea.

Probenecid may prolong or enhance the action of oral sulfonylureas and thereby increase the risk of hypoglycemia. The concomitant administration of probenecid increases the mean plasma elimination half-life of a number of drugs which can lead to increased plasma concentrations. These include agents such as indomethacin, acetaminophen, naproxen, ketoprofen, meclofenamate, lorazepam, and rifampin. The clinical significance of this observation has not been established. Please see probenecid product label for more pharmacology information.

Rationale for dosing with food

In a multiple dose (A8811003) study, at higher doses of oral sulopenem etzadroxil, there was a higher rate of gastrointestinal symptoms especially diarrhea in a fasted state. It has therefore been postulated that if the fraction of sulopenem etzadroxil absorbed and bioavailability of sulopenem (CP-70,429, the active moiety) can be increased, the gastrointestinal toleration and pharmacokinetics of the compound can be improved.

In Study A8811008 there was an increase in relative bioavailability of sulopenem when oral sulopenem etzadroxil was administered in the fed state (~82% increase in mean AUC). In Study IT001-101, oral sulopenem etzadroxil was evaluated in a fasted and fed state at a dose of 500 mg BID. Results from this study indicate that food significantly increases bioavailability of sulopenem and consequently results in decreased rates of diarrhea. Therefore, dosing of oral sulopenem-etzadroxil with food whenever possible is recommended. Since adequate target attainment appears to be achieved in the fasted state, an inability to administer the dose with food should not preclude dosing.

1.2.3 Dose Rationale

Sulopenem etzadroxil

Doses of oral sulopenem etzadroxil were chosen by PK/PD modeling using a combination of (1) modeling (Naïve Pool analysis) of the sulopenem effect on net change in colony forming units (CFU) over 24 hours of clinically relevant organisms in an immunocompetent mouse thigh infection model, (2) defining targets of percent time above the MIC (T>MIC) for sulopenem from this mouse model, and (3) population PK modeling using nonlinear mixed effects models, generated from clinical data in multiple oral sulopenem etzadroxil Phase 1 studies in healthy volunteers.

Monte Carlo simulations were performed using the human population PK parameters for sulopenem etzadroxil and mean pharmacodynamic parameters from murine thigh infection model to determine % target achievement (TA) for the selected doses. A %TA of ≥90% was deemed desirable for selecting particular doses. The 500 mg dose of oral sulopenem etzadroxil co-administered with 500 mg of probenecid administered twice daily meets the criteria of %T>MIC for achieving 1-log kill in bacteria.

Probenecid

The maximum total daily dose of probenecid will be 1000 mg (500 mg BID) which is within the recommended dosage of 2000 mg daily in divided doses.

Amoxicillin/clavulanate

The FDA approved (NDA 50-720/S024) dose of 875/125 mg oral amoxicillin/clavulanate administered twice daily for 5 days for treatment of uncomplicated UTI, per the Augmentin USPI, will be used in this study. This dose was chosen to justify the use of

amoxicillin/clavulanate CLSI breakpoints for uncomplicated urinary tract infection (M100 Performance Standards for Antimicrobial Susceptibility Testing, 32nd edition).

For the full prescribing information for probenecid or amoxicillin/clavulanate, please refer to respective local country product labels.

2 STUDY OBJECTIVES

2.1 Objectives

Non-inferiority Trial:	
Objective	**Estimand/Endpoint**
Primary:	**Primary Estimand:**
To compare the overall response (clinical and microbiologic combined response) at Day 12 (±1 day)/test of cure (TOC) of oral sulopenem etzadroxil/probenecid tablets (500 mg/500 mg) versus oral amoxicillin/clavulanate (875 mg/125 mg) tablets for the treatment of uncomplicated urinary tract infection in adult women.	Endpoint of interest: Overall success at Day 12 (±1 day)/TOC (clinical and microbiologic combined) Intercurrent events: non-susceptibility or resistance to amoxicillin/clavulanate, use of rescue antibiotic, study discontinuation Population level summary of variable: Comparison of overall success rates between treatment groups
Secondary:	**Secondary Endpoints:**
To evaluate the clinical efficacy at Day 12 (±1 day)/TOC.	Clinical cure (resolution of the symptoms of uUTI present at trial entry and no new uUTI symptoms) at Day 12 (±1 day)/TOC.
To evaluate the rate of post-treatment asymptomatic bacteriuria at Day 12 (±1 day)/TOC.	Clinical cure (resolution of the symptoms of uUTI present at trial entry and no new uUTI symptoms) and microbiologic persistence (≥ 10^3 CFU/mL of the baseline uropathogen) at Day 12 (±1 day)/TOC
To evaluate the microbiologic efficacy at Day 12 (±1 day)/TOC.	Microbiologic eradication (<10^3 CFU/mL of the baseline uropathogen) at Day 12 (±1 day)/TOC
To further evaluate the safety profile of oral sulopenem etzadroxil/probenecid tablets (500 mg/500 mg) when used for treatment of uUTI in adult women.	Incidence of TEAEs through Day 28 (±2 days); Changes from baseline in clinical laboratory tests at the Day 12 (±1 day)/TOC visit; Changes from baseline in vital signs at the Day 5 (+1 day)/EOT and Day 12 (±1 day)/TOC visits

Additional:	**Additional Endpoints:**
To evaluate the clinical efficacy at Day 5 (+1 day) and Day 28 (±2 days).	Clinical cure (resolution of the symptoms of uUTI present at trial entry and no new uUTI symptoms) at Day 5 (+1day) and Day 28 (±2 days).
To evaluate the rate of post-treatment asymptomatic bacteriuria at Day 5 (+1 day) and Day 28 (±2 days).	Clinical cure (resolution of the symptoms of uUTI present at trial entry and no new uUTI symptoms) and microbiologic persistence ($\geq 10^3$ CFU/mL of the baseline uropathogen) at Day 5 (+1 day) and Day 28 (±2 days).
To evaluate the microbiologic efficacy at Day 5 (+1 day) and Day 28 (±2 days).	Microbiologic eradication ($<10^3$ CFU/mL of the baseline uropathogen) at Day 5 (+1 day) and Day 28 (±2 days).
To evaluate overall response at other relevant timepoints	Overall success (clinical and microbiologic combined response) at Day 5 (+1 day) and Day 28 (±2 days) visits
To evaluate the investigator determined clinical response	Investigator determined clinical response (clinical success, failure, and indeterminate) at Day 5 (+1 day), Day 12 (±1 day)/TOC, and Day 28 (±2 days)
To evaluate overall success, clinical success, and microbiologic success by key baseline pathogens	Overall success, clinical success, and microbiologic success at Day 5 (+1 day), Day 12 (±1 day)/TOC, and Day 28 (±2 days) by key baseline pathogen

3 STUDY DESIGN

Study IT001-310 is a prospective, Phase 3, randomized, multicenter, double-blind, double dummy, controlled study to compare oral sulopenem to oral amoxicillin/clavulanate for the treatment of patients with uUTI. Approximately 1966 adult women with uUTI will be randomized in a 1:1 fashion to receive either oral 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. End of Therapy is defined as Day 5 (+ 1 day). The primary efficacy assessment will be overall response (combined clinical and microbiologic response [success, failure or indeterminate]) in the micro-MITT, micro-MITTS and micro-MITTR populations on Day 12 (± 1 day)/TOC. Secondary efficacy assessments will include the clinical response (success, failure, or indeterminate), and microbiologic response (success [eradication], failure [persistence or persistence with increasing MIC] or indeterminate) on Day 12 (± 1 day)/TOC. See Appendix 2, Schedule of Activities Table.

3.1 Investigational Study Medications

Patients will be randomized to receive either a bilayer tablet with sulopenem etzadroxil/probenecid 500 mg/500 mg PO twice daily for 5 days or amoxicillin/clavulanate 875 mg/125 mg PO twice daily for 5 days.

Sulopenem etzadroxil treatment group: The study drug will be supplied as a study kit containing one bottle with 10 bilayer tablets containing sulopenem etzadroxil/probenecid 500 mg/500 mg and one blister wallet containing 10 amoxicillin/clavulanate placebo capsules.

Comparator treatment group: The study drug will be supplied as a study kit containing one blister wallet containing 10 over-encapsulated amoxicillin/clavulanate 875 mg/125 mg tablets, and one bottle with 10 placebo tablets to match sulopenem etzadroxil/probenecid tablets.

3.2 Adjunctive Systemic Antibiotics

None allowed except as described in Section 5.4.2.

3.3 Additional Non-Study Therapy Antibiotics

For *Clostridioides difficile* infections, metronidazole (IV or oral), vancomycin (oral or rectal), or fidaxomicin (oral) may be used in both treatment groups. Patients with a co-infection with a gram-positive uropathogen known or suspected to be resistant to study drugs are allowed to receive agents with narrow spectrum gram-positive coverage (such as oral linezolid) at the discretion of the investigator.

4 STUDY POPULATION SELECTION

Female patients who present with uUTI, defined by symptoms and a urinalysis suggestive of a uUTI per Section 4.1, and who meet all of the inclusion and none of the exclusion criteria will be eligible for participation in this study.

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular patient is suitable for enrollment under this protocol.

4.1 Inclusion Criteria

1. Female patients ≥18 years of age with ≥24 hours and ≤96 hours of urinary symptoms attributable to a UTI
2. Two of the following signs and symptoms of uUTI: urinary frequency, urinary urgency, pain or burning on micturition, suprapubic pain.
3. A mid-stream urine specimen with:

    a. a machine-read dipstick positive for nitrite AND any positive leukocyte esterase

    OR,

b. evidence of pyuria alone as defined by either:

i. a machine-read dipstick positive for large leukocyte 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

4. Has given written informed consent to participate in the study

4.2 Exclusion Criteria

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
2. Receipt of antibacterial drug therapy potentially effective as treatment of uUTI within the prior 7 days
3. 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. Note: Patients can be included if these medications were previously taken and have ceased at the time of Screening onward.
4. Any anatomical abnormality of the urinary tract, including surgically modified urinary tract anatomy, and obstructive uropathy due to nephrolithiasis, stricture, tumor, or fibrosis
5. Ongoing urinary retention
6. Neurogenic bladder
7. Current resident of a long-term care facility
8. Instrumentation of urinary tract in the previous 30 days
9. An indwelling urinary catheter, ureteral stent or other foreign material in the urinary tract
10. Any history of trauma to the pelvis or urinary tract
11. Current urine culture, if available while evaluating eligibility, that is positive for more than 2 microorganisms regardless of colony count (contaminated), or confirms a fungal UTI
12. Receiving hemodialysis, hemofiltration, peritoneal dialysis, or had a renal transplant
13. Immunocompromised as evidenced by any of the following:
    a. Known HIV positive, with either a recent (in the past 6 months) AIDS-defining condition or a CD4 + T lymphocyte count <200/mm^3
    b. Known neutropenia (defined as absolute neutrophil count <1000 cells/mm^3)

c. Systemic or hematological malignancy requiring chemotherapeutic or radiation/immunologic interventions within 6 weeks prior to randomization or anticipated to begin prior to completion of study
d. Immunosuppressive therapy, including maintenance corticosteroid therapy (>40 mg/day equivalent prednisolone for 5 days or more in the 30 days prior to randomization)

14. Known liver function abnormalities as defined by the following laboratory criteria:
    - ALT or AST > 3x upper limit of normal, and/or
    - Total bilirubin > 2x upper limit of normal
15. Females of child-bearing potential who are unable to take adequate contraceptive precautions (refer to Sections 4.4 and 4.5), have a positive pregnancy test result within 24 hours of study entry, are otherwise known to be pregnant, or are currently breastfeeding
16. Poorly controlled Diabetes mellitus, including the presence of ketoacidosis and hyperosmolar hyperglycemia
17. History of seizures
18. History of blood dyscrasias
19. History of uric acid kidney stones
20. Acute (current) gouty arthritis
21. Concomitant administration of valproic acid
22. History of allergy or hypersensitivity to carbapenems, β-lactams or probenecid, as formulated with their excipients
23. Unlikely to survive the 4-week study period or has a rapidly progressive or terminal illness, including septic shock, associated with a high risk of mortality
24. The use of any other investigational drug in the 30 days prior to the first dose of study drug, or prior participation in any sulopenem clinical trial

Urine samples, including results from urine tests, collected as part of routine standard of care, prior to obtaining informed consent, may be used to assess eligibility for enrollment into study and/or for baseline urine culture.

4.3 Randomization Criteria

Patients will be randomized in a 1:1 ratio to oral sulopenem versus oral amoxicillin/clavulanate using an IWRS into the study provided they have satisfied all patient selection criteria.

4.4 Lifestyle Guidelines

For the duration of the study, all female patients of child-bearing potential must agree to be strictly abstinent from sexual intercourse with any individual of the opposite sex, or to follow the following instructions for contraception.

4.5 Women of Child-Bearing Potential

If the patient is a woman of childbearing potential (women of child-bearing potential and peri-menopausal women include females <50 years of age or those ≥ 50 years of age who have been post-menopausal [amenorrheic] for < 2 years) , and not practicing abstinence, that patient is required to simultaneously use 2 effective contraceptive methods, from the following list of five:

1. A barrier (condoms, diaphragm or cervical cap) with spermicide;
2. A second, different barrier method (condoms, diaphragm or cervical cap);
3. Oral or similar contraceptive, which includes, but is not limited to: injectable, implanted, or patch hormone therapy, and intrauterine device (IUD);
4. Documented surgical sterilization at least 4 weeks prior to baseline;
5. Partner vasectomy at least 6 months prior to baseline.

She must agree to continue all of these contraceptive methods until the last Study Visit. Within these limits, the specific forms of contraception employed are left to the discretion of the patient, and/or the principal investigator, and/or the patient's physician and documented in source.

5 STUDY TREATMENTS

5.1 Allocation to Treatment

This is a randomized, double-blind, double dummy, controlled study comparing oral sulopenem with oral amoxicillin/clavulanate in the treatment of uUTI. Approximately 1966 patients will be randomized to receive either oral sulopenem twice daily for 5 days or oral amoxicillin/clavulanate twice daily for 5 days in a 1:1 allocation ratio using an IWRS.

A patient will be eligible for randomization once it has been determined that the patient meets all inclusion criteria and has none of the exclusion criteria. On the day the patient is to receive the first dose of study drug, a designated member of the site staff will contact the IWRS to obtain the study treatment assignment and dispense therapy accordingly. The IWRS will associate that patient with the next available treatment on the randomization schedule. The IWRS will then give the investigative site information which corresponds to study medication that has been previously shipped to the site and is in the site's inventory ready to be dispensed. A patient is considered randomized when the site personnel receive the treatment assignment associated with the patient entered into the IWRS.

5.2 Drug Supplies

5.2.1 Formulation and Packaging

Sulopenem etzadroxil/probenecid treatment group: The study drug will be supplied as a study kit containing one bottle with 10 bilayer tablets containing sulopenem etzadroxil/probenecid 500 mg/500 mg and one blister wallet containing 10 amoxicillin/clavulanate placebo capsules.

Patients found to have pathogens isolated from urine cultures that are resistant to amoxicillin/clavulanate or carbapenems, may be allowed to continue on study drug therapy to complete the 5-day duration of treatment based on clinical response and investigator judgement, and are not required to receive alternative antibiotic therapy.

Comparator treatment group: The study drug will be supplied as a study kit containing one blister wallet containing 10 over-encapsulated amoxicillin/clavulanate 875 mg/125 mg tablets, and one bottle with 10 placebo tablets to match sulopenem etzadroxil/probenecid tablets.

All supplies packed and labeled will be formally released in accordance with both Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines.

5.2.2 Preparation and Dispensing

All kits of study drug will be provided to the study site by Iterum Therapeutics. Dispensing of study medication will be done and documented in accordance with the treatment schedule as outlined in the study protocol. Written dispensing instructions will be provided to each study site in a study pharmacy manual.

5.2.3 Administration

Patients randomized to the sulopenem treatment group will take one sulopenem etzadroxil/probenecid tablet and one placebo capsule twice daily for 5 days and those randomized to the amoxicillin/clavulanate treatment group will take one over-encapsulated amoxicillin/clavulanate tablet and one placebo tablet twice daily for 5 days (10 doses total over a 5-day period; if Dose 1 is taken in the evening of Day 1, Dose 10 will be taken in the morning of Day 6). The first dose of each medication will be administered under the supervision of study site personnel to help ensure compliance with dosing directions.

Study drug administration will be documented in accordance with the Pharmacy Manual.

Dosing with food:

Food significantly increases bioavailability of sulopenem and consequently results in decreased rates of diarrhea. Therefore, dosing of oral sulopenem with food whenever possible is recommended. Since adequate target attainment appears to be achieved in the fasted state, an inability to administer the dose with food should not preclude dosing.

Amoxicillin and clavulanate are well absorbed from the gastrointestinal tract after oral administration. Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin. While amoxicillin/clavulanate can be given without regard to meals, absorption of clavulanate when taken with food is greater relative to the fasted state. Therefore, dosing of oral amoxicillin/clavulanate with food whenever possible is also recommended.

5.2.4 Compliance

All patients should be informed that compliance with taking all oral medication as instructed is imperative.

Patients will be asked to bring all study medication containers (used and unused) to the next scheduled study visit for drug accountability. The total amount of oral dosing completed (determined by tablet or capsule count from returned containers) will be recorded in the IWRS/EDC systems.

A study-specific diary will be provided to every patient to capture compliance with study medications.

A urine sample will be collected and frozen at the Day 5 visit which can be used to confirm compliance, safety, or efficacy assessments.

5.3 Drug Storage and Drug Accountability

The investigator, or an approved representative, e.g., pharmacist/designee, will ensure that all investigational products are stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. To ensure adequate records, the IWRS will be used to document site standard accountability.

At the end of the study, Iterum Therapeutics will provide instructions as to disposition of any unused investigational product including oral sulopenem and amoxicillin/clavulanate. If Iterum Therapeutics authorizes destruction at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Iterum Therapeutics. Destruction must be adequately documented.

5.4 Concomitant Medication(s), Adjunctive Therapy, and Non-drug Therapy

5.4.1 Concomitant Medications

Any medication taken by the patient during the study, other than study drug, is considered concomitant medication. All concomitant medications from Baseline (Day 1) through the Final Visit must be recorded in the patient's source record and on the Case Report Form (CRF).

At each visit, the investigator/site designee will obtain information on any therapeutic interventions (e.g., drug therapy, surgery, etc.) provided. The use of any other investigational drug is prohibited, and patients may not participate in any other studies involving marketed products concomitantly while in this study.

The use of other (non-antibacterial) medications should be limited to those essential for the care of the patient. All medications required by the patient to manage underlying illnesses, and any drugs that may be required for emergency treatments, must be recorded on the CRF. Of note, the use of medications to alleviate UTI symptoms (such as analgesics [e.g., non-steroidal anti-inflammatory drugs, aspirin, paracetamol etc.], phenazopyridine or cranberry products) is prohibited until after the Day 12 (± 1 day)/TOC visit.

5.4.2 Adjunctive Systemic Antibiotics (Rescue Therapy)

In general, adjunctive systemic antibiotics are not allowed for patients enrolled in the study. At any time during the study period, and at the discretion of the principal investigator (PI), additional antibiotics—oral or IV, as appropriate—can be prescribed as rescue therapy, e.g., in the event of worsening signs and symptoms of uUTI, or if the patient develops fever and/or flank pain suggestive of upper urinary tract involvement. In the event that rescue therapy is prescribed, patient symptoms will be collected as an unscheduled event; such patients will be considered as failures and will be asked to still complete all protocol-specified assessments through the Final Visit. Use of adjunctive antibiotics without clinical symptoms is strongly discouraged.

5.4.3 Additional Non-Study Therapy Antibiotics

Concomitant systemic antibacterials are prohibited during the study, up to the Day 28 (± 2 days) visit, with the following exceptions:

- For *Clostridioides difficile* infections, metronidazole (IV or oral), vancomycin (oral or rectal), or fidaxomicin (oral) may be used in both treatment groups. The Sponsor will not provide therapy for *Clostridioides difficile* infections.
- Patients with a co-infection with a gram-positive uropathogen known or suspected to be resistant to study drugs are allowed to receive agents with narrow spectrum gram-positive coverage (such as oral linezolid) at the discretion of the investigator. The Sponsor will not provide therapy for co-infection with a gram-positive uropathogen resistant to study drugs.

6 STUDY PROCEDURES

6.1 Screening (Day -1) - Within 24 Hours Prior to First Dose

The investigator (or an appropriate delegate at the investigator site) will obtain written informed consent from each patient prior to the initiation of any study related activities.

Urine samples, including results from urine tests, collected as part of routine standard of care, prior to obtaining informed consent, may be used to assess eligibility for enrollment into study and/or for baseline urine culture.

The following screening procedures will be performed prior to randomization and study drug administration (Screening and Day 1 Visit will typically occur on the same calendar day):

- Obtain signed informed consent
- Review demographics and medical history
- Review eligibility criteria
- Review previous drug and non-drug treatments (defined as within the prior 30 days)
- Review concomitant medications
- Review adverse events occurring after signing the ICF
- Targeted physical examination (including general appearance, examination of heart, lungs, abdomen, and extremities)
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate), height and weight
- Perform urine pregnancy test on women of child-bearing potential, including peri-menopausal women, and confirm negative result.
    - Women of child-bearing potential and peri-menopausal women include females <50 years of age or those ≥ 50 years of age who have been post-menopausal [amenorrheic] for < 2 years
- Collect urine for urinalysis and urine culture and susceptibility
- Blood for laboratory testing including hematology and chemistry studies
- Banked serum and urine for retrospective safety and efficacy assessments

To prepare for trial participation, patients will be instructed on the use of Lifestyle Guidelines and Concomitant Medications.

6.2 Treatment Period

For the study period described below, where multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, where possible.

- Blood pressure/pulse rate: obtain prior to blood specimen collection

6.2.1 Day 1

- Review concomitant medications and adverse events if Day 1 visit not on same day as Screening/Day -1 visit
- Confirm eligibility if Day 1 visit not on same day as Screening/Day -1 visit
- Randomize patient
- Provide patient daily dosing diary along with instructions on how to complete
- Have patient complete patient symptom assessment questionnaire
- Administer the study medication as described in Section 5.2.3

6.2.2 Day 5 (+ 1 day) (End of Treatment/EOT)

- Targeted physical examination, if required, based on patient's symptoms (as determined by the investigator)
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate)
- Bank urine for retrospective assessments
- Collect urine for urinalysis and urine culture and sensitivity
- Review concomitant medications
- Assess symptoms by spontaneous reporting of adverse events and by asking the patients to respond to a non-leading question such as "How do you feel?
- Confirm and document study medication compliance by pill count and patient daily dosing diary
- Collect patient daily dosing diary and review for completeness
- Have patient complete patient symptom assessment questionnaire
- Investigator Assessment of Clinical Response (Section 7.2.4)

6.3 Follow-up Period

6.3.1 Day 12 (± 1 day) (Test of Cure/TOC)

- Targeted physical examination, if required, based on patient's symptoms (as determined by the investigator)
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate)

- Blood for laboratory testing (including hematology and chemistry studies)
- Bank serum and urine for retrospective safety and efficacy assessments
- Collect urine for urinalysis and urine culture and sensitivity
- Review concomitant medications
- Assess symptoms by spontaneous reporting of adverse events and by asking the patients to respond to a non-leading question such as “How do you feel?
- Have patient complete patient symptom assessment questionnaire
- Investigator Assessment of Clinical Response (Section 7.2.4)

6.3.2 Day 28 (± 2 days) (Final Visit/FV)

- Targeted physical examination, if required, based on patient’s symptoms (as determined by the investigator)
    - Perform urine pregnancy test on women of child-bearing potential, including peri-menopausal women, and confirm negative result. Women of child-bearing potential and peri-menopausal women include females <50 years of age or those ≥ 50 years of age who have been post-menopausal [amenorrheic] for < 2 years
- Collect urine for urinalysis, urine culture and sensitivity
- Review concomitant medications
- Assess symptoms by spontaneous reporting of adverse events and by asking the patients to respond to a non-leading question such as “How do you feel?
- Have patient complete patient symptom assessment questionnaire
- Investigator Assessment of Clinical Response (Section 7.2.4)

6.4 Premature Discontinuation

- Targeted physical examination, if required, based on patient’s symptoms (as determined by the investigator)
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate)
- Blood for laboratory testing including hematology and chemistry studies
- Perform urine pregnancy test on women of child-bearing potential, including peri-menopausal women, and confirm negative result
    - Women of child-bearing potential and peri-menopausal women include females <50 years of age or those ≥ 50 years of age who have been post-menopausal [amenorrheic] for < 2 years
- Collect urine for urinalysis and urine culture and sensitivity
- Review concomitant medications
- Assess symptoms by spontaneous reporting of adverse events and by asking the patients to respond to a non-leading question such as “How do you feel?

- Confirm and document study medication compliance by pill count and patient daily dosing diary
- Have patient complete patient symptom assessment questionnaire
- Investigator Assessment of Clinical Response (Section 7.2.4)

6.5 Patient Withdrawal from Treatment or Study

Patients may withdraw from the study or study drug at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. If the patient withdraws or is withdrawn from study drug treatment, the investigator should inquire about the reason for withdrawal, request the patient to return for all protocol-specified assessments, if possible, and follow-up with the patient regarding any unresolved AEs through the final visit.

For patients who withdraw from the study early, a Premature Discontinuation visit should be performed within 3 calendar days after decision to discontinue (Section 6.4 and no further visits are required.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further study-specific evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7 ASSESSMENTS

7.1 Safety

7.1.1 Physical Examination

A targeted physical examination will be performed at Baseline (including general appearance, examination of heart, lungs, abdomen, and extremities). A targeted physical exam may be conducted at any visit to address patient's symptoms if needed (as determined by the investigator).

7.1.2 Vital Signs (Temperature, Blood Pressure, Pulse Rate, Respiratory Rate)

Vital signs are performed at Baseline, Day 5 (+ 1 day), Day 12 (± 1 day)/TOC, or Premature Discontinuation.

Blood pressure will be measured and recorded to the nearest mm Hg. All blood pressure measurements should be taken at rest. The same size blood pressure cuff should be used to measure blood pressure each time. When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate are to be obtained first. Temperature may be measured as an oral, rectal, tympanic (ear) or temporal temperature.

7.1.3 Clinical Laboratory Assays

The following laboratory parameters will be measured:

- Hematology: Complete blood count (CBC), including white blood cell (WBC) and differential counts; at Baseline, Day 12 (± 1 day)/TOC or Premature Discontinuation
- Serum Clinical Chemistry: AST, ALT, GGT, alkaline phosphatase, albumin, total and direct bilirubin, BUN or urea, creatinine, Na+, K+, Cl-, total CO2 (Bicarbonate), glucose, high sensitivity C-reactive protein (CRP) and LDH at Baseline, Day 12 (± 1 day)/TOC or Premature Discontinuation.
- Urinalysis and urine culture and sensitivity at Baseline, Day 5 (+ 1 day), Day 12 (± 1 day)/TOC and Day 28 (± 2 days) or Premature Discontinuation.
  - Susceptibility results of pathogens to amoxicillin/clavulanate and carbapenems from cultures obtained at Screening, EOT, and TOC should not be reported to sites/investigators until after the TOC visit, unless requested by the Principal Investigator and clinically warranted, so as not to influence the investigator's decision to prescribe a rescue antibiotic in the case of presence of a non-susceptible pathogen.
- Urine pregnancy test performed at the site for women of child-bearing potential, including peri-menopausal women; at Baseline and Day 28 (± 2 days)) or Premature Discontinuation.
  - Women of child-bearing potential and peri-menopausal women include females <50 years of age or those ≥ 50 years of age who have been post-menopausal [amenorrheic] for < 2 years
- Serum pregnancy test performed by laboratory at the discretion of the principal investigator
- Serum and urine samples will be banked for retrospective safety and efficacy analyses as needed at Baseline, Day 5 [(+ 1 day); urine only], and Day 12 (± 1 day)/TOC. Banked serum and urine samples may be stored up to 10 years.

7.1.4 Clinically Significant Laboratory Tests

Clinical laboratory tests may be repeated during the study if deemed necessary as part of routine practice based on investigator judgment. All clinically significant abnormal laboratory test results occurring during the study will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the Iterum appointed medical monitor.

7.2 Efficacy

7.2.1 Overall Response

Overall Response (at a given Visit) is assessed using the definitions listed below:

A patient will be defined as a success if the following criteria are met (programmatically, based on the data on the eCRF):

- The patient is alive
- The patient has received no rescue therapy for uUTI
  - If an antibiotic active against the urinary tract pathogen is given for other reasons, 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)

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

- Urine culture demonstrates $<10^3$ CFU/mL of the baseline uropathogen based on results of quantitative cultures performed on collected urine specimens.

Results of susceptibility testing to differentiate between pathogens isolated at baseline and follow-up visits will be used in a sensitivity analysis to be specified in the SAP; whole genome sequencing (WGS) of isolated organisms may be performed if needed and results will be used in a sensitivity analysis to be specified in the SAP.

All other patients will be considered as failures unless data are unavailable to determine if the patient is a confirmed overall success or a failure. In this case, the patient will be considered as having an indeterminate response. Patients with an indeterminate response are included in the denominator for determination of the response rate.

7.2.2 Microbiologic

Microbiologic Response is assessed using the definitions listed below:

Microbiological response	**Definition**
Success	The urine culture demonstrates $<10^3$ CFU/mL of the baseline uropathogen (also referred to as eradication) at the time-point of analysis, i.e., Day 5 (+ 1 day), Day 12 (± 1 day)/TOC, or Day 28 (± 2 days) visit
Persistence	A uropathogen present at baseline grew at $\geq 10^3$ CFU/mL at the time-point of analysis, i.e., Day 5 (+ 1 day), Day 12 (± 1 day)/TOC, or Day 28 (± 2 days) visit
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 uropathogen and displayed ≥4-dilutions higher MIC, as compared to baseline, to study drug received at the time-point of analysis, i.e., Day 5 (+ 1 day), Day 12 (± 1 day)/TOC, or Day 28 (± 2 days) visit
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 time-point of analysis, i.e., Day 5 (+ 1 day), Day 12 (± 1 day)/TOC, or Day 28 (± 2 days) visit

7.2.3 Patient-Determined Clinical Response

A patient will be defined as a clinical success if the following criteria are met (programmatically, based on the data on the eCRF):

- The patient is alive

- The patient has received no rescue therapy for uUTI
  - If an antibiotic active against the urinary tract pathogen is given for other reasons, 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)
  - 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 a failure. In this case, the patient will be considered as having an indeterminate response. Patients with an indeterminate response are included in the denominator for determination of the response rate.

7.2.4 Investigator Assessment of Clinical Response

Investigators will use the definitions below to document clinical response, irrespective of microbiologic findings, at Day 5 (+ 1 day), Day 12 (± 1 day)/TOC, Day 28 (± 2 days), 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 to be considered as failure:
	Death related to uUTI prior to visit
	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 the visit
	Death prior to study visit, where uUTI was clearly noncontributory

7.2.5 Patient Symptom Assessment Questionnaire (PSAQ)

Patients will score their UTI symptoms and record them on a Patient Symptom Assessment Questionnaire. PSAQ is administered on Day 1 (prior to first dose), Day 5 (+ 1 day)/EOT, Day 12 (± 1 day)/TOC, and Day 28 (± 2 days) visit, or Premature Discontinuation. In the event that rescue therapy is prescribed, patient symptoms will be collected as an unscheduled event.

8 ADVERSE EVENT REPORTING

8.1 Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain adequate information both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious AE (SAE) requiring immediate notification to Iterum Therapeutics' designated pharmacovigilance provider (Medpace Safety). For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. All AEs will be followed-up by the investigator until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Iterum concurs with that assessment.

8.2 Reporting Period

Adverse events will be collected from the time that the patient provides informed consent through the Day 28 (± 2 days) (Final Visit).

For SAEs, the reporting period to Iterum Therapeutics' designated pharmacovigilance provider (Medpace Safety) begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through the Final Visit. Any SAE occurring any time after the reporting period must be promptly reported if a causal relationship to investigational product is suspected.

All AEs should be recorded on the CRF if they occur from the time the patient provides informed consent through Final Visit.

8.3 Definition of an AE

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device, unless the event is captured in the study endpoint, as defined below; the event need not necessarily have a causal relationship with the treatment or usage.

An event would be considered as adequately captured in the study endpoint if it is accurately and fully represented by a protocol-defined reason for clinical failure (other than mortality) or relapse. Such an event should not be reported as an adverse event unless it is a serious adverse event as defined in this protocol.

Events represented by the study endpoints, which would not be considered AEs, include all of the following:

- Symptoms of uUTI have not resolved from Baseline to such an extent that new antibiotics are needed for the infection under study
- Development of new uUTI symptoms not present at Baseline
- Follow up urine cultures do not reveal eradication of causative uropathogen

Except for circumstances as defined above, examples of AEs include but are not limited to:

- Abnormal test findings (see Section 8.4)
- Clinically significant symptoms and signs
- Changes in physical examination findings
- Hypersensitivity to study drugs
- Progression/worsening of underlying disease (not UTI)

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose
- Drug withdrawal
- Drug abuse
- Drug misuse
- Drug interactions
- Drug dependency
- Exposure during Pregnancy

8.4 Abnormal Test Findings

An abnormal objective test finding (e.g., an abnormal liver function test result) should be reported as an AE only if the following conditions apply:

- Test result is associated with accompanying symptoms and/or signs, constituting a clinical syndrome (e.g., abnormal liver function test results, jaundice, and hepatic tenderness suggesting a diagnosis of hepatitis), and/or
- Test result requires medical/surgical intervention, and/or
- Test result leads to a change in study dosing or withdrawal from the study, significant additional concomitant drug treatment, or other therapy.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not define the abnormal objective test finding as an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE. Additional diagnostic testing and /or medical/surgical interventions that occur as a result of an adverse event due to an abnormal lab test finding should be noted in the CRF.

8.5 Serious Adverse Events (SAE)

An SAE or serious adverse drug reaction is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect;

- Is assessed as being a medically important event based on medical and scientific judgment. Such medically important events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient and may require medical or surgical intervention to prevent one of the above outcomes. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.6 Hospitalization

Adverse events associated with hospitalization or prolongations of hospitalization are considered serious. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room evaluation;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment laboratory abnormality);
- Social admission (e.g., patient has no place to sleep);
- Administrative admission (e.g., for yearly physical exam);
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery). Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as an AE. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded as treatment of the AE.

8.7 Severity Assessment

The investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

- MILD: Does not interfere with the patient's usual function.
- MODERATE: Interferes to some extent with the patient's usual function.
- SEVERE: Interferes significantly with the patient's usual function.

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

8.8 Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE. If the investigator does not know whether or not investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see Section 8.12 on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records. Specifically, the investigator will choose whether the AE is unrelated, unlikely related, possibly related or probably related to the investigational product.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

The Investigator will assess causality of the event in relation to study drugs based on the following defined criteria:

- UNRELATED: No relationship between the event and medicinal product
- UNLIKELY: Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible); Disease or other drugs provide plausible explanations
- POSSIBLY: Event or laboratory test abnormality, with reasonable time relationship to drug intake; Could also be explained by disease or other drugs; Information on drug withdrawal may be lacking or unclear
- PROBABLY: Event or laboratory test abnormality, with reasonable time relationship to drug intake; Unlikely to be attributed to disease or other drugs; Response to withdrawal clinically reasonable; Rechallenge not required

8.9 Exposure during Pregnancy

For investigational products and for marketed products, an exposure during pregnancy (also referred to as exposure in-utero [EIU]) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (e.g., environmental exposure) the investigational product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product (maternal exposure);
2. A male has been exposed, either due to treatment or environmental exposure, to the investigational product prior to or around the time of his partner's conception and/or is exposed during his partner's pregnancy (paternal exposure).

If any study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, no further study drugs should be given, and the investigator must submit this information to Iterum Therapeutics' designated pharmacovigilance provider (Medpace Safety) on a Pregnancy Form.

This reporting must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all Pregnancy reports with an unknown outcome. The investigator will follow the pregnancy until reporting of birth or until pregnancy termination (i.e., induced abortion) and then notify Iterum of the outcome. The investigator will provide this information as a follow up to the initial Pregnancy Form. The reason(s) for an induced abortion should be specified. A Pregnancy report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, an SAE case is created with the event of ectopic pregnancy.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth or neonatal death]), the investigator should follow the procedures for reporting SAEs.

In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (i.e., no minimum follow-up period of a presumably normal infant is required before a Pregnancy Form can be completed). The "normality" of an aborted fetus can be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly.

Additional information about pregnancy outcomes that are classified as SAEs follows:

- "Spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 1 month that the investigator assesses as possibly related to the exposure during pregnancy to the investigational medication should be reported.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis

(e.g., follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator must obtain permission from the patient's partner in order to conduct any follow-up or collect any information.

8.10 Discontinuation from Study Drug Due to AEs (See also Patient Withdrawal, Section 6.5)

Discontinuation from study drug due to an AE should be distinguished from discontinuation due to insufficient response, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient discontinues study drug due to an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.11 Eliciting AE Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient through the Final Visit. In addition, each study patient will be questioned about the occurrence of any AEs.

8.12 Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs that is considered by the investigator or the Sponsor to be at least possibly related to study drug, expedited reporting will follow local and international regulations, as appropriate.

8.12.1 SAE Reporting Requirements

If an SAE or exposure during pregnancy occurs, Iterum Therapeutics' designated pharmacovigilance provider (Medpace Safety) is to be notified within 24 hours of awareness of the event by the investigator electronically in the EDC system for the study. When the form in EDC is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at medpace-safetynotifications@medpace.com or call the Medpace SAE reporting line (phone number listed below), and fax/email the completed paper SAE form to Medpace within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available. If the SAE is fatal or life-threatening, notification to Iterum must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of Pregnancy cases.

In the rare instance that the investigator does not become aware of the occurrence of an SAE immediately (e.g., if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs and pregnancies, the investigator is obligated to pursue and provide information to Iterum in accordance with the timeframes for reporting specified above. In addition, an

investigator may be requested by Iterum Therapeutics' designated pharmacovigilance provider (Medpace Safety) to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the SAE form. In general, this information may include hospital discharge summary, laboratory test and X-ray results. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Iterum Therapeutics' designated pharmacovigilance provider (Medpace Safety). The information should be reported on an SAE/Pregnancy form and sent to Iterum Therapeutics' designated pharmacovigilance provider (Medpace Safety).

8.12.2 Non-SAE Reporting Requirements

All AEs/SAEs will be reported on the AE page(s) of the CRF. Adverse events should be reported using concise medical terminology on the CRFs.

8.12.3 Sponsor Reporting Requirements to Regulatory Authorities

Adverse event reporting, including reporting of Suspected, Unexpected Serious Adverse Reactions (SUSARs), will be carried out in accordance with applicable local regulations. Death and life-threatening SUSARs are subject to expedited reporting within a 7-calendar day (life-threatening and fatal) or 15 calendar day (all other SUSARs) timeframe.

9 DATA ANALYSIS/STATISTICAL METHODS

9.1 Sample Size Determination

The study is designed to determine whether oral sulopenem is 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 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 and amoxicillin/clavulanate groups assumed to be 58% in this population.

One blinded interim analysis for sample size re-estimation is planned (See Section 9.7).

9.2 Definition of Analysis Populations

1. **Intent-to-Treat (ITT)**: all randomized patients regardless of whether or not the patient received study drug
2. **Modified ITT (MITT)**: randomized patients who received at least a single dose of study medication. Patients will be analyzed according to the treatment to which they were randomized.
3. **Safety**: randomized patients who received at least a single dose of study medication. Patients will be analyzed according to the treatment that they received.
4. **Micro-MITT**: All MITT patients with a positive study entry urine culture defined as $\geq 10^5$ CFU/mL of a uropathogen (Enterobacterales or *Staphylococcus saprophyticus* only) and no more than 2 species of microorganisms identified in the study entry urine culture, regardless of colony count.
5. **Micro-MITTS**: All micro-MITT patients with a baseline uropathogen susceptible (defined as MIC $\leq$8/4 mg/L) to the comparator drug, amoxicillin/clavulanate, and no baseline pathogen non-susceptible to amoxicillin/clavulanate.
6. **Micro-MITTR**: All micro-MITT patients with a baseline uropathogen non-susceptible [intermediate (MIC 16/8 mg/L) or resistant (MIC $\geq$ 32/16 mg/L)] to the comparator drug, amoxicillin/clavulanate.
7. **Clinically Evaluable: Clinically Evaluable (CE) at the Day 5 (+1 day), Day 12 (±1 day)/TOC, and Day 28 (±2 days) visits population:**
   All patients who were included in the MITT population and:
   a) Received a minimum number of days of study drug (to be defined in the SAP)
   b) Had no important protocol deviations that would affect the assessment of efficacy (to be defined in the SAP)
   c) Had a clinical outcome assessment at the relevant visit and the assessment was within the protocol allowed visit window.
   d) Had not received antibacterial drug therapy potentially effective as treatment of uUTI within 7 days prior to study entry
   e) Did not receive any antibiotic therapy with potential activity against any of the baseline uropathogens collected at Baseline between the time of the baseline culture and the Day 5 (+1 day) or Day 12 (±1 day)/TOC culture, respectively. This excludes the protocol defined study therapy and patients who were considered clinical failures and required additional rescue antibiotic therapy. Patients with a 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).
8. **Microbiologically evaluable (ME):** all patients included in both the micro-MITT and CE populations at the Day 5 (+1 day) visit (ME-Day 5), Day 12 (±1 day)/TOC visit (ME-Day 12) and at the Day 28 (±2 days) visit (ME-Day28) and have an appropriately

collected urine culture specimen and interpretable urine culture result at the Day 5 (+1 day), Day 12 (±1 day)/TOC and Day 28 (±2 days) visits, respectively.

Amoxicillin/clavulanate breakpoints as per CLSI (M100 Performance Standards for Antimicrobial Susceptibility Testing, 32nd edition).

9.3 General Statistical Considerations

Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided. All comparisons will be for the oral sulopenem treatment group and the amoxicillin/clavulanate treatment group. Exploratory analyses may also be performed. Listings of individual patient's data will be produced.

9.4 Patient Characteristics

Enrollment, protocol deviations, discontinuations from the study drug and withdrawal from the study will be summarized by treatment group. Demographics (age, race, sex), medical history, baseline assessment of the symptoms of uUTI, microbiological assessment of the urine, and study drug administration will also be summarized.

9.5 Efficacy Analysis

For all efficacy analyses, patient data will be analyzed in the treatment group to which the patient was randomized.

9.5.1 Analysis of Primary Outcome Measure

The primary efficacy outcome is overall success (combined clinical and microbiologic success) at Day 12 (± 1 day)/TOC in the micro-MITT, micro-MITTS and micro-MITTR populations.

Patients will be programmatically categorized as a success, failure, or indeterminate based on data in the eCRF and from the microbiology lab. Patients with missing data or who are lost to follow-up are defined as indeterminate for the primary analyses and are included in the denominator for the calculation of the success rate. 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. From a regulatory perspective, these results will help put into context the outcomes in the culture and susceptibility-driven subpopulations.

The primary comparisons for regulatory approval 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 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 testing, 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:

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

where p_1 is the primary efficacy outcome rate in the oral sulopenem group, p_2 is the primary efficacy outcome rate in the amoxicillin/clavulanate group, and Δ is the non-inferiority margin of 10.0%.

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 rate (oral sulopenem 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 -10.0%, the null hypothesis will be rejected and the NI of oral sulopenem to amoxicillin/clavulanate will be concluded.

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

Micro-MITTS population: the subset of the micro-MITT population in which the baseline pathogen is determined to be susceptible to the comparator study drug, amoxicillin/clavulanate. For this population, a NI test of the overall success rate will be conducted. The null and alternative hypotheses are as follows:

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

A 2-sided 95% CI for the observed treatment difference in success rates will be determined. If the lower bound of the 95% CI is greater than -10.0%, the null hypothesis will be rejected and the NI of oral sulopenem to amoxicillin/clavulanate in the micro-MITTS population will be concluded.

Micro-MITTR population: the subset of the micro-MITT population in which the baseline pathogen is determined to be non-susceptible to the comparator study drug, amoxicillin/clavulanate. For this population, a superiority test will be conducted. The null and alternative hypotheses are as follows:

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

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. If the lower bound of the 95% CI is greater than 0%, the null hypothesis will be rejected and superiority of oral sulopenem to amoxicillin/clavulanate will be concluded in the micro-MITTR population.

Each of the 2 null hypotheses in this step will be tested at the 2.5% level and if either hypothesis is rejected, then testing will proceed to the next step.

(3) Superiority test of overall success, $H_0: p_1 = p_2$ and $H_A: p_1 \neq p_2$, in the micro-MITT population. If the lower bound of the 95% CI (calculated for the hypothesis test in (1) is greater than 0%, the null hypothesis will be rejected and the superiority of oral sulopenem to amoxicillin/clavulanate in the micro-MITT population will be concluded.

9.5.2 Additional Analyses of the Primary Efficacy Outcome

Sensitivity analyses of the primary outcome will be conducted in the micro-MITT, micro-MITTS and micro-MITTR populations. An analysis will consider all patients who have missing data for the primary outcome (i.e., an indeterminate response) as successes. A 2-sided 95% unstratified CI will be computed for the difference in the success rates between the treatment groups. A sensitivity analysis applying multiple imputation methods for missing data will be conducted. A sensitivity analysis based on results of whole genome sequencing to confirm susceptibility testing results will also be conducted. An analysis of the overall response at Day 12 (±1 day)/TOC may be performed after adjusting for covariates.

Additional sub-group analyses, such as the effect of food or based on baseline variables including geographic region if applicable, may be conducted as exploratory analyses.

9.5.3 Analysis of Secondary Efficacy Outcome Measure

The number and percentage of patients in each treatment group with a clinical response of success, failure and indeterminate at Day 12 (±1 day)/TOC will be presented for the MITT, micro-MITT, micro-MITTS, and micro-MITTR populations. The number and percentage of patients in each treatment group with a clinical response of success and failure at Day 12 (±1 day)/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 for descriptive purposes; no conclusion of NI will be made.

The number and percentage of patients in each treatment group with asymptomatic bacteriuria at Day 12 (±1 day)/TOC will be presented for the micro-MITT, micro-MITTS, micro-MITTR and ME populations. The difference in rate of asymptomatic bacteriuria (oral sulopenem group minus the amoxicillin/clavulanate group) will be determined and 2-sided 95% unstratified CIs will be constructed for the observed difference between the treatment groups for descriptive purposes; no conclusion of NI will be made.

The number and percentage of patients in each treatment group with a microbiologic response of success, failure and indeterminate at Day 12 (±1 day)/TOC will be presented for the micro-MITT, micro-MITTS, and micro-MITTR populations. The number and percentage of patients in each treatment group with a microbiologic response of success and failure at Day 12 (±1 day)/TOC will be presented for the ME populations. 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.

9.5.4 Analyses of Additional Efficacy Outcome Measures

The number and percentage of patients in each treatment group with a clinical response of success, failure and indeterminate at Day 5 (+1 day), and Day 28 (±2 days) will be presented for the MITT, micro-MITT, micro-MITTS, and micro-MITTR populations. The number and percentage of patients in each treatment group with a clinical response of success and failure at Day 5 (+1 day), and Day 28 (±2 days) 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 for descriptive purposes; no conclusion of NI will be made.

The number and percentage of patients in each treatment group with asymptomatic bacteriuria at Day 5 (+1 day), and Day 28 (±2 days) will be presented for the micro-MITT, micro-MITTS, micro-MITTR and ME populations. The difference in rate of asymptomatic bacteriuria (oral sulopenem group minus the amoxicillin/clavulanate group) will be determined and 2-sided 95% unstratified CIs will be constructed for the observed difference between the treatment groups for descriptive purposes; no conclusion of NI will be made.

The number and percentage of patients in each treatment group with a microbiologic response of success, failure and indeterminate at Day 5 (+1 day), and Day 28 (±2 days) will be presented for the micro-MITT, micro-MITTS, and micro-MITTR populations. The number and percentage of patients in each treatment group with a microbiologic response of success and failure at Day 5 (+1 day), and Day 28 (±2 days) 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.

The number and percentage of patients in each treatment group with an overall response of success, failure and indeterminate at Day 5 (+1 day), and Day 28 (±2 days) will be presented for the micro-MITT, micro-MITTS and micro-MITTR populations. The number and percentage of patients in each treatment group with an overall response of success and failure at Day 5 (+1 day), Day 12 (±1 day)/TOC and Day 28 (±2 days) will be presented for the ME population. 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.

Investigator determined clinical response (clinical success, failure and indeterminate) at the Day 5 (+1 day), Day 12 (±1 day)/TOC, and Day 28 (±2 days) visits will be presented by treatment group for the MITT, micro-MITT, micro-MITTS, micro-MITTR, and the respective 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.

A shift table of the severity of each uUTI symptom based on the Patient Symptom Assessment Questionnaire from baseline to Day 5 (+1 day), Day 12 (±1 day)/TOC, Day 28 (±2 days) and relevant unscheduled visits will be provided by treatment group for the micro-MITTS and micro-MITTR populations.

Overall success, clinical success, and microbiologic success at the Day 5 (+1 day), Day 12 (±1 day)/TOC and Day 28 (±2 days) visits by baseline pathogen (key pathogens) will be summarized by treatment group in the micro-MITT, micro-MITTS, micro-MITTR and ME populations.

The number and percentage of patients in each treatment group with a microbiologic response of complete eradication (defined as no growth of baseline pathogen on a follow-up urine culture at

Day 12 (±1 day)/TOC) will also be presented for the micro-MITT, micro-MITTS, micro-MITTR and ME populations.

The number and percentage of patients in each treatment group with a microbiologic response of complete eradication (defined as no growth of baseline pathogen on a follow-up urine culture at Day 12 (±1 day)/TOC) and monomicrobial infection will also be presented for the micro-MITT, micro-MITTS, micro-MITTR and ME populations.

An assessment of the impact of antibiotic therapy on the *in vitro* susceptibility of study uropathogens (Enterobacterales and *S. saprophyticus*) identified at baseline will be performed at the D12 (±1 day)/TOC and Day 28 (±2 days) visits in order to determine if study drug selected for organisms with higher MIC's.

An assessment of overall response by baseline uropathogen resistance class(es) will be presented in each treatment group for the micro-MITT, micro-MITTS, micro-MITTR and ME populations.

Sub-group analyses, such as the effect of food, may be conducted for selected secondary safety and efficacy outcomes as exploratory analyses.

9.6 Safety Analyses

Safety will be assessed through summaries of AEs, clinical laboratory tests, and vital signs. All safety analyses will be based on 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.

Adverse events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA). Summary tables of treatment-emergent AEs (TEAEs) will be provided. A TEAE is any AE that newly appeared or worsened in severity following initiation of study drug. The incidence of TEAEs will be tabulated by system organ class (SOC) and preferred term (PT) for each treatment group, by SOC, PT and severity and by SOC, PT and relationship to treatment. Tables of TEAEs leading to study drug discontinuation, withdrawal from the study or an SAE will be provided. AEs occurring prior to the first dose of study drug (AEs are recorded from the time of informed consent) will be provided in a listing.

Descriptive statistics summarizing central laboratory data (hematology and chemistry) will be presented for the Baseline and Day 12 (± 1 day)/TOC study visits. The change from baseline to each post-baseline visit and to the overall worst post-baseline value will also be summarized by treatment group. Laboratory values will be classified as potentially clinically significant and the number and percentage of patients with a PCS lab value will be summarized by visit and treatment group. Descriptive statistics of the vital signs will be presented by treatment group for the Baseline, Day 5 (+1 day), and Day 12 (± 1 day)/TOC study visits, as well as the change from baseline at the Day 5 (+1 day) and Day 12 (± 1 day)/TOC study visits.

9.7 Interim Analysis

To ensure that the point estimate of overall success (combined clinical and microbiologic success) used in the estimation of sample size, and 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 Day 12 (± 1 day)/TOC are available for approximately 50% of the patients (approximately 983 patients). The FDA Guidance "Non-inferiority Clinical Trials" [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. The sample size of the study will be computed to ensure that there is sufficient power for determining whether oral sulopenem 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 and micro-MITTR populations as well. 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 ITT population in the micro-MITT population), higher- than-expected rate of asymptomatic bacteriuria or lower than expected percentage of patients with a susceptible pathogen. 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 (micro-MITT population)
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)
3. Determine the overall success rate and overall rate of asymptomatic bacteriuria 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 and overall rate of asymptomatic bacteriuria
    a. If NO, then increase the sample size in the micro-MITTS population to have sufficient power, up to a maximum number of 2500 patients.
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 by the DMC to assess if the study should continue. Further details of how the DMC will decide to do the futility analysis, how the sponsor will be involved and how the analysis will be conducted will be provided in the SAP and the DMC charter.

9.8 Handling of Missing Data

Details of the handling of missing data will be provided in the SAP. For the primary and secondary efficacy analyses, if any data field needed to determine overall response (primary) and microbiological response (secondary) is missing at the Day 12 (±1 day)/TOC (primary) and Day 28 (±2 days) (secondary) visit, the patient will be considered an indeterminate response. By definition, patients with an indeterminate response are included in the denominator in the micro-MITT population and thus, are analyzed in the same manner as failures in the primary and secondary analyses. Additional sensitivity analyses for handling missing data will be detailed in the SAP. Imputation may be performed to understand the impact of any imbalance

in indeterminate outcomes between treatment regimens. By definition, patients with missing data are excluded from the CE and ME populations.

10 QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Iterum or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Iterum monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the institutional review board (IRB)/independent ethics committee (IEC), and/or to quality assurance audits performed by Iterum, or companies working with or on behalf of Iterum, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits, or inspections and that sufficient time is devoted to the process.

11 DATA HANDLING AND RECORD KEEPING

11.1 Case Report Forms / Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Iterum and should not be made available in any form to third parties, except for authorized representatives of Iterum or appropriate regulatory authorities, without written permission from Iterum.

The investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, laboratory data entered on the CRFs and any other data collection forms. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs and source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

11.2 Record Retention

To enable evaluations and/or audits from regulatory authorities or Iterum, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, SAE forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone call reports). The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Iterum should be prospectively notified. The study records must be transferred to a designee acceptable to Iterum, such as another investigator, another institution, or to Iterum. The investigator must obtain Iterum's written permission before disposing of any records, even if retention requirements have been met.

12 ETHICS

12.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Iterum.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/IEC and Iterum in writing immediately after the implementation.

12.2 Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Patients, adopted by the General Assembly of the World Medical Association (2013).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonisation (ICH) guideline on Good Clinical Practice (GCP), and applicable local regulatory requirements and laws.

12.3 Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by law. In case of data transfer, Iterum will maintain high standards of confidentiality and protection of patient personal data.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Iterum before use.

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. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

12.4 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator becomes aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Iterum should be informed immediately.

In addition, the investigator will inform Iterum immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13 DEFINITION OF END OF STUDY

13.1 End of Study in all Participating Countries

End of Study in all participating countries is defined as the last patient's Final Visit.

14 SPONSOR STUDY TERMINATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Iterum. In addition, Iterum retains the right to discontinue development of sulopenem at any time.

If a study is prematurely terminated, Iterum will promptly notify the investigator and the investigator must also inform the IRB/IEC. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within 90 days. As directed by Iterum, all study materials must be collected and all CRFs completed to the greatest extent possible.

15 PUBLICATION OF STUDY RESULTS

Publication of study results is outlined in the Clinical Study Agreement.

15.1 Communication of Results by Iterum

Iterum fulfills its commitment to publicly disclose the results of studies through registration and posting of the results of this study on clinicaltrials.gov and EudraCT (eudract.ema.europa.eu) as applicable.

15.2 Publications by Investigators

Iterum has no objection to publication by the Investigator of any information collected or generated by the Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, the Investigator will provide Iterum an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Iterum at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The Investigator will, on request, remove any previously undisclosed Confidential Information (other than the study results themselves) before disclosure.

If the study is part of a multi-center study, the Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the Investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Iterum and the Institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16 REFERENCE LIST

Banerjee R and Johnson JR. A New Clone Sweeps Clean: the Enigmatic Emergence of *Escherichia coli* Sequence Type 131. AAC 2014:58:4997-5004.

Brannon JR, Dunigan TL, Beebout CJ, et al. Invasion of vaginal epithelial cells by uropathogenic *Escherichia coli*. Nature Communications 2020;11:2803.

Brumfitt W, and Hamilton-Miller JMT. Amoxicillin plus clavulanic acid in the treatment of recurrent urinary tract infections. Antimicrob Agents Chemother 1984;25(2):276-278.

CLSI M100-ED32:2022 Performance Standards for Antimicrobial Susceptibility Testing, 32nd Edition.

Cooper J, Raeburn AL, Brumfitt W, and Hamilton-Miller JMT. General practitioner study: Fosfomycin trometamol versus amoxycillin clavulanate in acute urinary tract infections. Chemother 1990:36(suppl 1):24-26.

Critchley IA, Cotroneo N, Pucci MJ, Mendes R (2019) The burden of antimicrobial resistance among urinary tract isolates of *Escherichia coli* in the United States in 2017. *PLoS ONE* 14(12): e0220265. https://doi.org/10.1371/ journal.pone.0220265

Dunne MW, Aronin SI, Yu KC, Watts JA, and Gupta V. A multicenter analysis of trends in resistance in urinary Enterobacterales isolates from ambulatory patients in the United States: 2011-2020. BMC Infect Dis 2022;22:194. https://doi.org/10.1186/s12879-022-07167-y.

Dunne MW, Puttagunta S, Aronin SI, Brossette S, Murray J, Gupta V. Impact of empirical antibiotic therapy on outcomes of outpatient urinary tract infection due to nonsusceptible Enterobacterales. Microbiology Spectrum 2022;10(1):e02359-21.

Edowik Y, Caspari T, Williams HM. The Amino Acid Changes T55A, A273P and R277C in the Beta-Lactamase CTX-M-14 Render E. coli Resistant to the Antibiotic Nitrofurantoin, a First-Line Treatment of Urinary Tract Infections. Microorganisms. 2020; 8(12).

Foulds G, Knirsch A, Lazar J, et al. Pharmacokinetics of the penem CP 65,207 and its separate stereoisomers in humans. Antimicrob Agents Chemother 1991;35:665 71.

Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. AAC 1993;37:1073-1081.

Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, Soper DE; Infectious Diseases Society of America; European Society for Microbiology and Infectious Diseases. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011 Mar 1;52(5):e103-20. doi: 10.1093/cid/ciq257. PMID: 21292654.

Gurwith MJ, Stein GE, and Gurwith D. Prospective comparison of amoxicillin-clavulanic acid and cefaclor in treatment of uncomplicated urinary tract infections. Antimicrob Agents Chemother 1983;24(5):716-719.

Hooten TM, Scholes D, Gupta K, Stapleton AE, Roberts PL, Stamm WE. Amoxicillin-clavulanate vs ciprofloxacin for the treatment of uncomplicated cystitis in women. A randomized trial. JAMA 2005; 293:949-955.

Hooton TM, Roberts PL, Stapleton AE. Cefpodoxime vs ciprofloxacin for short-course treatment of acute uncomplicated cystitis. A Randomized Trial. JAMA 2012;307:583-589.

Huttner A, et al. Effect of 5-day nitrofurantoin vs single-dose fosfomycin on clinical resolution of uncomplicated lower urinary tract infection in women. JAMA. 2018;319(17):1781-1789. doi:10.1001/jama.2018.3627.

Kaye KS, et al. Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection: The TANGO I Randomized Clinical Trial. JAMA 2018;319(8):788-799. doi: 10.1001/jama.2018.0438. PMID: 29486041; PMCID: PMC5838656.

Kaye KS, Gupta V, Mulgirigama A, Joshi AV, Scangarella-Oman NE, Yu K, Ye G, Mitrani-Gold FS. Antimicrobial Resistance Trends in Urine *Escherichia coli* Isolates From Adult and Adolescent Females in the United States From 2011 to 2019: Rising ESBL Strains and Impact on Patient Management. Clin Infect Dis. 2021 Dec 6;73(11):1992-1999. doi: 10.1093/cid/ciab560. PMID: 34143881; PMCID: PMC8664433.

Lan KKG, and Wittes, J. The B-value: A tool for monitoring data. Biometrics 1988; 44: 579-585

Le VVH, Rakonjac J (2021) Nitrofurans: Revival of an "old" drug class in the fight against antibiotic resistance. PLoS Pathog 17(7): e1009663. https://doi.org/10.1371/journal.ppat.1009663

Martinez-Casanova J, Gomez-Zorilla S, Prim N, et al. Risk Factors for Amoxicillin-Clavulanate Resistance in Community-Onset Urinary Tract Infections Caused by *Escherichia coli* or *Klebsiella pneumoniae*: The Role of Prior Exposure to Fluoroquinolones. Antibiotics 2021, 10, 582.

Mehta CR and Pocock SJ. Adaptive increase in sample size when interim results are promising: A practical guide with examples. Statist. Med. 2011, 30 3267–3284.

Munoz-Davila MJ. Role of old antibiotics in the era of antibiotic resistance. Antibiotics 2014; 3:39-48.

National Institute for Health and Care Excellence. Urinary tract infection (lower): antimicrobial prescribing guideline. Evidence review for NICE Guideline. October 2018.

Paterson DL. "Collateral damage" from cephalosporin or quinolone antibiotic therapy. Clin Infect Dis 2004; 38(Suppl. 4):S341–5.

Ramphal R, Ambrose PG. Extended-spectrum b-lactamases and clinical outcomes: current data. Clin Infect Dis 2006; 42(Suppl. 4):S164–72.

Sanchez GV, Master RN, Karlowsky JA, Bordon JM. *In vitro* antimicrobial resistance of urinary *Escherichia coli* isolates among U.S. outpatients from 2000 to 2010. Antimicrob Agents Chemother 2012; 56:2181–3.

Schito GC, Naber KG, Botto H, Palou J, Mazzei T, Gualco L, Marchese A. The ARESC study: an international survey on the antimicrobial resistance of pathogens involved in uncomplicated urinary tract infections. Int J Antimicrob Agents. 2009 Nov;34(5):407-13. doi: 10.1016/j.ijantimicag.2009.04.012. Epub 2009 Jun 7. PMID: 19505803.

Thomas-White K, Forster SC, Kumar N, et al. Culturing of female bladder bacteria reveals an interconnected urogenital microbiota. Nature Communications 2018;9:1557 DOI: 10.1038/s41467-018-03968-5.

US Department of Health and Human Services. Non-inferiority Clinical Trials to Establish Effectiveness. Guidance for Industry. Washington, DC: US Food and Drug Administration; Clinical/Medical. November 2016.

Wagenlehner FM, et al. Ceftazidime-avibactam Versus Doripenem for the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis: RECAPTURE, a Phase 3 Randomized Trial Program. *Clinical Infectious Diseases* 2016;63(6):754762; https://doi.org/10.1093/cid/ciw378.

Wagenlehner FME, et al. Once-Daily Plazomicin for Complicated Urinary Tract Infections. N Engl J Med 2019;380:729-40. DOI: 10.1056/NEJMoa1801467.

Westfall PH, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. Journal of Statistical Planning and Inference 2001; 99:25-40.

Zhanel GG, et al. In vitro activity of sulopenem and comparative agents against bacterial pathogens isolated from Canadian patients with urinary tract infections: CANWARD surveillance study 2014-2020. Poster presentation World Microbe Forum, June 2021.

APPENDIX 1 RATIONALE FOR AMOXICILLIN/CLAVULANATE AS COMPARATOR IN UNCOMPLICATED UTI TRIAL

Amoxicillin/clavulanate is an oral antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the β-lactamase inhibitor, clavulanate (the potassium salt of clavulanic acid). The formulation of amoxicillin and clavulanic acid protects amoxicillin from degradation by β-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other β-lactam antibiotics.
Amoxicillin/clavulanate has activity against gram-positive and gram-negative aerobes and anaerobes, including the following Enterobacterales responsible for the majority of cases of uUTI: *E. coli*, *Klebsiella* species, and *Proteus mirabilis*. FDA-approved indications for amoxicillin/clavulanate include treatment of urinary tract infections, lower respiratory tract infections, otitis media, sinusitis, and skin and skin structure infections [Augmentin USPI].
Amoxicillin/clavulanate is also approved in Europe for the treatment of UTI and is still the most prescribed antimicrobial (in 26.5% of the cases) to treat community-onset UTI in some European countries [Martinez-Casanova 2021].
Amoxicillin/clavulanate was chosen as the comparator for Study IT001-310 because it is an approved antibiotic for the indication of urinary tract infection [Augmentin USPI], it is considered as a treatment option for acute uUTI in the IDSA Treatment Guideline [Gupta 2011], and as a β-lactam antibiotic, it is likely to have a similar effect to sulopenem on the female urogenital microbiome, thus allowing for a fair comparison of efficacy. The dose of amoxicillin/clavulanate (875 mg/125 mg PO twice daily) was chosen to justify the use of amoxicillin/clavulanate CLSI breakpoints for uncomplicated urinary tract infection (M100 Performance Standards for Antimicrobial Susceptibility Testing, 32nd edition).
1. Per the approved label [Augmentin USPI], amoxicillin/clavulanate is an approved antibiotic for the indication of urinary tract infection.

> ***'Indication:***
> ***Urinary Tract Infections*** *– caused by β-lactamase–producing strains of E. coli, Klebsiella spp., and Enterobacter spp.*
> *While AUGMENTIN is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with AUGMENTIN due to its amoxicillin content; therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase–producing organisms susceptible to AUGMENTIN should not require the addition of another antibiotic.'*
>
> ***'Dosage Adults:*** *The usual adult dose is one 500-mg tablet of AUGMENTIN every 12 hours or one 250-mg tablet of AUGMENTIN every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be one 875-mg tablet of AUGMENTIN every 12 hours or one 500-mg tablet of AUGMENTIN every 8 hours.'*

Based on the Guidance for "Non-inferiority clinical trials to establish effectiveness" amoxicillin/clavulanate is therefore an approved agent to use as a comparator in a noninferiority trial for patients with urinary tract infection.
2. Amoxicillin/clavulanate is listed as a treatment option in the IDSA Treatment Guidelines [Gupta, 2011].

> 'β-Lactam agents, including amoxicillin/clavulanate, cefdinir, Cefaclor, and cefpodoxime-proxetil, in 3-7-day regimens are appropriate choices for therapy when other recommended agents cannot be used (B -1). Other β-lactams, such as cephalexin, are less well studied but may also be appropriate in certain settings (B-III).'

It is important to understand that the IDSA Treatment Guidelines were last updated in 2010 (published in 2011). At that time, the authors aimed to balance issues of *in vitro* resistance and collateral damage (a term describing ecological adverse effects of antimicrobial therapy, such as the selection of drug-resistant organisms and colonization or infection with multidrug-resistant organisms) when making their recommendations for optimal and alternative treatment options. At that time, rising rates of resistance to quinolones and trimethoprim-sulfamethoxazole (TMP-SMX) had been shown for outpatient urinary isolates 2000-2010 [Sanchez 2012], and increased collateral damage was found to be associated with broad-spectrum cephalosporins and quinolones [Paterson 2004; Ramphal 2006]. As shown in the Table below, pivmecillinam, a β-lactam, had the lowest estimated clinical and microbiological efficacy of all the optimal and alternative treatment agents in the IDSA Guideline, yet it was listed as an optimal choice given its low resistance rates and low propensity to cause collateral damage. Other β-lactams were listed as alternative agents, yet their estimated clinical and microbiologic efficacy was higher than pivmecillinam and comparable to fosfomycin, both listed as optimal agents. High resistance rates were noted for β-lactams, specifically ampicillin and amoxicillin, and high propensity to cause collateral damage was noted, specifically for broad-spectrum cephalosporins. Ciprofloxacin had one of the highest efficacy rates observed, an estimated clinical and microbiological efficacy of 90% and 91%, respectively, but was listed as an alternative agent due to rising resistance rates and its high propensity to cause collateral damage.

Table 2 Comparison of Optimal and Alternative Treatment Regimens, IDSA Guidelines

Antibiotic / Class	Dose	Estimated clinical efficacy, Mean % (range)	Estimated microbiological efficacy Mean %, (range)	Efficacy Comments	Estimated *E. coli* Resistance Rate, 2011	Resistance Comments	Propensity to Cause Collateral Damage
Optimal Treatment Options							
Nitrofurantoin	100 mg BID x 5-7d	93 (84-95)	88 (86-92)	Efficacy comparable to 3 days of TMP-SMX	1.6-4.8%	Minimal resistance	Minimal propensity for collateral damage
TMP-SMX	160/800 mg BID x 3d	93 (90-100)	94 (91-100)	Favorable efficacy as assessed in numerous clinical trials	24.2-27.7%	Appropriate choice if local resistance rates of uropathogens causing acute uncomplicated cystitis do not exceed 20%	Has been demonstrated to significantly affect the normal fecal flora, but generally not thought to have a propensity for collateral damage
Fosfomycin	3 gm single dose sachet	91 (NA)	80 (78-83)	Appears to have inferior efficacy compared with standard short-course regimens	1.9% (ex-US data)	Minimal resistance	Minimal propensity for collateral damage

Pivmecillinam	400 mg BID x 3-7d	73 (55-82)	79 (74-84)	May have inferior efficacy compared with other available therapies	4.2% (ex-US data)	Minimal resistance	Minimal propensity for collateral damage
Alternative antimicrobial choices							
Quinolones	Dose varies by agent; 3-d regimen	90 (85-98)	91 (81-98)	Highly efficacious	17.1–26%	Rising rates of resistance	Propensity for collateral damage
β-lactams	Dose varies by agent; 3-5d regimen	89 (79-98)	82 (74-98)	Generally, have inferior efficacy	43.4-50.3%	High rates of resistance for ampicillin and amoxicillin	Propensity for broad-spectrum cephalosporins to cause collateral damage

Source: Schito 2009; Gupta 2011; Sanchez 2012; Kaye 2021; Dunne 2022

The IDSA Treatment Guideline specifically warned against the empiric use of TMP-SMX for acute cystitis if local resistance rates of uropathogens causing acute uncomplicated cystitis exceeded 20%. Due to the resistance rates at the time, a similar recommendation was not made for other agents, but it has since become a common clinical practice to apply this 20% threshold to local resistance data in order to guide empiric therapy for patients with acute uncomplicated cystitis.

Since the 2011 IDSA Treatment Guidelines were written, resistance rates have exceeded or approached the 20% threshold for quinolones and nitrofurantoin, respectively. For nitrofurantoin, resistance to *E. coli* is approximately 4%, but nitrofurantoin resistance rates for Enterobacterales other than *E. coli* are markedly elevated (88-100% for *Proteus mirabilis*, 58-63.0% for *Klebsiella pneumoniae*, and approximately 57% for all other Enterobacterales) making the empirical use of this agent problematic [Huttner 2018, Zhanel 2021, Dunne 2022].

Rising nitrofurantoin resistance rates are likely a direct consequence of increased nitrofurantoin utilization in response to high TMP-SMX and quinolone resistance rates. In one United Kingdom location, the authors believe that increased exposure of *E. coli* to nitrofurantoin resulted in the emergence of a mutated version of the ESBL CTX-M-14 enzyme. When this mutated CTX-M-14 enzyme was recombinantly overexpressed in a laboratory strain of *E. coli*, a strain emerged that was hyper-resistant to nitrofurantoin while retaining β-lactam resistance [Edowik 2021]. Given that globally CTX-M-14 is one of the predominant ESBL types [Banerjee 2014], over time with continued *E. coli* exposure to nitrofurantoin, selection for this nitrofurantoin-resistant mutant is likely [Le 2021].

To add to the complexity, there has been a rapid increase in both the rate of ESBL-producing pathogens, and the rate of co-resistance to two or more standard agents [Critchley 2019, Kaye 2021, Dunne 2022].

Resistance rates for amoxicillin/clavulanate are not provided in the IDSA Guidelines. As shown in Table 3 below, based on the results of Study IT001-301, the expected rate of resistance to amoxicillin/clavulanate is less than to quinolones and TMP-SMX, and comparable to nitrofurantoin. These findings, in conjunction with what is known about clinical response, microbiologic response, and propensity to cause collateral damage for uUTI patients treated with amoxicillin/clavulanate, support the use of amoxicillin/clavulanate as a safe and effective comparator in a non-inferiority uUTI trial.

Table 3 Resistance Rate for Baseline Pathogen(s), IT001-301

Antibiotic/Class	Resistance Rate n (%) N=1071
Amoxicillin/clavulanate	**205 (19.1)**
Nitrofurantoin	**192 (17.9)**
Trimethoprim-sulfamethoxazole	**338 (31.6)**
Ciprofloxacin	**293 (27.4)**

Source: IT001-301 CSR; posthoc Table 198

While amoxicillin/clavulanate is listed as a treatment option in the 2011 IDSA Guidelines, and the document provides useful historical information to help guide the management of patients with suspected and confirmed acute uncomplicated cystitis, the Guidelines are outdated, not based on efficacy alone, and cannot be relied upon to steer the choice of a comparator agent for a non-inferiority trial in uUTI in 2022.

A more recent antimicrobial prescribing guideline for lower UTI from the National Institute for Health and Care Excellence published in October 2018 indicates that the efficacy of β-lactams is not significantly different than that compared to nitrofurantoin, trimethoprim-sulfamethoxazole or quinolones based on a large meta-analysis of randomized controlled trials [NICE Guideline 2018].

3. Availability of data regarding the degree of asymptomatic bacteriuria:

In Study IT001-301, sulopenem was not non-inferior to ciprofloxacin in patients whose baseline uropathogen was susceptible to ciprofloxacin. The difference in response rates was driven almost exclusively by a greater proportion of asymptomatic patients with the baseline uropathogen isolated at the test of cure visit in patients who received sulopenem. The presence of asymptomatic bacteriuria a week or more after completing therapy was not associated with a higher rate of clinical relapse, making it likely that the presence of pathogens in the urine culture was not a reflection of incomplete eradication of the offending baseline organism and more likely due to recolonization of the bladder.
A possible explanation why asymptomatic bacteriuria would occur sooner post-treatment for patients receiving sulopenem than for those receiving ciprofloxacin is that ciprofloxacin has a more significant impact on the vaginal flora than a β-lactam such as sulopenem, and that this effect on the vaginal flora affects the rate at which women recolonize the bladder. Similar observations have been made in two previous studies of the treatment of uncomplicated urinary tract infection and recently in a mouse model of urinary tract infection [Hooton 2005, Hooton 2012, Brannon 2020]. The area under the curve (AUC) of ciprofloxacin in plasma over 24 hours after a 250 mg bid dose is approximately 9.6 µg • h/mL [Cipro USPI]. An AUC_{24}/MIC of approximately 125 is the ratio required for achieving clinical and microbiologic success with ciprofloxacin [Forrest 1993] and this ratio would be achieved for

organisms with an MIC of <0.06 µg/mL. Consistent with this potential effect, and assuming tissue concentrations are equal to plasma, a lower rate of asymptomatic bacteriuria was only seen in those ciprofloxacin-treated patients whose baseline uropathogen had an MIC of <0.06 mg/mL. This effect would be relevant not for organisms residing in the urine as the urine concentrations of ciprofloxacin are significantly higher than plasma, but rather for those organisms in the colonizing flora of the perineum and vaginal mucosa, a potential source of organisms for recolonization of the bladder [Thomas-White 2018, Brannon 2020].

This concentration dependent effect of ciprofloxacin on the vaginal flora would also carry with it the potential for selection of increasingly more resistant pathogens in the post-treatment flora. In Study IT001-301, 35/415 (8.4%) patients without culture evidence of a ciprofloxacin resistant pathogen at baseline had a ciprofloxacin resistant pathogen in their urine culture post-treatment. More worrisome was that many of these ciprofloxacin resistant isolates also carried the blaCTX-M-15 extended spectrum β-lactamase resistance gene, a commonly circulating plasmid among *E. coli* [Banerjee 2014], making treatment in the future with either a quinolone or a β-lactam other than a penem less likely to be successful.

While the antibiotic effect on a woman's vaginal flora, and subsequently the rate of bladder recolonization, is likely a class effect, other host factors and mechanisms may be at play, and the association between specific antibiotics and post-treatment asymptomatic bacteriuria is not known. This makes it challenging to confidently choose a comparator in a noninferiority trail, as long as microbiologic outcome remains part of the primary endpoint. It is reasonable to assume that a β-lactam comparator such as amoxicillin/clavulanate will have a similar effect to sulopenem on the urogenital microbiome, thus allowing for a fair comparison of efficacy. Additional data from Study IT001-302 supports using amoxicillin/clavulanate as the comparator. As shown in Table 4 below, in Study IT001-302, a higher incidence of asymptomatic bacteriuria was observed in complicated UTI patients receiving sulopenem. This difference in the proportion of patients with asymptomatic bacteriuria was observed primarily among the patients who had ciprofloxacin-susceptible uropathogens and, per protocol, received ciprofloxacin as step-down treatment. Of the patients who received IV sulopenem and stepped down to oral sulopenem, 21.8% failed due to asymptomatic bacteriuria at TOC compared to just 4.7% of those who received IV ertapenem and stepped down to oral ciprofloxacin. Of the patients with ciprofloxacin-nonsusceptible uropathogens, those in the ertapenem group, depending on their clinical status, either received their entire treatment course IV or were stepped down to amoxicillin/clavulanate. The rate of asymptomatic bacteriuria as the reason for failure among these patients was similar to that of sulopenem patients, supporting the use of amoxicillin/clavulanate as the comparator in our planned uncomplicated UTI noninferiority trial.

Table 4 Overall Response at TOC by Stepdown Category, IT001-302, micro-MITT Population

Outcome	Sulopenem n (%)	Ertapenem n (%)	Difference (%), (95% CI)
All patients			
Primary Endpoint: Overall Success (TOC)	301/444 (67.8)	325/440 (73.9)	-6.1 (-12.0, -0.1)
Reason for failure: Asymptomatic bacteriuria	93 (20.9)	59 (13.4)	
Patients with ciprofloxacin susceptible isolates by treatment regimen			
	Sulopenem IV / oral Sulopenem n (%)	Ertapenem IV / oral ciprofloxacin n (%)	
Overall Success	168/248 (67.7)	186/215 (86.5)	-18.8 (-26.1, -11.0)
Reason for failure: Asymptomatic bacteriuria	54 (21.8)	10 (4.7)	
	Sulopenem IV	Ertapenem IV (n=26) or Ertapenem IV / oral Amoxicillin/clavulanate (n=6)	
Overall Success	19/34 (55.9)	17/32 (53.1)	2.8 (-20.9, 26.2)
Reason for failure: Asymptomatic bacteriuria	7 (20.6)	7 (21.9)	
Patients with ciprofloxacin non-susceptible isolates by treatment regimen			
	Sulopenem IV only or Sulopenem IV / Sulopenem-Etzadroxil + Probenecid n (%)	Ertapenem IV only or Ertapenem IV / Amoxicillin/clavulanate n (%)	
Overall Success	114/162 (70.4)	122/193 (63.2)	7.2 (-2.7, 16.8)
Reason for failure: Asymptomatic bacteriuria	32 (19.8)	42 (21.8)	

Source: IT001-302 CSR

Further support for the degree and rate of post-treatment asymptomatic bacteria being a class effect comes from the fact that efficacy rates for sulopenem in IT001-302 are consistent with those seen for other IV penems in recent cUTI trials where step-down to an oral agent was not allowed [Wagenlehner 2016, Kaye 2018, Wagenlehner 2019]. These approved penems have proven to be effective life-saving drugs.

In conclusion, amoxicillin/clavulanate is an appropriate comparator for our proposed non-inferiority trial in patients with uUTI. It is an FDA-approved agent for the treatment of UTI,

there is support for its use in the IDSA Treatment Guidelines and the 2018 NICE Guidelines, and of the potential oral comparator agents, it has a predictable impact on the female urogenital microbiome. Amoxicillin/clavulanate breakpoints as per CLSI (M100 Performance Standards for Antimicrobial Susceptibility Testing, 32nd edition).

REFERENCES:

See Reference List in Section 16 above.

APPENDIX 2 SCHEDULE OF STUDY ASSESSMENTS

	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 3 MICROBIOLOGY

Method of Collection of Urine Specimens:
To obtain a clean catch sample of urine from a female patient and avoid specimen contamination, a thorough cleansing of the periurethral area is essential before specimen collection. Clean the area with a disinfectant and make all efforts to avoid any contact until urination is complete. Urine samples should be collected by clean-catch midstream. Details of appropriate methodology for urine sample collection, handling, and storage will be provided in the laboratory manual.

All patients should void the first part of the specimen into the toilet, then collect the remainder of the specimen in a sterile container. Urine samples for routine culture must be transported in the urine transport tubes provided by the Sponsor.

If feasible, urine specimens should be collected 4 hours after the last void.

Culture and Susceptibility testing

All gram-negative pathogens and *S. saprophyticus* will be tested by the Central laboratory for antimicrobial susceptibility.

The Central laboratory should retain all isolates until the end of the study, if possible. Additional samples for culture may be requested if the Central laboratory does not receive a viable culture.

Susceptibility results of pathogens to amoxicillin/clavulanate and carbapenems from cultures obtained at Screening, EOT, and TOC should not be reported to sites/investigators until after the TOC visit, unless requested by the Principal Investigator and clinically warranted, so as not to influence the investigator's decision to prescribe a rescue antibiotic in the case of presence of a non-susceptible pathogen.

Organisms considered as pathogens

For the purpose of this study protocol, the following organisms will always be considered a pathogen when isolated from an acceptable urine culture specimen:

- Monomicrobial or polymicrobial infections caused by:
  - Enterobacterales
  - Enterococci
  - *Pseudomonas aeruginosa*
  - *S. saprophyticus*

  The micro-MITT population for this study will only include patients with uUTI caused by Enterobacterales and/or *S. saprophyticus.*
- Even if the organism was isolated from an acceptable urine culture specimen, the following are never a pathogen for this study:
  - *Corynebacterium* spp.
  - *S. epidermidis*
  - *S. aureus*
  - *Bacillus* spp.
  - Diphtheroids

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

- A study urine culture positive for more than 2 species of microorganisms, regardless of colony count, will be considered contaminated.

All isolates not defined above will be assessed on a case-by-case basis via manual review by the Sponsor. If needed, patient clinical and microbiological information will be used to assist in determining if the isolate is a pathogen.

Based on the results of *in vitro* testing, animal studies, PK/PD modeling, surveillance programs and clinical trial data, a provisional breakpoint for susceptibility of sulopenem to Enterobacterales, Streptococci and methicillin-susceptible *Staphylococcus aureus* is ≤ 0.5 µg/mL. Tentative disc diffusion interpretive criteria are available for sulopenem. A detailed description of the relevant microbiology data is available in the investigator brochure.

APPENDIX 4 CRITERIA FOR SAFETY LABORATORY 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 5 SUMMARY OF CHANGES

Appendix 5.1 Amendment 1

Minor editorial revisions that have been made for ease of reading, formatting, spelling, grammar, and consistency are not included in this summary of changes.

Section	Change
Study Population Selection (Section 4, page 35)	Female patients who present with uUTI, defined by symptoms and a urinalysis suggestive of a uUTI per Section 4.1~~positive for pyuria~~, and who meet all of the inclusion and none of the exclusion criteria will be eligible for participation in this study. ***Rationale:*** To align with changes made to Section 4.1 below.
Inclusion Criteria (Synopsis and Section 4.1, page 35)	1. Female patients ≥18 years of age with ≥24 hours and ≤96 hours of urinary symptoms attributable to a UTI 2. Two of the following signs and symptoms of uUTI: urinary frequency, urinary urgency, pain or burning on micturition, suprapubic pain 3. A mid-stream urine specimen with: a. a machine-read dipstick positive for nitrite AND any positive leukocyte esterase OR b. evidence of pyuria alone as defined by either: i. a machine-read dipstick positive for large leukocyte 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 4. Has given written informed consent to participate in the study ***Rationale:*** To optimize enrollment of patients with the disease under study and to increase successful collection of a positive urine culture for ≥100,000 CFU/mL of a uropathogen.
Women of Child-Bearing Potential (Section 4.5, page 38)	She must agree to continue all of these contraceptive methods until the last Study Visit. Within these limits, the specific forms of contraception employed are left to the discretion of the patient, and/or the principal investigator, and/or the patient's physician and documented in source. ***Rationale:*** To improve clarity regarding site documentation of forms of contraception for women of child-bearing potential.

Administration (Synopsis and Section 5.2.3, page 39)	Patients randomized to the sulopenem treatment group will take one sulopenem etzadroxil/probenecid tablet and one placebo capsule twice daily for 5 days and those randomized to the amoxicillin/clavulanate treatment group will take one over-encapsulated amoxicillin/clavulanate tablet and one placebo tablet twice daily for 5 days (10 doses total over a 5-day period; if Dose 1 is taken in the evening of Day 1, Dose 10 will be taken in the morning of Day 6). The first dose of each medication will be administered under the supervision of study site personnel to help ensure compliance with dosing directions. Study drug administration will be documented in accordance with the Pharmacy Manual. ***Rationale:*** To improve clarity regarding administration of study medications.
Appendix 2 (page 78)	Study Drug Treatment X (BID x 10 doses total~~for 5 days~~) ***Rationale:*** To improve clarity regarding administration of study medications. [3]Day 1 and Screening are generally on the same day. ***Rationale:*** To improve clarity regarding timing of Day 1 in relation to Screening activities.
Appendix 4 (page 81)	~~Calcium <0.9 or >1.1 times the limits of the reference range~~ ***Rationale:*** To clarify list of safety laboratory tests being performed.

APPENDIX 6 INVESTIGATOR'S SIGNATURE

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*
Final Date:	July 7, 2022
Amendment 1 Date:	December 5, 2022

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol. I understand the study protocol and will conduct the study according to the procedures therein and according to the principles of good clinical practice.

Name: _____

Signature: _____ **Date:** _____