Clinical Trial Protocol: IT001-301

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 ciprofloxacin for treatment of uncomplicated urinary tract infections in adult women.
Study Number:	IT001-301
Study Phase:	Phase 3
Product Name:	sulopenem etzadroxil/probenecid (PF-03709270/probenecid)
IND Number:	129,849
EudraCT Number	2017-003771-57
Indication:	Uncomplicated urinary tract infection
Investigators:	Multicenter
Sponsor:	Iterum Therapeutics US Limited
Sponsor Contact:	Sailaja Puttagunta
Sponsor's Legal Representative:	Iterum Therapeutics US Limited 20 Research Parkway, Suite A Old Saybrook, CT 06475
Medical Monitor:	Steven Aronin, M.D Email: saronin@iterumtx.com
Pharmacovigilance Contact	PSI Pharmacovigilance Email: SafetyDesk@psi-cro.com

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Original Draft Protocol	August 1, 2017
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Confidentiality Statement

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SYNOPSIS

Sponsor:

Iterum Therapeutics US Limited

Name of Finished Product:

Sulopenem etzadroxil/probenecid (PF-03709270/probenecid)

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 ciprofloxacin for treatment of uncomplicated urinary tract infections (uUTI) in adult women.

Study Number:

IT001-301

Study Phase: Phase 3

Primary Objective(s):

To compare the overall response of oral sulopenem etzadroxil/probenecid versus oral ciprofloxacin for the treatment of uncomplicated urinary tract infection in adult women at the primary time-point.

Secondary Objective(s):

a) To compare the overall response (clinical and microbiologic combined response) at other relevant time-points.

b) To compare the microbiologic efficacy across treatment groups.

c) To compare the clinical efficacy outcomes of oral sulopenem etzadroxil/probenecid versus oral ciprofloxacin at other relevant time points

d) To compare the safety profile of treatment with oral sulopenem etzadroxil/probenecid versus oral ciprofloxacin for treatment of uncomplicated urinary tract infection in adult women.

e) To assess the population PK profile of oral sulopenem etzadroxil/probenecid.

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 Enterobacteriaceae including those that encode Extended Spectrum Beta-lactamase (ESBL) or AmpC-type β-lactamases that confer resistance to third generation cephalosporins. Sulopenem etzadroxil is expected to be the first

oral penem 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 prospective Phase 3, randomized, multicenter, double-blind, controlled study compares oral sulopenem etzadroxil/probenecid to oral ciprofloxacin for the treatment of patients with uUTI. Approximately 1,128 adult women with uUTI will be randomized in a 1:1 fashion to receive either a bilayer tablet with sulopenem etzadroxil 500 mg/probenecid 500 mg twice daily for 5 days or oral ciprofloxacin 250 mg twice daily for 3 days.

The primary outcome measure for efficacy evaluation will be the overall success (combined clinical and microbiologic success) on Day 12 (± 1 day).

For the primary efficacy evaluations, these percentages will be compared in two subsets of the microbiologic-modified intent to treat population (micro-MITT): 1) where the baseline pathogen is determined to be susceptible (ciprofloxacin MIC ≤ 1 mg/L) to the comparator study drug, ciprofloxacin (micro-MITTS population), and 2) where the baseline pathogen is determined to be non-susceptible/resistant (ciprofloxacin MIC ≥ 2 mg/L; includes strains with intermediate susceptibility and resistance to ciprofloxacin) to the comparator study drug, ciprofloxacin (micro-MITTR population). 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 (Enterobacteriaceae and *Staphylococcus saprophyticus* only) isolated from a urine culture specimen taken at baseline, prior to initiation of study drug therapy.

Study Population:

A total of approximately 1,128 patients are planned. The sample size may be adjusted at the blinded interim analyses (one at 33% of planned sample size and the other at 66% of planned or original sample size) if the baseline assumptions for overall success rate, evaluability rate and susceptibility rate are not met, which, specifically, are an overall success rate of 79%, the proportion of ITT patients eligible to be included in the micro-MITT population of 80%, and a susceptibility rate of 80%. The sample size may also be adjusted at an unblinded interim analysis (66% of randomized patients) based on the conditional power analysis in the micro-MITTR population.

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, gross hematuria
3. A mid-stream urine specimen with:
    a. a dipstick analysis positive for nitrite

AND, in the same urine specimen

b. evidence of pyuria as defined by either:

i. a dipstick analysis positive for leukocyte esterase AND/OR

ii. at least 10 white blood cells per cubic millimeter on microscopic analysis of unspun urine AND/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 3 days, unless the recovered pathogen demonstrates resistance to the initial antibiotic (other than quinolone or penem antibiotics) and clinical symptoms persist
3. Causative uropathogen for the presenting illness known to be resistant to a carbapenem
4. Patients requiring concurrent use of non-study treatments that would have a potential effect on outcome evaluations in patients with uUTI, including analgesics (e.g., non-steroidal anti-inflammatory drugs, aspirin, paracetamol etc.), phenazopyridine, and cranberry products
5. Patients with ileal loops or urinary stoma
6. Patients with an indwelling urinary catheter in the previous 30 days
7. Patients with paraplegia
8. Patients who are likely to receive ongoing antibacterial drug prophylaxis after treatment of uUTI (e.g., patients with vesico-ureteral reflux)
9. Any history of trauma to the pelvis or urinary tract
10. Patient's urine culture results, if available at study entry, identify more than 2 microorganisms regardless of colony count or patient has a confirmed fungal UTI
11. Patient is receiving hemodialysis, peritoneal dialysis or had a renal transplant
12. Creatinine clearance <50 mL/min as calculated by Cockcroft and Gault equation (Appendix 3)
13. Patient known to be immunocompromised (e.g. absolute neutrophil count [ANC] < 500 cells/mm^3, human immunodeficiency virus (HIV) infected patients with a CD4 cell count < 200 cells/mm^3, patients with a bone marrow/organ transplant in the 3 months prior to study enrollment, patients receiving oral steroids > 20 mg prednisolone per day [or equivalent] or receiving immunosuppressant drugs after bone marrow/organ

transplantation)

14. Patients known to have a history of liver disease as defined by the following laboratory criteria:
    - ALT or AST > 3 X Upper Limit of Normal
    - Total bilirubin > 1.5 X Upper Limit of Normal
15. Patients who are pregnant
16. Patients with uncontrolled Diabetes mellitus (defined as the presence of ketoacidosis, hyperosmolar hyperglycemia, random or fasting serum glucose ≥ 250 mg/dL at screening)
17. History of seizures
18. Patients with a history of blood dyscrasias
19. Patients with a history of uric acid kidney stones
20. Patients with acute gouty attack
21. Patients on chronic methotrexate therapy
22. Patients with a known history of myasthenia gravis
23. Patients who require concomitant administration of tizanidine or valproic acid
24. Patients with a history of allergy or hypersensitivity to carbapenems, β-lactams, quinolones or probenecid, as formulated with their excipients
25. Patient is considered 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
26. 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

Test Product, Dose, and Mode of Administration:

Patients will be randomized to receive either a bilayer tablet with sulopenem etzadroxil 500 mg/probenecid 500 mg PO twice daily for 5 days or oral ciprofloxacin 250 mg PO twice daily for 3 days.

Other Systemic Antibiotics:

For *Clostridium difficile* infections, metronidazole (IV or oral) or oral vancomycin may be used in both treatment groups. Patients with a co-infection with a gram-positive uropathogen resistant to study drugs are allowed to receive agents with narrow spectrum gram-positive coverage (such as oral linezolid).

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 500 mg/probenecid 500 mg and one blister pack with 6 ciprofloxacin placebo capsules.

Comparator treatment group: The study drug will be supplied as a study kit containing one blister pack with 6 over-encapsulated ciprofloxacin 250 mg tablets, and one bottle with 10 placebo bilayer tablets to match sulopenem etzadroxil/probenecid tablets.

Preparation and Dispensing:

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

Administration:

Patients will take one tablet from the kit bottle twice daily (sulopenem etzadroxil/probenecid or placebo) for 5 days and they will take one capsule from the blister pack twice daily (over-encapsulated ciprofloxacin or placebo capsules) for 3 days. The first dose of each medication will be administered under the supervision of study site personnel to help ensure compliance with dosing directions.

Efficacy Assessments:
The assessment of clinical response includes a review of the following symptoms at the Baseline, Day 3, Day 5 (± 1 day), Day 12 (± 1 day), and Day 28 (± 2 days) visits or at premature discontinuation: urinary frequency, urinary urgency, pain or burning on micturition, suprapubic pain and gross hematuria.

Microbiologic response assessments will be made based on quantitative cultures performed on collected urine specimens at the Baseline, Day 3, Day 5 (± 1 day), Day 12 (± 1 day), and Day 28 (± 2 days) visits or at premature discontinuation.

Other Assessments:

Plasma samples for population PK evaluations will be collected in a subset of patients at selected study sites.

Safety Assessments:

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

Physical examination will be performed at the Baseline visit, and a targeted exam will be conducted if needed at Day 3, Day 5 (± 1 day), Day 12 (± 1 day), 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) 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 and at the Day 12 (± 1 day) visit, in follow-up of any clinically significant laboratory finding, as well as at premature discontinuation.

Statistical Methods:

Sample Size Considerations:

The study is designed to determine whether oral sulopenem etzadroxil/probenecid is non-inferior to oral ciprofloxacin for the outcome measure of overall success (combined clinical and microbiologic success) at Day 12 (± 1 day) in the micro-MITTS population and/or whether oral sulopenem etzadroxil/probenecid is superior to oral ciprofloxacin for overall success at Day 12 (± 1 day) 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 352 patients per arm (total sample size of 704 patients) based on the method of Farrington and Manning. This assumes a non-inferiority margin of 10%, a power of 90%, a one-sided alpha level of 0.025 and a 79% treatment success rate. With 99 patients per treatment group in the micro-MITTR population, there is 90% power to show superiority given a 75% and 52% overall success rate in the sulopenem etzadroxil/probenecid and ciprofloxacin groups, respectively. Assuming that 80% of the randomized patients will meet criteria for inclusion into the micro-MITT population (902 patients), the sample size for the ITT population is 1,128.

Two blinded interim analyses for sample size re-estimation, based on the pooled, blinded overall response as defined in the primary endpoint, will be conducted when 33% and 66% of the patients (approximately 372 and 745 patients, respectively) have clinical and microbiologic response data available (see Section 9.7) to assess overall success and evaluability rates. As indicated in the draft FDA Guidance "Adaptive Design and Clinical Trials for Drugs and Biologics", no statistical adjustment is required when a blinded analysis is completed of the overall event rate. Thus, the one-sided alpha level used for the sample size calculation is 0.025. The final sample size may be revised based on the observed overall success rate, the evaluability rate (proportion of MITT patients with a baseline pathogen) and the proportion of the micro-MITT population with a susceptible pathogen at the blinded interim analysis, to maintain a power of 90%.

An additional unblinded interim analysis for sample size re-estimation based on conditional power will be conducted when 66% of patients have clinical and microbiologic response data available to assess overall success rates in the micro-MITTR population (patients with a pathogen non-susceptible to comparator agent, ciprofloxacin). The alpha level does not need to be adjusted if the hypothesis test is not completed due to futility based on a conditional power of <40%.

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 etzadroxil/probenecid versus oral ciprofloxacin. Exploratory analyses may also be performed. Listings of individual patient's data will be produced.

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

Efficacy Analyses:

The study is designed to determine whether oral sulopenem etzadroxil/probenecid is NI to oral ciprofloxacin for the outcome measure of overall success (combined clinical and microbiologic success) at Day 12 (± 1 day) in the micro-MITTS population and/or whether oral sulopenem etzadroxil/probenecid is superior to oral ciprofloxacin for overall success at Day 12 (± 1 day) 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) demonstrates $<10^3$ CFU/mL of the baseline uropathogen

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-MITTS population and the micro-MITTR population. For each analysis population, the observed difference in the percentage of patients with success at Day 12 (± 1 day) (sulopenem etzadroxil/probenecid group minus the ciprofloxacin 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), is defined below.

The primary comparisons for regulatory approval are in two mutually exclusive populations 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, ciprofloxacin); and 2) the micro-MITTR population (the subset of the

micro-MITT population in which the baseline pathogen is determined to be non-susceptible {defined as MIC ≥2 mg/L; includes pathogens with intermediate susceptibility [2 mg/L] and resistance [≥4 mg/L]} to the comparator study drug, ciprofloxacin).

- NI test of overall success in the micro-MITTS population: the NI hypothesis test is a one-sided hypothesis test performed at the 2.5% level of significance. If the lower limit of the 95% CI for the difference in success rates in the micro-MITTS population is greater than -10% the NI of sulopenem etzadroxil/probenecid to the ciprofloxacin group will be concluded.
- Superiority test of overall success in the micro-MITTR population: the superiority hypothesis test is based on the lower limit of the two-sided 95% CI for the difference in success rates. If the lower limit of the CI is greater than 0, sulopenem etzadroxil/probenecid will be considered superior to ciprofloxacin.

If either NI is declared for the primary comparison in the micro-MITTS population or if superiority is established in the micro-MITTR population, then an NI test of overall success followed by a superiority test of overall success (if the null hypothesis is rejected for the NI test) in the micro-MITT population will be conducted. When testing in a sequential manner with pre-planned testing, no adjustment to the alpha level is required.

The number and percentage of patients with a microbiologic eradication, persistence, or persistence with increasing MIC at the Day 12 (±1 day) visit in each treatment group in the microbiologic evaluable (ME-Day 12) population will be determined. The observed difference in percentage of patients with a microbiologic eradication (sulopenem etzadroxil/probenecid group minus the ciprofloxacin group) will be determined and a 2-sided unstratified 95% CI for the observed difference will be computed using the method of Miettinen and Nurminen.

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.

Date of Original Approved Protocol: 062 March 2018

Date of Most Recent Protocol Amendment (if applicable): NA

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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
Cmax	Maximum concentration
CrCl	Creatinine Clearance
CRE	Carbapenem Resistant Enterobacteriaceae
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*
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
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
MeDRA	Medical Dictionary of Regulatory Activities
MIC	Minimal Inhibitory Concentration

MITT	Modified ITT
Micro-MITT	Microbiologic-MITT
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
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
uUTI	Uncomplicated urinary tract infection
WBC	White Blood Cell
2-EBA	2-Ethylbutryic Acid

1 INTRODUCTION

1.1 Indication

Sulopenem is 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 Enterobacteriaceae 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-sulphamethoxazole. 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-sulphamethoxazole 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]. Even with these limitations, almost two-thirds of patients with a uUTI receive therapy with a quinolone antibiotic. Efficacy outcomes for patients treated with quinolones for uUTI caused by quinolone non-susceptible pathogens are not known. The currently proposed study will compare the safety, tolerability and efficacy of oral sulopenem etzadroxil/probenecid versus oral ciprofloxacin for the treatment of uncomplicated urinary tract infection 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 Enterobacteriaceae 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 Enterobacteriaceae (CRE) were excluded from the analysis shown below, but the MIC_{90} of Enterobacteriaceae 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}	MIC_{90}
Enterobacteriaceae		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 subjects 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. Phase 2 studies in patients with urinary tract infection or intra-abdominal infection have not been conducted in the United States.

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, ciprofloxacin, in an era of significant antibacterial resistance to fluoroquinolones. The activity of sulopenem will be compared to ciprofloxacin in patients with organisms susceptible to ciprofloxacin, to provide a quantitative estimate of relative activity established by non-inferiority testing as well as in patients with organisms that are resistant to fluoroquinolones 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.

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.

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. Fourteen hundred and seventy-eight 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 are available in the respective Investigator's Brochures.

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-sulphamethoxazole among *Escherichia coli* is now > 20% in the United States (CDC summary data). However, quinolones continue to be the most prescribed category of medicines used to treat uUTI in the US.

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.

The current study will compare oral sulopenem etzadroxil/probenecid with oral ciprofloxacin for the treatment of patients with uUTI.

Rationale for probenecid

Probenecid is known to increase plasma levels of weak organic acids such as penicillins, cephalosporins, and other beta-lactam antibiotics, including penems, by competitively inhibiting their renal tubular secretion. Probenecid has been used safely with other beta-lactam antibiotics, to either reduce dose or dosing frequency of beta-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 etzadrozil 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 is encouraged, but not required.

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.

Ciprofloxacin

The recommended dose of 250 mg oral ciprofloxacin administered twice daily for 3 days for treatment of uncomplicated UTI, per the Ciprofloxacin USPI and Ciprofloxacin SmPC, will be used in this study.

For the full prescribing information for probenecid or ciprofloxacin, please refer to respective local country product labels (USPI or SmPC).

2 STUDY OBJECTIVES

2.1 Objectives

The primary objective of this study is to compare the overall response of oral sulopenem etzadroxil/probenecid versus oral ciprofloxacin for the treatment of uncomplicated urinary tract infection in adult women at the primary time-point.

The secondary objectives of this study are:

a) To compare the overall response (clinical and microbiologic combined response) at other relevant time-points

b) To compare the microbiologic success across treatment groups.

c) To compare the clinical efficacy outcomes of oral sulopenem etzadroxil/probenecid versus oral ciprofloxacin at relevant time points

d) To compare the safety profile of treatment with oral sulopenem etzadroxil/probenecid versus oral ciprofloxacin for treatment of uncomplicated urinary tract infection in adult women.

e) To assess the population PK profile of oral sulopenem etzadroxil/probenecid.

3 STUDY DESIGN

This prospective, Phase 3, randomized, multicenter, double-blind, controlled study compares oral sulopenem etzadroxil/probenecid with oral ciprofloxacin for the treatment of patients with uUTI. Approximately 1,128 adult women with uUTI will be randomized in a 1:1 fashion to receive either oral sulopenem etzadroxil 500mg/probenecid 500 mg twice daily for 5 days or oral ciprofloxacin 250 mg twice daily for 3 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-MITTS and micro-MITTR populations on Day 12 (± 1 day). A key secondary efficacy assessment will be the microbiologic response

(success [eradication], failure [persistence or persistence with increasing MIC] or indeterminate) on Day 12 (± 1 day). See Appendix 1, Schedule of Activities Table.

3.1 Investigational Study Medications

Patients will be randomized to receive either sulopenem etzadroxil 500 mg/probenecid 500 mg PO twice daily for 5 days or ciprofloxacin 250 mg PO twice daily for 3 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 500 mg/probenecid 500 mg and one blister pack with 6 ciprofloxacin placebo capsules.

Comparator treatment group: The study drug will be supplied as a study kit containing one blister pack with 6 over-encapsulated ciprofloxacin 250 mg tablets, and one bottle with 10 placebo bilayer tablets to match sulopenem etzadroxil/probenecid tablets.

3.2 Adjunctive Systemic Antibiotics

None allowed

3.3 Additional Non-Study Therapy Antibiotics

For *Clostridium difficile* infections, IV or oral metronidazole, or oral vancomycin may be used in both treatment groups (see Section 5.4.2 for further details).

Patients with a co-infection 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).

4 STUDY POPULATION SELECTION

Female patients who present with uUTI, defined by symptoms and a dipstick positive for leukocyte esterase and nitrite, 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, gross hematuria.

3. A mid-stream urine specimen with:

    a. a dipstick analysis positive for nitrite

    AND, in the same specimen

    b. evidence of pyuria as defined by either:

        i. a dipstick analysis positive for leukocyte esterase AND/OR

        ii. at least 10 white blood cells per cubic millimeter on microscopic analysis of unspun urine AND/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 3 days, unless the recovered pathogen demonstrates resistance to the initial antibiotic (other than quinolone or penem antibiotics) and clinical symptoms persist
3. Causative uropathogen for the presenting illness known to be resistant to a carbapenem
4. Patients requiring concurrent use of non-study treatments that would have a potential effect on outcome evaluations in patients with uUTI, including analgesics (e.g., non-steroidal anti-inflammatory drugs, aspirin, paracetamol etc.), phenazopyridine, and cranberry products
5. Patients with ileal loops or urinary stoma
6. Patients with an indwelling urinary catheter in the previous 30 days
7. Patients with paraplegia
8. Patients who are likely to receive ongoing antibacterial drug prophylaxis after treatment of uUTI (e.g., patients with vesico-ureteral reflux)
9. Any history of trauma to the pelvis or urinary tract
10. Patient's urine culture results, if available at study entry, identify more than 2 microorganisms regardless of colony count or patient has a confirmed fungal UTI
11. Patient is receiving hemodialysis, peritoneal dialysis or had a renal transplant

12. Creatinine clearance <50 mL/min as calculated by Cockcroft and Gault equation (Appendix 3)
13. Patient known to be immunocompromised (e.g. absolute neutrophil count [ANC] < 500 cells/mm^3, human immunodeficiency virus (HIV) infected patients with a CD4 cell count < 200 cells/mm^3, patients with a bone marrow/organ transplant in the 3 months prior to study enrollment, patients receiving oral steroids > 20 mg prednisolone per day [or equivalent] or receiving immunosuppressant drugs after bone marrow/organ transplantation)
14. Patients known to have a history of liver disease as defined by the following laboratory criteria:
    - ALT or AST > 3 X Upper Limit of Normal
    - Total bilirubin > 1.5 X Upper Limit of Normal
15. Patients who are pregnant
16. Patients with uncontrolled Diabetes mellitus (defined as the presence of ketoacidosis, hyperosmolar hyperglycemia, random or fasting serum glucose ≥ 250 mg/dL at screening)
17. History of seizures
18. Patients with a history of blood dyscrasias
19. Patients with a history of uric acid kidney stones
20. Patients with acute gouty attack
21. Patients on chronic methotrexate therapy
22. Patients with a known history of myasthenia gravis
23. Patients who require concomitant administration of tizanidine or valproic acid
24. Patients with a history of allergy or hypersensitivity to carbapenems, β-lactams, quinolones or probenecid, as formulated with their excipients
25. Patient is considered 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
26. The use of any other investigational drug in the 30 days prior to study to the first dose of study drug, or prior participation in any sulopenem clinical trial

4.3 Randomization Criteria

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

4.4 Life Style 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, she is required to simultaneously use 2 effective contraceptive methods, from the following list of 5:

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.

5 STUDY TREATMENTS

5.1 Allocation to Treatment

This is a randomized double-blind study comparing oral sulopenem etzadroxil/probenecid with oral ciprofloxacin in the treatment of uUTI. Approximately 1,128 patients will be randomized to receive either oral sulopenem etzadroxil/probenecid twice daily for 5 days or oral ciprofloxacin twice daily for 3 days in a 1:1 allocation ratio using an IWRS.

A patient will be eligible for randomization once it has been determined that she 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 receives the treatment assignment associated with the patient entered into the IWRS.

5.2 Drug Supplies

5.2.1 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 500 mg/probenecid 500 mg and one blister pack with 6 ciprofloxacin placebo capsules.

Comparator treatment group: The study drug will be supplied as a study kit containing one blister pack with 6 over-encapsulated ciprofloxacin 250 mg tablets, and one bottle with 10 placebo bilayer 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 will take one tablet from the kit bottle twice daily (sulopenem etzadroxil/probenecid or placebo) for 5 days and they will take one capsule from the blister pack twice daily (over-encapsulated ciprofloxacin or placebo capsules) for 3 days. The first dose of each medication will be administered under the supervision of study site personnel to help ensure compliance with dosing directions. In the event a patient's first dose is taken in the PM on Day 1, the patient will be expected to take an AM dose on Day 6 to complete the regimen.

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

Patients are encouraged, but not required, to take their study drug with food.

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 bottles and blister packs (used and unused) to the next scheduled study visit for drug accountability. The total amount of oral dosing completed (determined by tablet count from returned bottles and blister packs) will be recorded in the IWRS.

To enhance documentation of compliance, this study may employ a Health Insurance Portability and Accountability Act (HIPAA) compliant medication adherence monitoring platform

("Platform") for all subjects in the study. The Platform uses artificial intelligence on smartphones to confirm medication ingestion. In addition, built-in reminders and a communication system allow real-time intervention in case of drug interruptions. Complete details regarding this Platform will be provided to the sites.

A urine sample will be collected and frozen at the EOT visit if a need to confirm compliance with study drug therapy arises for any patient.

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 sulopenem etzadroxil/probenecid and ciprofloxacin. 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 Forms (CRF).

At each visit, the investigator/site designee will obtain information on any therapeutic interventions (e.g., drug and non-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 the Day 12 (± 1 day) visit.

The bioavailability of ciprofloxacin is significantly reduced when co-administered with magnesium or aluminum containing antacids. As a result, co-administration of these antacids with study drug is not permitted.

Dosing with food does not affect the overall absorption of ciprofloxacin.

5.4.2 Concomitant Antibacterial Medications

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

- Vancomycin oral 125 mg or 250 mg every 6 hours may be used in both treatment groups for the treatment of *Clostridium difficile* infections and may be continued as required throughout the duration of the study. The Sponsor will not provide oral vancomycin.
- Metronidazole IV or oral 500 mg every 8 hours may be used in both treatment groups for the treatment of *Clostridium difficile* infections and may be continued as required throughout the duration of the study. The Sponsor will not provide metronidazole.
- Patients with a co-infection 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).

5.4.3 Adjunctive Antibacterial Therapy

None allowed

5.4.4 Non-drug Adjunctive Therapy

None allowed

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. Sites participating in the population PK substudy should offer the PK sampling substudy and obtain written consent from willing patients. PK sampling procedures are detailed in Appendix 5.

The following procedures will be performed prior to randomization and study drug administration:

- Demographics and medical history.
- Targeted physical examination (including general appearance, examination of heart, lungs, abdomen, and extremities)
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate) and height and weight
- Blood for laboratory testing (including hematology and chemistry studies as well as urine or serum (βhCG) pregnancy test (women of child-bearing potential, including peri-menopausal women until FSH value is known); serum follicle stimulating hormone [FSH] for post-menopausal [amenorrheic for at least 1 year] females <50

years of age or those ≥50 years of age who have been post-menopausal [amenorrheic] for <2 years.

- Banked serum and urine for retrospective safety and efficacy assessments
- Collect urine for urinalysis and urine culture (including gram stain) and sensitivity
- Review previous drug and non-drug treatments (defined as within the prior 30 days) and concomitant drug treatments
- Adverse events occurring after signing of ICF
- Administer and collect patient symptom assessment questionnaire from patient (Appendix 4)

To prepare for trial participation, subjects will be instructed on the use of Life Style 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.
- Pharmacokinetic blood specimens: obtain at scheduled time.

6.2.1 Day 1

- Review concomitant medications
- Administer the study medication as described in Section 5.2.3
- Collect blood samples for PK analyses for patients in the PK substudy (Appendix 5)
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?

6.2.2 Day 3

- Targeted physical examination, if required, based on patient’s symptoms
- Collect urine for urinalysis and urine culture (including gram stain) and sensitivity
- Review concomitant medications
- Check and document compliance with study medication
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?
- Administer and collect patient symptom assessment questionnaire from patient (Appendix 4)

6.2.3 Day 5 (± 1 day) (End of Treatment/EOT)

- Targeted physical examination, if required, based on patient's symptoms
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate)
- Collect urine for urinalysis and urine culture (including gram stain) and sensitivity
- Review concomitant medications
- Check and document compliance with study medication
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?
- Administer and collect patient symptom assessment questionnaire from patient (Appendix 4)
- 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
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate)
- Blood for laboratory testing (including hematology and chemistry studies)
- Banked serum and urine for retrospective safety and efficacy assessments
- Collect urine for urinalysis and urine culture (including gram stain) and sensitivity
- Review concomitant medications
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?
- Administer and collect patient symptom assessment questionnaire from patient (Appendix 4)
- 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
- Collect urine for urinalysis and urine culture (including gram stain) and sensitivity, and pregnancy test
- Review concomitant medications
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?
- Administer and collect patient symptom assessment questionnaire from patient (Appendix 4)
- Investigator Assessment of Clinical Response (Section 7.2.4)

- Targeted physical examination, if required, based on patient's symptoms
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate)
- Blood for laboratory testing (including hematology and chemistry studies as well as urine or serum (βhCG) pregnancy test (women of child-bearing potential, including peri- menopausal women until FSH value is known); serum follicle stimulating hormone [FSH] for post-menopausal [amenorrheic for at least 1 year] 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 (including gram stain) and sensitivity
- Review concomitant medications
- Check and document compliance with study medication
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?
- Administer and collect patient symptom assessment questionnaire from patient (Appendix 4)
- Investigators 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 discontinue 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 discontinues 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.

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), 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 will 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 will 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) 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, C-reactive protein (CRP) and LDH at Baseline, Day 12 (± 1 day) or premature discontinuation.
- Urinalysis and urine culture (including gram stain) at Baseline, Day 3, Day 5 (± 1 day), Day 12 (± 1 day) and Day 28 (± 2 days) or premature discontinuation.
- Pregnancy Test (women of child-bearing potential)/serum FSH (for post-menopausal [amenorrheic for at least 1 year] females <50 years of age or those ≥50 years of age who have been post-menopausal for <2 years): Urine or serum (βhCG) only at Baseline; urine (βhCG) at Day 28 (± 2 days) and premature discontinuation; FSH at Baseline only, as needed. Pregnancy test at Baseline should also be performed on peri-menopausal women until FSH value is available.
- Serum and urine samples will be banked for retrospective safety and efficacy analyses as needed at Baseline and Day 12 (± 1 day).

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 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)
- Urine culture taken on Day 12 (± 1 day) demonstrates $<10^3$ CFU/mL of the baseline uropathogen (ie, microbiologic response of success [eradication])

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.

7.2.2 Microbiologic

Microbiologic Response is assessed using the definitions listed below:

Microbiological response	**Definition**
Success	The urine culture obtained at the Day 3 visit, Day 5 (± 1 day) visit, Day 12 (± 1 day) or Day 28 (± 2 days) visit demonstrates $<10^3$ CFU/mL of the baseline uropathogen; also referred to as eradication.

Microbiological response	Definition
Persistence	A uropathogen present at baseline grew at $\geq 10^3$ CFU/mL at the time-point of analysis, i.e. Day 3, Day 5 (± 1 day), Day 12 (± 1 day) or Day 28 (± 2 days).
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-fold higher MIC to study drug received at Day 3, Day 5 (± 1 day), Day 12 (± 1 day) or Day 28 (± 2 days), respectively.
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 either the Day 3, Day 5 (± 1 day), Day 12 (± 1 day) 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)

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 at Day 5 (± 1 day), Day 12 (± 1 day), 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 response	Definition
Clinical failure	Patients who met any one of the criteria below were considered as failure:
	Death related to uUTI prior to Day 5, Day 12, or Day 28, respectively
	Persistence or progression of any pre-therapy uUTI signs and symptoms or use of additional antibiotics for the current infection
	Patient previously met criteria for failure and received rescue antibiotics
Indeterminate	Data not available for evaluation of efficacy for any reason, including but not limited to:
	Patient lost to follow-up or assessment not undertaken such that a determination of clinical response could not be made at either the Day 5, Day 12 or Day 28 visit
	Death prior to Day 5, Day 12, or Day 28, respectively, 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 (Appendix 4).

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. 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 sequel 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 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 subject'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 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 completion 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 (Iterum's PV Service provider) is to be notified within 24 hours of awareness of the event by the investigator on an SAE form or Pregnancy form. 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 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. The information should be reported on an SAE/Pregnancy form and sent to the Iterum PV Service Provider.

8.12.2 Non-SAE Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. Please note that while all AEs are reported on the AE page of the CRF, there is an additional form used for collection of SAE information, as described in Section 8.12.1, which is not the same as the AE CRF. When the same data are collected, the two forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information. The information on the AE CRF and the SAE form must be the same and will be reconciled at defined periods throughout the study to ensure that they do.

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 etzadroxil/probenecid is NI to oral ciprofloxacin for the outcome measure of overall success (combined clinical and microbiologic success) at Day 12 (± 1 day) in the micro-MITTS population and/or whether oral sulopenem etzadroxil/probenecid is superior to oral ciprofloxacin for overall success at Day 12 (± 1 day) in the micro-MITTR population. The 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 352 patients per arm (total of 704 patients) based on the method of Farrington and Manning. This assumes a non-inferiority margin of 10%, a power of 90%, a one-sided alpha level of 0.025 and a 79% treatment success rate. With 99 patients per treatment group in the micro-MITTR population, there is 90% power to show superiority given a 75% and 52% overall success rate in the sulopenem etzadroxil/probenecid and ciprofloxacin groups, respectively. Assuming that 80% of the randomized patients will meet criteria for inclusion into the micro-MITT population (902 patients), the sample size for the ITT population is 1,128.

The expected treatment success rate is estimated from 2 large randomized controlled trials of quinolones in a similar patient population. In those studies, the estimated success rate for the proposed primary efficacy outcome measure of combined clinical and microbiologic success around Day 7 in the micro-MITT population was 88%. This was further corroborated by findings from a review of the summary basis of approval documents for ciprofloxacin XR and levofloxacin for the indication of uUTI, where the estimated number of patients with combined clinical and microbiologic cure rates in the microbiologically evaluable populations were noted to be between 88.4% and 92%. The overall success rate in uUTI studies that utilized complete resolution of uUTI symptoms to define clinical success was 80%. However, these studies defined microbiologic eradication as a follow up culture that yielded $<10^4$ CFU/mL of the baseline pathogen. The overall point estimate could be reduced by about 1% point if the definition of microbiologic eradication requires a follow up culture that yields $<10^3$ CFU/mL of the baseline pathogen, thus bringing the expected overall success rate in the subset of micro-MITTS population to 79%.

There are no recent studies in patients with uUTI caused by resistant pathogens to provide an estimate of the overall clinical success rate in this population. With 99 patients per treatment group in the micro-MITTR population, there is 90% power to show superiority given a 75% and 52% overall success rate in the sulopenem etzadroxil/probenecid and ciprofloxacin groups,

respectively.

The primary populations for this study are: the micro-MITTS population, defined as all randomized patients with a positive baseline urine culture defined as $\geq 10^5$ CFU/mL of a uropathogen (and no more than 2 species of microorganisms), with a pathogen susceptible (ciprofloxacin MIC ≤1 mg/L) to the comparator study drug, ciprofloxacin; and the micro-MITTR population defined as all randomized patients with a positive baseline urine culture defined as $\geq 10^5$ CFU/mL of a uropathogen (and no more than 2 species of microorganisms), with a pathogen non-susceptible (ciprofloxacin MIC ≥2 mg/L; includes strains with intermediate susceptibility and resistance to ciprofloxacin) to the comparator study drug, ciprofloxacin.

A review of the literature showed that only approximately 60% of symptomatic uUTI patients will have $\geq 10^5$ CFU/mL of a uropathogen. Thus, in order to optimize the enrollment of patients with $\geq 10^5$ CFU/mL of a uropathogen, the inclusion criteria were designed to require a urine dipstick analysis to be positive for nitrite in addition to having evidence of pyuria, as this has been shown to increase the sensitivity and specificity of enrolling patients with $\geq 10^5$ CFU/mL of a uropathogen to 84% and 98% respectively [Semeniuk 1999].

Two blinded interim analyses for sample size re-estimation and one unblinded interim analysis for sample size re-estimation are 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

3. **Safety**: randomized patients who received at least a single dose of study medication

4. **Micro-MITT**: All MITT patients with a positive study entry urine culture defined as $\geq 10^5$ CFU/mL of a uropathogen (Enterobacteriaceae 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 to the comparator drug, ciprofloxacin, and no baseline pathogen non-susceptible to ciprofloxacin.

6. **Micro-MITTR**: All micro-MITT patients with a baseline uropathogen non-susceptible (defined as MIC ≥2 mg/L) to the comparator drug, ciprofloxacin.

7. **Clinically Evaluable: Clinically Evaluable (CE) at the Day 5 and Day 12 visits population:**

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 an outcome assessment at the relevant visit and the assessment was within the protocol allowed visit window.

d) Had not received prior antibiotic before the initiation of study therapy for this infection unless the recovered pathogen demonstrates resistance to initial antibiotic (other than quinolone and carbapenems) and clinical symptoms persist

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 or Day 12 culture, respectively. This excludes the protocol defined study therapy and patients who were considered clinical failures and required additional 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)

f) Had a study entry urine culture obtained ≤48 hours before study drug administration

Clinically Evaluable (CE) at the FV population

All patients who:

a) Were included in the CE population at the Day 12 visit

b) Had an outcome assessment at the FV and the assessment was within the protocol allowed visit window

c) Had no important protocol deviations that would affect the assessment of efficacy (to be defined in the SAP).

d) Did not receive any antibiotic therapy with potential activity against any of the baseline uropathogen(s) collected at Baseline through the Day 28 visit, except resuming oral antibiotic prophylaxis therapy after the Day 12 urine culture was obtained. This does not include antibiotic therapy taken for the treatment of uUTI by patients who were considered investigator-assessed clinical failures.

8. **Microbiologically evaluable (ME):** all patients included in both the micro-MITT and CE populations at the Day 3 (ME-Day 3), Day 5 visit (ME-Day 5), Day 12 visit (ME-Day 12) and at the Day 28 visit (ME-Day28) and have an appropriately collected urine culture specimen and interpretable urine culture result at the Day 3, Day 5, Day 12 and Day 28 visits, respectively.

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 sulopenem etzadroxil/probenecid treatment group and the ciprofloxacin treatment group. Exploratory analyses may also be performed. Listings of individual patient's data will be produced. A comprehensive SAP will be finalized prior to the first interim analysis.

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 and surgical history, baseline assessment of the symptoms of uUTI, microbiological assessment of the urine, and study drug administration will also be summarized. Differences between treatment groups will be analyzed using the chi-square or Fisher's exact test for dichotomous variables and the Wilcoxon Rank Sum test for ordinal variables and continuous variables.

9.5 Efficacy Analysis

For all efficacy analyses, patient data will be analyzed in the treatment group to which the patient was randomized. Unless otherwise stated, for the ITT analyses, patients who were randomized to the wrong geographic region strata will be analyzed in the stratum to which they were 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) in the 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-MITTS and micro-MITTR populations.

The primary comparisons for regulatory approval are in two mutually exclusive populations 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, ciprofloxacin). 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 sulopenem etzadroxil/probenecid group, p_2 is the primary efficacy outcome rate in the ciprofloxacin group, and Δ is the non-inferiority margin of 10%.

The NI hypothesis test is a 1-sided hypothesis test performed at the 2.5% level of significance. This is based on the lower limit of the 2-sided 95% CI for the observed difference in the overall success rate (sulopenem etzadroxil/probenecid group minus ciprofloxacin 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-MITTS population is greater than -10%, the null hypothesis will be rejected and the NI of sulopenem etzadroxil/probenecid to ciprofloxacin will be concluded.

2) the 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, ciprofloxacin). 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% 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 sulopenem etzadroxil/probenecid to ciprofloxacin will be concluded.

9.5.1.1 Additional Hypothesis Testing of the Primary Outcome Measure

Additional hypothesis testing of the primary efficacy outcome will be conducted following the framework detailed below.

1) 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 continue testing hypotheses of the primary efficacy outcome. If NI or superiority is declared for the primary comparisons, the secondary comparisons will be statistically tested in the order presented 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. NI test of overall success, $H_{01} : p_1 - p_2 \leq -\Delta$ and $H_{A1} : p_1 - p_2 > -\Delta$, in the micro-MITT population. The number and percentage of subjects in each treatment group with an overall response of success, failure, and indeterminate will be provided for the micro-MITT population. 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%, the null hypothesis will be rejected and the NI of sulopenem etzadroxil/probenecid to ciprofloxacin in the micro-MITT population will be concluded.

2) Superiority test of overall success, $H_{02} : p_1 = p_2$ and $H_{A2} : p_1 \neq p_2$, 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 sulopenem etzadroxil/probenecid to ciprofloxacin in the micro-MITT population will be concluded.

9.5.1.2 Additional Analyses of the Primary Efficacy Outcome

The primary efficacy outcome will also be assessed within each geographic region stratum by treatment group. For each geographic region stratum, a 2-sided 95% CI for the observed difference in the overall success rates in the micro-MITTS and the micro-MITTR populations will be calculated.

Sensitivity analyses of the primary outcome will also be conducted in the micro-MITTS and micro-MITTR populations. An adjusted analysis (95% CI will be adjusted for the geographic region using the stratified method of Miettinen and Nurminen) will be provided for the difference in the overall success rate between the two treatment groups. Cochran-Mantel-Haenszel weights will be used for the stratum weights in the calculation of the CI. An analysis will consider all patients who have missing data for the primary outcome (ie, 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 also be conducted.

A sub-group analysis of the primary efficacy outcome in those patients with and without hypoalbuminemia (serum albumin <2.5 g/dL) at baseline will be conducted. Additional sub-group analyses, such as the effect of food, may be conducted as exploratory analyses.

9.5.2 Analysis of Secondary Efficacy Outcome Measure

The number and percentage of patients with a microbiologic response of success (eradication) or failure (persistence or persistence with increasing MIC), at the Day 12 (± 1 day) visit will be determined in each treatment group in the ME-Day 12 population. The observed difference in percentage of patients with microbiologic success (eradication) (sulopenem etzadroxil/probenecid group minus the ciprofloxacin group) will be determined and a 2-sided 95% CI for the observed difference will be computed using the unstratified method of Miettinen and Nurminen.

9.5.3 Analysis of Additional Efficacy Outcome Measures

The number and percentage of subjects in each treatment group with an overall response of success, failure and indeterminate at Day 3, Day 5, and Day 28 will be presented for the micro-MITT, micro-MITTS, and micro-MITTR populations. The number and percentage of subjects in each treatment group with an overall response of success and failure at Day 3, Day 5, Day 12 and Day 28 will be presented for the CE and ME populations. Two-sided 95% unstratified CIs will be constructed for the observed difference in the overall success rates between the treatment groups for descriptive purposes; no conclusion of NI will be made.

The number and percentage of subjects in each treatment group with a clinical response of success, failure and indeterminate at Day 3, Day 5, Day 12 and Day 28 will be presented for the micro-MITT, micro-MITTS, and micro-MITTR populations. The number and percentage of subjects in each treatment group with a clinical response of success and failure at Day 3, Day 5, Day 12 and Day 28 will be presented for the CE and ME populations. Two-sided 95% unstratified CIs will be constructed for the observed difference in the overall success rates between the treatment groups for descriptive purposes; no conclusion of NI will be made.

The number and percentage of subjects in each treatment group with a microbiologic response of success, failure and indeterminate at Day 3, Day 5, Day 12 and Day 28 will be presented for the micro-MITT, micro-MITTS, and micro-MITTR populations. The number and percentage of subjects in each treatment group with a microbiologic response of success and failure at Day 3, Day 5, Day 12 and Day 28 will be presented for the CE and ME populations. Two-sided 95% unstratified CIs will be constructed for the observed difference in the overall success rates between the treatment groups for descriptive purposes; no conclusion of NI will be made.

Investigator determined clinical response (clinical success, failure and indeterminate) at the Day 5, Day 12, and Day 28 Visits will be presented by treatment group for the micro-MITT, micro-MITTS, micro-MITTR, CE-Day12 and ME-Day12 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 3, Day 5, Day 12 and Day 28 will be provided by treatment group for the micro-MITTS and micro-MITTR populations.

Overall success and microbiologic success at the Day 5 and Day 12 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 subjects 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 will also be presented 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, increased in frequency, 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 all 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 and study visit, as well as the change from baseline at each study visit.

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 is valid for this study, two interim analyses for sample size re-estimation will be performed when response data at Day 12 (± 1 day) are available for approximately 33% and 66% of the patients (approximately 372 and 745 patients respectively). The FDA Guidance "Non-inferiority Clinical Trials" [FDA Guidance 2010] notes that such a sample size re-estimation if based on the blinded overall response rates is not only acceptable but is advisable. The interim analysis will involve a sample size re-estimation to either confirm the initial sample size estimate is adequate or increase the sample size (number of randomized patients) to ensure the study has adequate power for determining whether oral sulopenem etzadroxil/probenecid is NI to oral ciprofloxacin for the primary outcome measure in the micro-MITTS population. 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) or lower than expected percentage of subjects with a susceptible pathogen. The sample size re-estimation will be based on the blinded overall (not by treatment group) outcome and evaluability rates.

The blinded interim analyses 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, ciprofloxacin) pathogen (micro-MITTS population) and a non-susceptible (to ciprofloxacin) pathogen (micro-MITTR population)

3. Determine the overall success rate aggregated across treatment groups in the micro-MITTS population

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

a. If NO, then increase the sample size in the micro-MITTS population to have sufficient power, up to a maximum number of subjects.

In addition, the micro-MITT rate (i.e. evaluability rate) and proportion of subjects with a susceptible pathogen (micro-MITTS evaluability rate) will be used to determine the total number of subjects needed.

In order to determine whether the sample size is sufficient to determine if sulopenem etzadroxil/probenecid is superior to ciprofloxacin in the patients whose baseline pathogen is non-susceptible to ciprofloxacin, a conditional power analysis for the superiority hypothesis in the micro-MITTR population will be conducted when 66% of patients have been enrolled. A conditional power analysis using the approach of Lan and Wittes [Lan 1988] will be conducted to determine if the sample size needs to be adjusted. The sample size adjustment would be conducted as described by Mehta and Pocock [Mehta 2011]. If the conditional power is <40%, the superiority hypothesis in the micro-MITTR population will not be tested at the end of the study. If the conditional power is 40%-<80%, the sample size for micro-MITTR population will be calculated based on the observed overall success rates in each treatment group and increased to a maximum number. If the conditional power is ≥80%, no change to the sample size will be made. The final sample size in the ITT population will be adjusted to take into account the proportion of subjects in the micro-MITT population and the micro-MITTR population. No adjustment to the overall alpha level is needed if given a conditional power <40%, the superiority hypothesis is not conducted at the end of the study.

The sample size re-estimations will be conducted by an independent, unblinded statistician. A Data Monitoring Committee (DMC) will be provided the results of the interim analysis by the independent, unblinded statistician and make a recommendation regarding changes to the sample size. A detailed DMC charter will be developed which outlines the analyses to be completed, statistical rules, the potential changes to the sample size, and the recommendations that can be made to the Sponsor.

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 (primary) and Day 28 (secondary) visit, the patient will be considered an indeterminate response. By definition, patients with an indeterminate response are included in the denominator in the m-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 laws. 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 is 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 discussed 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.

If posting of study results to clinicaltrials.gov jeopardizes a planned publication of the study results, a Pending Full Publication notice is substituted for the synopsis until the study results publication has been issued or 2 years have elapsed, whichever occurs first.

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

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Appendix 1 Schedule of Activities

	SCREENING	TREATMENT PERIOD			FOLLOW-UP PERIOD		
Protocol Activity	**D-1 to D1** **Baseline**	**D1**	**D3**	**D5 (± 1 day) EOT**	**D12 (± 1 day) TOC**	**D28 (± 2 days) FV**	**Premature Discontinuation**
Informed Consent	X						
Medical History and Demographics	X						
Targeted Physical Examination	X		X[1]	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/FSH[2]	X					X	X
Banked serum sample	X				X		
Banked urine sample	X				X		
Urinalysis	X		X	X	X	X	X
Urine Culture and gram stain	X		X	X	X	X	X
Plasma PK sampling for CP-70,429[3]		X					
Previous Drug and Non-drug Treatments	X						
Concomitant Medications		X	X	X	X	X	X
Treatment		X (BID for 5 days)					
Treatment Compliance Check			X	X			X
Adverse Events	X	X	X	X	X	X	X
Patient Symptom Assessment Questionnaire	X		X	X	X	X	X
Investigator Assessment of Clinical Response				X	X	X	X

Schedule of Activities Footnotes:

[1] If needed, based on symptoms

[2] Baseline: Pregnancy test (women of childbearing potential) or serum FSH (to confirm post-menopausal status for 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; Day 28 or Premature Discontinuation: urine pregnancy test for women of childbearing potential only.

[3] In subset of patients enrolled in the PK substudy, collect plasma for PK analysis 2 hours, 4 hours, and 6 hours post-dose after first oral dose.

Appendix 2 Microbiology

Method of Collection of Urine Specimens:

To obtain a clean catch sample of urine from a female patient, a thorough cleansing of the periurethral area is essential before specimen collection. Wash the area with a disinfectant and make all efforts to avoid any contact until urination is complete.

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 will be tested locally for antimicrobial susceptibility, as appropriate.

The local laboratory should retain all isolates until the end of the study, if possible, or until confirmation of a viable organism is received from the central laboratory. Back-up cultures will be requested when the central laboratory does not receive a viable culture or recovers an organism different from the one recorded by the local laboratory.

Gram-staining of urine

One slide for Gram-stain is to be prepared from each unspun specimen obtained from the urine. The slide is to be stained and read by the local laboratory and then sent to the central laboratory for rereading and confirmation.

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:
    - Enterobacteriaceae
    - Enterococci
    - *Pseudomonas aeruginosa*
    - *S. saprophyticus*

  The micro-MITT population for this study will only include patients with UTIs caused by Enterobacteriaceae and/or *S. saprophyticus.*

- Even if the organism was isolated from an acceptable urine culture specimen, the following are never a pathogen:

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

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 (e.g., Gram stain) 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 Enterobacteriaceae, 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 3 Method for Determination of Creatinine Clearance

Creatinine clearance should be determined by the method of Cockroft-Gault based on serum creatinine concentrations obtained at Baseline, using ideal body weight instead of actual weight.

For females:

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

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

Ideal body weight is calculated as:

For females:

If H > 152.5 cm

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

If H < 152.5 cm

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

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

Appendix 4 Patient Symptom Assessment Questionnaire (PSAQ)

UTI symptoms	Symptom assessment
Gross hematuria (blood in urine)	No symptom
	Mild
	Moderate
	Severe
Pain or uncomfortable pressure in the lower abdomen/pelvic area	No symptom
	Mild
	Moderate
	Severe
Pain or burning when passing urine	No symptom
	Mild
	Moderate
	Severe
Frequency of urination or going to the toilet very often	No symptom
	Mild
	Moderate
	Severe
Urgency of urination or a strong and uncontrollable urge to pass urine	No symptom
	Mild
	Moderate
	Severe

Source: Adapted from Wagenlehner et al, Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections including acute pyelonephritis: RECAPTURE, a phase 3 randomized trial program. CID 2016:63; 754-762.

Appendix 5 Population PK Substudy

1 INTRODUCTION

This study will be conducted within the context of an ongoing Phase 3 sulopenem clinical trial in order to generate confirmatory data for the population PK profile of oral sulopenem etzadroxil.

1.1 Overall Study Design and Plan

This protocol appendix describes the plan for collection, processing and analysis of population PK samples collected within Study IT001-301.

At selected IT001-301 study sites, randomized patients will also be asked to provide plasma samples for population PK, according to the schedule noted below. Samples will be collected from subjects in both treatment arms. The study will remain blinded, regardless of whether or not any individual patient chooses to participate in the population PK sampling.

See Schedule of Events Table in Section 6.

1.2 Rationale for Study Design and Control Group

Population PK analysis requires sampling from an adequate number of patients and must necessarily be done in the setting of a therapeutic clinical trial. The number of subjects and samples, and the sampling schedule has been determined using accepted population PK principles. A subset of the treatment population is needed for the study to meet its objectives, thus this study will be conducted at a subset of sites selected for their ability and willingness to collect and process the additional plasma samples.

2 STUDY PROCEDURES

2.1 Study Population

Patients at selected investigational sites who meet the inclusion criteria and none of the exclusion criteria for study IT001-301 will be eligible for participation in this study.

This study can fulfill its objectives only if appropriate patients are enrolled. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular patient is suitable for enrollment in this sub-study.

2.2 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study.

- Patient is randomized into study IT001-301
- Patient has given informed consent to participate in the population PK sampling

2.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study.

- Patients who are not participating in clinical study IT001-301
- Patients in study IT001-301 who have not received study treatment

2.4 Pharmacokinetic Assessments

A blood sample will be collected at the following time points:

- Two hours (± 1 hour) after first oral dose of study medication is administered
- Four hours (± 2 hours) after first oral dose of study medication is administered
- Six hours (± 2 hours) after first oral dose of study medication is administered

4 mL of blood will be collected at each time point in Gray top Sodium Fluoride (2.5 mg/mL)/Potassium Oxalate (2 mg/mL) tubes (BD part#368587).

The labels for all biological sample collection and storage containers will contain, at a minimum, the subject's number, study number, collection date, and collection time. Additional details are provided in the Study Laboratory Manual.

Table 1: Sulopenem Pharmacokinetic Blood Sample Collection Schedule

Relative Time on Day 1, post first oral dose	**Volume** (mL)
2 hr (±1 hr)	4.0
4 hr (±2 hr)	4.0
6 hr (±2hr)	4.0
Total Blood Collected	**12.0 mL**

3. PLANNED STATISTICAL METHODS

3.1 General Considerations

The statistical methods for analysis of clinical data are described in detail in the protocol for the primary study. Relevant clinical data, including baseline and demographic data and data on clinical outcomes will be excerpted from the primary database for use in the PK/PD analyses.

3.2 Sample Size Considerations

For this class of drugs, the pharmacokinetic-pharmacodynamic (PK-PD) index which best describes efficacy is the time of free concentration of sulopenem above MIC (T_{free}>MIC). Therefore, the sparse pharmacokinetic (PK) sampling strategy chosen for this study are the times which are most informative of the T_{free}>MIC. The optimal times at which the three samples should be drawn, in hours after the administration of the first dose of oral medication, are as follows: 2 (1-3), 4 (2-6), and 6 (4-8).

The intention is to gather quality PK-PD data in several studies and to pool the concentration and effect data to achieve reasonable precision. Approximately 125 sulopenem-treated patients from this study are targeted to provide a significant contribution to these PKPD analyses.

4 PLASMA SAMPLE HANDLING AND ANALYSIS

Detailed instructions for the collection, processing, storage and shipment of samples will be provided in the study Laboratory Manual.

4.1 Sample Collection and Processing

- Blood samples for PK analysis of sulopenem levels will be collected via direct venipuncture using 4 mL Gray top Sodium Fluoride (2.5 mg/mL)/Potassium Oxalate (2 mg/mL) tubes (BD part#368587).
- Immediately after the sample is drawn, the tube must be mixed gently by inversion 8 to 10 times and placed on ice.
- The samples will be centrifuged at 2500 g for 10 minutes at 4ºC within 60 minutes of collection to achieve a clear plasma layer over the red cells.
- The plasma will be immediately separated into two 0.5 ml aliquots, transferred into 1.8 mL NUNC Cryovials and stored at approximately -70ºC within 60 minutes of collection.
- The time of the sampling as well as the time when the dose was administered prior to the sampling will be noted in the CRF.

4.2 Transport of Samples

The clinical staff will inventory the samples which are to be shipped to the central lab for accessioning and storage. The central lab will ship samples to the bioanalytic lab for measurement of sulopenem plasma concentrations. Each shipment will contain a complete set of samples.

For sample shipment, the samples will be packed in ample dry ice within a Styrofoam container to ensure the samples will remain frozen for at least 72 hours and shipped via express delivery to the central lab. Written notification of sample shipment will be communicated to the bioanalytical facility and Sponsor. The samples will be tracked to assure arrival in a safe and timely manner.

The shipment will be accompanied by logs showing the name of the study drug product, the protocol number, and the subjects and samples included in the shipment. Documentation noting the conditions of the samples upon arrival at the central lab and the bioanalytical laboratory will be forwarded to the Sponsor/and or Representative.

4.3 Bioanalytical Sample Analyses

The sulopenem plasma concentrations will be measured in plasma samples collected from patients in the sulopenem treatment group using a validated bioanalytical method and

according to the Bioanalytical Laboratory's Standard Operating Procedures and FDA Guidances.

4.4 Bioanalytical Methodology
A full validation of a sensitive assay for the appropriate analytes in each biological matrix, including precision, accuracy, reproducibility, limit of quantitation, recovery, and selectivity will be completed and approved prior to sample analysis. The bioanalytical summary report will include the stability of the frozen samples, and a summary of the standard curves and quality control samples.

4.5 Patient Withdrawal
Patients may withdraw from the study 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.

4.6 Handling Dropout and Withdrawn Subjects
Samples from subjects will be analyzed by the bioanalytical laboratory and concentration data will be included in the pharmacokinetic and statistical analyses if the subject completes the study.

Samples from subjects who choose to discontinue their participation in the study without submitting a written request to withdraw consent or are dropped by the Investigator(s), or the Sponsor, may be analyzed and included in the pharmacokinetic and statistical analyses, if pharmacokinetic parameters can be estimated using the remaining data points, or if requested by the Sponsor. Unanalyzed samples from subjects who submit a written request to withdraw consent authorization from the study will not be analyzed.

4.7 Final Integrated Report
A final report will be issued by the Sponsor after it has been reviewed and released by a quality assurance specialist, and this report may be appended to the clinical study report for the primary study. Where applicable, it will contain a narrative description of the clinical, bioanalytical, pharmacokinetic, and statistical procedures used during the conduct of the study. Appropriate tables and graphs will be created to summarize the data.

The regulatory agency for submission will include the U.S. Food and Drug Administration and other Health Agencies, as deemed appropriate for the purpose of study conduct or product registration.

5 PHARMACOKINETIC AND STATISTICAL DATA ANALYSES
Pharmacokinetic and statistical analyses will be performed for sulopenem plasma data.

Data from subjects with missing concentration values (missed blood draws, lost samples, samples unable to be quantitated) may be used if pharmacokinetic parameters can be estimated using the remaining data points.

5.1 Pharmacokinetic Data Analyses

PK-PD analyses will include all patients who are clinically and/or microbiologically evaluable and for whom sulopenem concentration-time data are available. An estimate of sulopenem PK parameters will be derived for every patient who undergoes PK sampling. This will be accomplished by fitting the population PK model developed for sulopenem using the data from patients from multiple Phase 1 studies to the sulopenem concentration-time data. The PK PD index (T_{free}>MIC) will be calculated. The PK-PD index data as well as patient demographics and outcome information may also be pooled with other Phase 3 studies of sulopenem for the conduct of the PK-PD analysis. The results of the PK-PD analysis may be reported separate from the clinical study report.

6 SCHEDULE OF EVENTS

Evaluation	**Baseline**		**Day 1**		
	Within 24 hours prior to first dose	**Dose Day 1[a]**	**Sample 1 2 hrs ± 1 hr**	**Sample 2 4 hrs ± 2 hrs**	**Sample 3 6 hrs ± 2 hrs**
Informed Consent	X				
Study drug dose		X			
PK sample collection			X	X	X

a Study "Day" is calendar day beginning with Day 1, the calendar day the first dose of study medication is started.

Appendix 6 Criteria for Safety Values of Potential Clinical Concern

Hematology	
Hemoglobin	<0.8 x baseline
Hematocrit	<0.8 x baseline
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
Alk 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
Calcium	<0.9 or >1.1 times the limits of the reference range
Albumin	<0.8 times the lower limit of the reference range
Total protein	<0.8 times the lower limit of the reference range
Creatine Kinase	>3.0 times upper 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 7 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 ciprofloxacin for treatment of uncomplicated urinary tract infections in adult women.

Study Number: *IT001-301*

Final Date: 06 March 2018

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:** _____