Statistical Analysis Plan: IT001-301

Study Title:	A prospective, Phase 3, randomized, multi-center, double-blind study of the efficacy, tolerability and safety of PF-03709270 with 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)
Indication:	Uncomplicated urinary tract infection
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SIGNATURE PAGE

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
BMI	Body Mass Index
CE	Clinical Evaluable
CFU	Colony Forming Unit
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
EOT	End of Treatment Visit
ESBL	Extended-Spectrum β-Lactamases
FDA	Food and Drug Administration
FV	Final Visit
GCP	Good Clinical Practice
IA	Interim Analysis
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
m-MITT	Microbiological Modified Intent-to-Treat
m-MITTR	Microbiological Modified Intent-to-Treat Resistant
m-MITTS	Microbiological Modified Intent-to-Treat Susceptible
ME	Microbiological Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MG	Milligram
MIC	Minimum Inhibitory Concentration
micro-MITT	Microbiological Modified Intent-to-Treat
MITT	Modified Intent-to-Treat
NDA	New Drug Application

PD	Pharmacodynamic
PK	Pharmacokinetic
PO	Orally
PSAQ	Patient Symptom Assessment Questionnaire
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
T_{free}>MIC	Time of free concentration above MIC
TOC	Test of Cure Visit
uUTI	Uncomplicated Urinary Tract Infection
WHODRUG	World Health Organization (WHO) Drug Dictionary

1 INTRODUCTION

This document presents the Statistical Analysis Plan (SAP) for the protocol IT001-301, "A prospective, Phase 3, randomized, multi-center, double-blind study of the efficacy, tolerability and safety of PF-03709270 with probenecid versus oral ciprofloxacin for treatment of uncomplicated urinary tract infections in adult women." The statistical plan described is an a priori plan, and the analyses outlined here have not been conducted on the final and unblinded data prior to the preparation of this plan. This SAP summarizes the design and objectives of protocol IT001-301 and provides details of the definitions of analysis populations, derived variables, the outcome measures and statistical methodology that will be used to analyze the data from the study.

Any deviation from the planned analysis after unblinding will be documented in the clinical study report (CSR). This SAP is based on the most recent version of the study protocol as noted on page 1.

2 STUDY DESIGN

This prospective Phase 3, randomized, multicenter, double-blind, double dummy, controlled study compares oral sulopenem etzadroxil/probenecid to oral ciprofloxacin for the treatment of patients with uncomplicated urinary tract infection (uUTI). Approximately 1,364 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.

Visits occur on Day 1, Day 3, Day 5 (± 1 day), Day 12 (± 1 day), and Day 28 (± 2 days). The Day 5 visit is the End of Therapy (**EOT**) visit, Day 12 is the Test of Cure (**TOC**) visit and Day 28 is the Final Visit (**FV**).

3 STUDY OBJECTIVES

3.1 Primary Objective

To compare the overall response (clinical and microbiologic combined 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, TOC.

3.2 Secondary Objectives

- To compare the overall response at other relevant time-points.
- To compare the microbiologic efficacy across treatment groups.
- To compare the clinical efficacy outcomes across treatment groups.
- 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.
- To assess the population PK profile of oral sulopenem etzadroxil/probenecid in selected patients.

4 DEFINITION OF ANALYSIS POPULATIONS

4.1 Intent-to-Treat (ITT)

The ITT population is comprised of all randomized patients regardless of whether the patient received study drug.

4.2 Modified Intent-to-Treat (MITT)

The MITT population will include all patients in ITT population who received at least a single dose of study medication and had the disease under study defined as having two of the four baseline uUTI symptoms and pyuria in the baseline UA.

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

All MITT patients with a positive study entry urine culture within 48 hours prior to first dose defined as $\geq 10^5$ colony forming units (CFU)/mL of a uropathogen (Enterobacteriaceae or *Staphylococcus saprophyticus* only) and no more than 2 species of microorganisms with $\geq 10^5$ (CFU)/ml (Wilson ML and Gaido L. Laboratory diagnosis of urinary tract infections in adult patients. Clin Infect Dis 2004;38:1150-8). See section 6.4 for further details on the use of lab results for determining eligibility.

4.3.1 Susceptible (micro-MITTS or m-MITTS)

All micro-MITT patients with a baseline uropathogen susceptible to the comparator drug, ciprofloxacin (ciprofloxacin MIC $\leq$ 1 mg/L), and no baseline pathogen non-susceptible to ciprofloxacin.

4.3.2 Resistant (micro-MITTR or m-MITTR)

All micro-MITT patients with a baseline uropathogen non-susceptible (defined as MIC $\geq$2 mg/L) to the comparator drug, ciprofloxacin.

4.4 Clinical Evaluable (CE)

Four CE populations will be defined based on the timing of the outcome assessment, CE-Day 3, CE-EOT, CE-TOC and CE-FV. The term "CE population" is used to refer to all CE populations. CE is a subset of MITT and follows the rules below.

a) Received all their active study medication up to the timepoint of assessment unless a failure at the time of discontinuing study drug due to insufficient therapeutic effect or need for concomitant systemic antibacterial therapy (must take all the doses by day 6 for sulopenem patients and day 4 for ciprofloxacin patients).

   For patients who appear to not have taken drug, based on the artificial intelligence data (see section 7.4), their banked urine samples at day 3 will be analyzed for study drug. If there is no active drug in the samples then these patients will be excluded from the CE.

b) Met the following inclusion criteria:
Inclusion Criterion 1. Female patients ≥18 years of age with ≥24 hours and ≤96 hours of urinary symptoms attributable to a UTI
Inclusion Criterion 2. Two of the following signs and symptoms of uUTI: urinary frequency, urinary urgency, pain or burning on micturition, suprapubic pain;

and didn't meet any of the following exclusion criteria:

Exclusion Criterion 1. Presence of signs and symptoms suggestive of acute pyelonephritis defined as: fever (temperature > 38° Celsius), chills, costovertebral angle tenderness, flank pain, nausea, and/or vomiting
Exclusion Criterion 2. Receipt of antibacterial drug therapy potentially effective as treatment of uUTI within the prior 7 days *(note, this will be checked against both the inclusion/exclusion and the prior concomitant medication eCRF pages)*
Exclusion Criterion 3. Patients requiring concurrent use of non-study treatments that would have a potential effect on outcome evaluations in patients with uUTI, including analgesics (e.g., non-steroidal anti-inflammatory drugs, aspirin, paracetamol etc.), phenazopyridine, and cranberry products
Exclusion Criterion 4. Patients with ileal loops or urinary stoma
Exclusion Criterion 5. Patients with an indwelling urinary catheter in the previous 30 days
Exclusion Criterion 6. Patients with paraplegia
Exclusion Criterion 7. Patients who are likely to receive ongoing antibacterial drug prophylaxis after treatment of uUTI (e.g., patients with vesico-ureteral reflux)
Exclusion Criterion 9. 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
Exclusion Criterion 15. Patients with uncontrolled Diabetes mellitus (defined as the presence of ketoacidosis, hyperosmolar hyperglycemia, or glucosuria with a random or fasting fingerstick or serum glucose ≥ 250 mg/dL at screening)

c) Had no major protocol deviations that would affect the assessment of efficacy prior to the visit as indicated in the protocol deviation log (see section 7.8)
d) Had a patient-determined clinical response of success or failure (and not indeterminate) at the timepoint of the visit (i.e., within the SAP defined allowed visit window), respectively.
e) Had not received antibacterial drug therapy potentially effective as treatment of uUTI within the prior 7 days to the initiation of study therapy.

f) For CE-Day 3, CE-EOT and CE-TOC, did not receive any systemic antibiotic therapy with potential activity against any of the uropathogens collected at baseline (excluding linezolid, daptomycin, vancomycin, azithromycin, metronidazole, josamycin, macrolide, nifuratel, tergynan, fluconazole, cystone, butoconazole nitrate, clindamycin hydrochloride, clotrimazole, tinidazole and clarithromycin, as well as 'antibiotics and chemotherapeutics for dermatological use' and 'ophthalmologicals' since they have no activity against the pathogens in the study) between the time of the baseline culture and the Day 3, EOT or TOC visits, 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, daptomycin and vancomycin).

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

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

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

i) Patients who receive study drug therapy beyond the protocol treatment period (Study Day 5) as a result of the investigator's assessment that additional drug therapy is needed for treatment of the underlying urinary tract infection will be defined as failures for patient determined clinical response at TOC. Thus, these patients will be included in the CE populations, if all other criteria are met.

4.5 Microbiological Evaluable (ME)

All patients included in both the micro-MITT and CE populations at the Day 3 (ME-Day 3), Day 5 visit (ME-EOT), Day 12 visit (ME-TOC) and at the Day 28 visit (ME-FV) and interpretable urine culture result at the Day 3, Day 5, Day 12 and Day 28 visits (i.e., within the SAP defined allowed visit window), respectively.

4.5.1 Susceptible (ME-S)

All ME patients with a baseline uropathogen susceptible to the comparator drug, ciprofloxacin (ciprofloxacin MIC ≤ 1 mg/L), and no baseline pathogen non-

susceptible to ciprofloxacin.

4.5.2 Resistant (ME-R)

All ME patients with a baseline uropathogen non-susceptible (defined as MIC ≥2 mg/L) to the comparator drug, ciprofloxacin.

4.6 Safety

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

4.7 Determination of Inclusion in Analysis Populations

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

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

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

5 DEFINITION OF ENDPOINTS

5.1 Overall Response

The primary endpoint for the study is the outcome of Overall Response at TOC.

A patient will be defined as a success at a given timepoint (Day 3, EOT, TOC and FV) if the following criteria are met:

- The patient is alive
- The patient has received no non-study antibacterial therapy for uUTI (excluding linezolid, daptomycin, vancomycin, azithromycin, metronidazole, josamycin, macrolide, nifuratel, tergynan, fluconazole, cystone, butoconazole nitrate, clindamycin hydrochloride, clotrimazole, tinidazole and clarithromycin, as well as ‘antibiotics and chemotherapeutics for dermatological use’ and ‘ophthalmologicals' since they have no activity against the pathogens in the study)
  - If an antibiotic active against the urinary tract pathogen is given for non-uUTI reasons, then the patient will be considered indeterminate
- The patient has resolution of the symptoms of uUTI present at trial entry and no new UTI symptoms (based on the Patient Symptom Assessment Questionnaire). Missing answers to PSAQ questions are treated as missing thus the outcome will be

indeterminate.

- Urine culture collected at the follow-up visit demonstrates $<10^3$ CFU/mL of the baseline uropathogen

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

- Patient died due to uUTI
- Patient received non-study antibacterial therapy for uUTI (excluding linezolid, daptomycin, vancomycin, azithromycin, metronidazole, josamycin, macrolide, nifuratel, tergynan, fluconazole, cystone, butoconazole nitrate, clindamycin hydrochloride, clotrimazole, tinidazole and clarithromycin, as well as 'antibiotics and chemotherapeutics for dermatological use' and 'ophthalmologicals' since they have no activity against the pathogens in the study)
- Patient has no resolution or worsening of symptoms of uUTI present at trial entry and/or has new uUTI symptoms. Missing answers to PSAQ questions are treated as missing thus the outcome will be indeterminate.
- Urine culture at the follow-up visit demonstrates $\geq 10^3$ CFU/mL of the baseline uropathogen.

Patients will also be defined to have an indeterminate outcome if any data needed to determine whether the outcome is success or failure are missing. For example, if the assessment of the UTI symptoms was not completed at TOC, the patient will be considered an indeterminate response for overall response at TOC (unless the urine culture demonstrates $\geq 10^3$ CFU/mL of the baseline uropathogen then the patient is a failure). Patients who died due to other reasons than the uUTI will have an indeterminate outcome.

5.2 Microbiologic Response

Per pathogen microbiologic response is assessed using the definitions listed below. It will be analyzed at each timepoint (Day 3, EOT, TOC and FV). It is assessed for each pathogen that a patient has at baseline.

Per patient microbiologic response is a patient level response determined by the outcome of any culture results at that visit.

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

5.2.1 Baseline Pathogens

Microbiological response	Definition
Eradication	The urine culture obtained at the timepoint of analysis demonstrates $<10^3$ CFU/mL of the baseline uropathogen.
Persistence	A uropathogen present at baseline regardless of susceptibility grew at $\geq 10^3$ CFU/mL at the timepoint of analysis.*

Persistence with increasing MIC	A urine culture taken after at least 2 full days of treatment grew $\geq 10^3$ CFU/mL of the baseline uropathogen and displayed ≥4-fold higher MIC to study drug received at the timepoint of analysis.
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*) at the timepoint of analysis (contaminated results are considered a negative culture and therefore an eradication[7]).

* The genus/species and susceptibility profiles need to match. Additional molecular testing by pulsed field gel electrophoresis (PFGE), PCR or whole genome sequencing (WGS) may be performed for confirmation; in the case of missing culture data PCR may be used to confirm the presence or absence of the baseline pathogen.

A per pathogen microbiologic success is defined as Eradication. A pathogen failure is Persistence or Persistence with Increasing MIC.

A per patient microbiologic success is defined as all pathogen responses for a patient are Eradication. A per patient microbiologic failure is one or more pathogens for a patient are Persistence or Persistence with increasing MIC. Otherwise, the patient will be Indeterminate.

5.2.2 Post-Baseline Pathogens

For patients with a baseline pathogen meeting the micro-MITT criteria, the following post-baseline pathogen definitions will be used.

Microbiologic response	**Definition**
Superinfection	A uropathogen not present at baseline grew with $\geq 10^5$ CFU/mL from the first dose of study drug through the EOT visit in the setting of recurrent/persistent/new uUTI symptoms requiring non-study systemic antibacterial treatment* (patient determined clinical failure at EOT).
New Infection	Isolation of a non-baseline pathogen from a culture post-EOT visit from a urine culture specimen with $\geq 10^5$ CFU/mL in a patient with one or more new uUTI signs/symptoms requiring new systemic antibacterial treatment* after the EOT visit (patient determined clinical failure post-EOT).
Recurrence	In a patient with clinical and microbiological success at EOT, isolation of

	a baseline pathogen from a urine culture specimen with $\geq 10^5$ CFU/mL post-EOT visit, along with new or recurrence of one or more uUTI signs/symptoms requiring new systemic antibacterial treatment* after the EOT visit (patient determined clinical failure post-EOT).
Colonization	Isolation of a micro-organism from the urine culture after EOT in a patient without one or more signs and symptoms of uUTI and not requiring new systemic antibiotic therapy* (patient determined clinical success post-EOT).

* excluding linezolid, daptomycin, vancomycin, azithromycin, metronidazole, josamycin, macrolide, nifuratel, tergynan, fluconazole, cystone, butoconazole nitrate, clindamycin hydrochloride, clotrimazole, tinidazole and clarithromycin, as well as 'antibiotics and chemotherapeutics for dermatological use' and 'ophthalmologicals' since they have no activity against the pathogens in the study

5.3 Patient-Determined Clinical Response (Clinical Response)

A patient will be defined as a clinical success at a given timepoint (Day 3, EOT, TOC and FV) if the following criteria are met (programmatically, based on the data on the eCRF):

- The patient is alive
- The patient has received no non-study antibacterial therapy for uUTI (excluding linezolid, daptomycin, vancomycin, azithromycin, metronidazole, josamycin, macrolide, nifuratel, tergynan, fluconazole, cystone, butoconazole nitrate, clindamycin hydrochloride, clotrimazole, tinidazole and clarithromycin, as well as 'antibiotics and chemotherapeutics for dermatological use' and 'ophthalmologicals' since they have no activity against the pathogens in the study) prior to the visit
  - If an antibiotic active against the urinary tract pathogen is given for non-UTI 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).
  - Missing answers to PSAQ questions are treated as missing thus the outcome will be indeterminate.
  - Baseline symptoms associated with anatomic abnormalities that predispose to symptoms of a uUTI (e.g., frequency and urgency associated with overactive bladder) do not need to be resolved.

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

5.4 Investigator-Determined Clinical Response:

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

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

5.5 Patient Symptom Assessment Questionnaire (PSAQ)

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

- Pain (uncomfortable pressure) in the lower abdomen/pelvic area
- Burning (dysuria) when passing urine
- Frequency of urination or going to the toilet very often
- Urgency of urination or a strong and uncontrollable urge to pass urine

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

5.6 Safety Endpoint Measures

The safety parameters include AEs, clinical laboratory evaluations and vital signs. Adverse

Events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) Version 21.0 or higher to the System Organ Class and Preferred Term levels.

6 STATISTICAL METHODS

6.1 Sample Size

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 TOC in the micro-MITTS population and/or whether oral sulopenem etzadroxil/probenecid is superior to oral ciprofloxacin for overall success at TOC in the micro-MITTR population. The primary endpoint 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]).

There are two primary populations for this study. One is the micro-MITTS population, defined as all randomized patients with a baseline urine culture demonstrating no more than 2 species of a uropathogen at $\geq 10^5$ CFU/mL susceptible (ciprofloxacin MIC $\leq$1 mg/L) to the comparator study drug, ciprofloxacin. The other is the micro-MITTR population, defined as all randomized patients with a baseline urine culture demonstrating among no more than 2 species of a uropathogen at least one pathogen at $\geq 10^5$ CFU/mL non-susceptible (ciprofloxacin MIC $\geq$2 mg/L) 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]. However, patients who were randomized and subsequently not found to have evidence of both pyuria and nitrites on their baseline urinalysis are still to be included in the micro-MITT populations if the baseline urine culture was positive as described above.

The proposed sample size in the micro-MITTS population is 441 patients per arm (total of 882 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 70% treatment success rate. With 105 patients per treatment group in the micro-MITTR population, there is 90% power to show superiority given a 66% and 43% overall success rate in the sulopenem etzadroxil/probenecid and ciprofloxacin groups, respectively. Assuming that 22% of the patients will have non-susceptible pathogens and 83% of the randomized patients will meet criteria for inclusion into the micro-MITT population (1,132 patients), the sample size for the ITT population is 1,364.

Historically, the treatment success rate in a similar patient population with susceptible pathogens was noted to be between 88.4% and 92%. However, preliminary results from an ongoing uUTI study (IT004-401) indicate that the point estimate for overall success in uUTI

patients with susceptible pathogens is closer to 70%, using the outcome measures defined in this study.

There are no recent studies in patients with uUTI caused by ciprofloxacin resistant pathogens but treated with another antibiotic to which the organism is susceptible to provide an estimate of the overall clinical success rate in this population. It is assumed the response rate in this group of patients will be slightly lower.

Two blinded interim analyses for sample size re-estimation and one unblinded interim analysis for sample size re-estimation are planned (See Section 7.6).

6.2 Randomization

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

6.3 Visit Windows

Visit windows are used in determining whether a patient will be included in the CE and ME populations at EOT, TOC or FV. If their assessments are out of window, they will not be included in that population.

For the ITT populations, patients are not dropped from the populations for assessments out of window. The nominal visit from the eCRF is used to assign assessments to the appropriate time point.

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

Visit	Window
Day 3	No window
Day 5 - End of Treatment (EOT)	± 1 day
Day 12 - Test of Cure (TOC)	± 1 day
Day 28 - Final Visit (FV)	± 2 days

6.4 Microbiology Data

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

- Monomicrobial or polymicrobial infections caused by:
    - Enterobacteriaceae
    - Enterococci

- *Pseudomonas aeruginosa*
- *S. saprophyticus*

- The micro-MITT population will only include patients with uUTIs caused by the following (study pathogens): Enterobacteriaceae and/or *S. saprophyticus*.

The following normal flora 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 will be assessed on a case-by-case basis via manual review of a spreadsheet by the Sponsor. This could include isolates not listed above. If needed, patient clinical and microbiological information (e.g., Gram stain, PFGE or other appropriate tests) will be used to assist in determining if the isolate is a pathogen.

The microbiology rules for identification of pathogens are in appendix D.

6.5 Handling of Missing Data

Missing data will be handled as outlined below:

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

treatment emergent unless it is possible to conclude that the stop date is prior to first dose (based on the available parts of stop date if it is partial).

- If the start date only contains the month and day, then if the month/day combination is prior to the month/day combination of first dose then the adverse event will not be treatment emergent. Otherwise, it will be treatment emergent unless it is possible to conclude that the stop date is prior to first dose (based on the available parts of stop date if it is partial).
- Other partial start dates will be treated as treatment-emergent unless it is possible to conclude that the stop date is prior to first dose (based on the available parts of stop date if it is partial).

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

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

6.6 Comments on Statistical Analysis

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

- Summaries will include frequency and percentages for categorical data; frequency and median for ordinal data; and number, mean, standard deviation, and median, minimum, maximum and quartiles for quantitative data.
- Duration variables will be calculated using the general formula (end date - start date) +1.
- If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table (e.g., a character string is reported for a parameter of the numerical type), a coded value must be appropriately determined and used in the statistical analyses. In general, a value or lower and upper limit of normal range such as '<10' or '≤ 5' will be treated as '10' or '5' respectively, and a value such as '>100' will be treated as '100'. However, the actual values as reported in the database will be presented in data listings.
- Individual patient listings of all data represented on the eCRFs will be provided to facilitate the investigation of tabulated values and to allow for the clinical review of all efficacy and safety parameters.
- Version 9.4 (or higher) of SAS® statistical software package will be used to provide all summaries, listings, graphs, and statistical analyses.

7 STATISTICAL ANALYSES

All tables except safety tables will be presented for three groups of patients, once each for patients whose pathogens are susceptible to ciprofloxacin, non-susceptible to ciprofloxacin and all patients regardless of susceptibility. Safety tables will be presented only once for the safety population regardless of susceptibility.

7.1 Patient Disposition

The number of patients included in each of the study populations (i.e., ITT, Safety, MITT, Micro-MITT, Micro-MITTS, Micro-MITT R, CE-Day 3, CE-EOT, CE-TOC, CE-FV, ME-Day 3, ME-EOT and ME-TOC, ME-FV) will be summarized by treatment group. A table and listing will be provided that details the reasons the patient is excluded from the population.

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

The frequency and percentage of patients completing the study, prematurely discontinuing from study drug, and prematurely discontinuing from the study will be presented for each treatment group and overall for each study population. Comparisons between treatment groups will be made using Fisher's exact test.

Reasons for premature discontinuation of study drug and/or withdrawal from the study as recorded on the eCRF will be summarized (frequency and percentage) by treatment group.

A listing of all patients who prematurely discontinued from study drug or withdrew from the study will be presented, and the primary reason for premature discontinuation of study drug or withdrawal from the study will be provided.

A listing of deaths will be presented separately.

7.2 Demographics and Baseline Characteristics

Demographic data and baseline characteristics will be presented by treatment group in all study populations. A table will present the patient demographics (e.g., gender, age, ethnicity, race, geographic region) and baseline characteristics (e.g., height, weight, BMI, diabetes status, creatinine clearance). Differences between treatment groups will be analyzed using Fisher‘s exact test for dichotomous variables (gender, ethnicity, race, geographic region, diabetes status, creatinine clearance as a categorical variable: <30, 30-<60, ≥60) and the Wilcoxon Rank Sum test for continuous variables (age, BMI, creatinine clearance).

Medical history will be summarized based on body site/system category and treatment group.

Signs and symptoms at baseline as captured on the PSAQ will be summarized by treatment group and compared using the Wilcoxon Rank Sum test for ordinal data.

7.2.1 Baseline Microbiology

The microbiological assessment of the baseline urine sample will be summarized by treatment group for all populations. A frequency distribution of the result of the central lab’s Gram stain, including organism characteristics will be presented. The number and percentage of patients with no growth, contaminant and positive for a pathogen will also be presented.

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

A table will be provided of the distribution of pathogens by culture concentration at baseline.

The number and percentage of patients with a gram-positive pathogen and with a gram-negative pathogen will be presented by genus and species.

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

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

- The distribution of MIC to sulopenem, ciprofloxacin and other drugs for the baseline pathogens

- MIC summary statistics (i.e., range, MIC_{50} and MIC_{90} for pathogens that have 10 or more occurrences) for the study pathogens: Enterobacteriaceae and *S. saprophyticus*

7.3 Prior and Concomitant Medications

All medications taken within 30 days prior to the first dose of the study drug and through the FV visit will be recorded on the eCRF. Medications will be summarized by WHODRUG (March 1, 2018 version or higher) ATC level 3 and generic medication name for all populations. Patients will be counted only once for an ATC class and generic medication name.

Medications are considered prior if taken prior to the first dose of study drug or if their start date is unknown. Medications are considered concomitant if taken on or after the first dose of study drug, or if their stop date is unknown or marked as continuing.

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

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

7.4 Study Drug Exposure

To enhance documentation of compliance, this study employs a platform that uses artificial intelligence on smartphones to confirm medication ingestion for U.S. sites. In addition, built-in reminders and a communication system allow real-time intervention in case of drug interruptions. For non-U.S. sites, a paper diary will be used to capture compliance.

A listing of patients not in compliance, based on the artificial intelligence data, will be provided. For patients who appear to not have taken drug, based on the artificial intelligence data, their banked urine samples at day 3 will be analyzed for study drug. If there is no active drug in the samples then these patients will be excluded from the CE.

A dosing summary by treatment group will be presented for all study populations. The distribution of patients by the number of active doses of study drug therapy in the 3-day regimen and 5-day regimen will be presented. Each tablet or capsule taken is considered a half day of therapy.

7.5 Efficacy Analyses

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

By definition, patients with an indeterminate response are included in the denominator for analyses in the ITT, MITT and micro-MITT populations, and are counted as failures.

For the ITT, MITT and micro-MITT populations, the proportion of successes is defined

using the following formula:

$$\frac{\text{Number of successes}}{\text{Number of successes + Number of failures + Number of indeterminates}}$$

By definition, patients in the CE and ME populations must have sufficient information for determination of overall response. Thus, for the CE and ME populations, the proportion of successes is defined using the following formula:

$$\frac{\text{Number of successes}}{\text{Number of successes + Number of failures}}$$

7.5.1 Primary Efficacy Analysis

The primary efficacy endpoint is based on the outcome of overall success (combined clinical and microbiologic success) at TOC in the micro-MITTS and, separately, in the 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 objective of this study is to compare the outcomes in patients with quinolone susceptible organisms as well as, in parallel, in patients with quinolone non-susceptible pathogens. The primary comparisons for regulatory approval are in these two mutually exclusive populations as defined by a baseline characteristic. If either of the two analyses are positive (i.e., reject null hypothesis), the efficacy of sulopenem will have been established consistent with the primary objective of the trial. These two populations are defined as follows:

1) The micro-MITTS population

This population is a 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 p1 is the primary efficacy endpoint rate in the sulopenem etzadroxil/probenecid group, p2 is the primary efficacy endpoint 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

This population is a 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:

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

A 2-sided 95% CI for the observed treatment difference in success rates will be determined using the method without stratification of Miettinen and Nurminen. If the lower bound of the 95% CI is greater than 0%, the null hypothesis will be rejected and superiority of sulopenem etzadroxil/probenecid to ciprofloxacin will be concluded.

7.5.2 Additional Hypothesis Testing of the Primary Efficacy Endpoint

Additional analyses will be performed to provide guidance to the practicing physician in the setting where culture results are not available. To do this, all randomized patients who received drug will be analyzed, this population being more consistent with what the practicing physician is faced with every day.

The table below presents a family of analyses to be conducted in the micro-MITTS and micro-MITTR populations in the sequence in which they will be conducted. The regulatory outcomes are focused on the primary analyses, as stated in Section 7.5.1. The secondary analyses, which sequentially progress towards an assessment in the randomized population prior to the benefit of culture data, may provide guidance to physicians who need to choose an empiric treatment regimen without the support of a urine culture.

Analysis	Populations	
Primary	1. micro-MITTS (if non-inferior then test #2)	1. micro-MITTR (if superior then test #2)
Secondary	2. NI in micro-MITT (if non-inferior then test #3)	2. NI in micro-MITT (if non-inferior then test #3)
	3. Superiority in micro-MITT (if superior then test #4)	3. Superiority in micro-MITT (if superior then test #4)
	4. NI in MITT* (if NI then test#5)	4. NI in MITT* (if NI then test#5)
	5. Superiority in MITT*	5. Superiority in MITT*

* Based on clinical response

To control for inflation of the overall type I error rate in assessment of the secondary analyses,

the hierarchical testing procedure of Westfall and Krishen (Westfall 2001) will be used to continue testing hypotheses of the primary efficacy endpoint. 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.

1) 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 patients 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.

7.5.3 Additional Analyses of the Primary Efficacy Endpoint

- Subgroup Analyses
  - Geographic Region (U.S. vs. non-U.S.)
  - Fed / Fasted State
- Sensitivity Analyses
  - Missing Data / Indeterminates Equal Success
  - Multiple Imputation for Missing Data
  - An analysis of the primary endpoint where microbiologic eradication contributing to the overall response requires complete eradication defined as no growth (<100 CFU/mL) of the baseline pathogen on a follow-up urine culture at TOC
  - Overall response defined by improvement of symptoms (instead of resolution) from baseline and no worse than mild and no new uUTI symptoms
  - Overall response defined by 'urgency and frequency are improved and no worse than mild and all other symptoms are resolved and no new uUTI symptoms'
  - Optional Analysis - Patients with Enterobacteriaceae $>10^5$ CFU/mL as identified by either urine culture or a rapid PCR diagnostic test with an equivalent number of copies/ml will be included in the adjusted micro-MITT population
  - Optional Covariate Analysis

All primary analyses are done at TOC in the micro-MITT populations

The primary efficacy endpoint at TOC will also be assessed within each geographic region (U.S. vs. non-U.S.) by treatment group. For each geographic region, 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.

A sub-group analysis of the primary efficacy endpoint by fed / fasted state will be conducted. A patient will be considered fed if they took 100% of their doses in a fed state. Different proportions of doses taken in a fed state may be explored if the analysis suggests that the fed state makes a difference.

Sensitivity analyses of the primary endpoint at TOC will also be conducted in the micro-MITTS and micro-MITTR populations. The below sensitivity analyses will be summarized and a 2-sided 95% unstratified CI will be computed for the difference in the success rates between the treatment groups.

- A sensitivity analysis will consider all patients who have missing data for the primary endpoint (i.e., an indeterminate response) as successes.

- A sensitivity analysis applying multiple imputation methods for missing data will also be conducted. The multiple imputation analysis assuming a monotone missing data pattern will be used to define the missing data (indeterminate response). One hundred datasets will be created using a logistic regression model with treatment, clinical response and microbiological response at EOT, baseline pathogen and possibly other variables included as predictive variables.
- An analysis of the primary endpoint where microbiologic eradication contributing to the overall response requires complete eradication defined as no growth (<100 CFU/mL) of the baseline pathogen on a follow-up urine culture at TOC.

- An analysis will consider the primary endpoint at TOC defined in section 5.1 except, improvement of symptoms (instead of resolution) from baseline and no worse than mild and no new uUTI symptoms.

- An analysis will consider the primary endpoint at TOC defined in section 5.1 except, urgency and frequency are improved and no worse than mild and all other symptoms are resolved and no new uUTI symptoms.

- An optional analysis of the primary efficacy endpoint measure will be conducted in an adjusted micro-MITT population utilizing results from rapid PCR-based diagnostic testing. The rapid diagnostic testing will be done on patients who did not meet the micro-MITT criterion of having a pathogen at baseline that was $\geq 10^5$ CFU/mL with susceptibility testing performed. If the rapid diagnostic testing shows $\geq 10^5$ copies/mL then that pathogen will be counted as a baseline pathogen and the patient will be included in a new adjusted micro-MITT population. See Appendix E for further details.
- An optional covariate exploratory analysis using logistic regression will be performed using baseline variables such as study drug, bacteremia at baseline, age, gender, race, *E. coli* at baseline, creatinine clearance, albumin, comorbidities, percentage of doses taken in fed state, diabetes and other variables if imbalances exist at baseline. For the latter, baseline tables will be reviewed by Iterum prior to the covariate analysis.

  Once the covariates are determined, a univariate logistic regression will be run for each covariate. Covariates with a p-value ≤ 0.10 will be used in a multivariate analysis with a stepwise selection method. The alpha level for both entering and removing a covariate will be 0.10.

7.5.4 Secondary Efficacy Analysis

The number and percentage of patients with a per patient microbiologic response of success (eradication) or failure (persistence or persistence with increasing MIC), at the TOC visit will be determined in each treatment group in the ME-TOCS and ME-TOCR populations. 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.

7.5.5 Additional Efficacy Analyses

Analysis	Day 3	EOT (Day 5)	TOC (Day 12)	FV (Day 28)
Overall Response	Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS[#] Micro-MITTR[#] ME	Micro-MITT Micro-MITTS Micro-MITTR ME
Overall Response by Baseline Pathogens		Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS Micro-MITTR ME
Overall Response by MIC			Micro-MITT Micro-MITTS Micro-MITTR ME	
Overall Response by Combination of Antibiotic Resistance Classes		Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS Micro-MITTR ME
Overall Response by Assessment Day*				
Overall Response with Requirement that Failure is Both Symptoms and a Pathogen ≥ 1000 CFU/mL	Micro-MITT ME	Micro-MITT ME	Micro-MITT ME	
Microbiologic Response	Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS Micro-MITTR	Micro-MITT Micro-MITTS Micro-MITTR ME
Per Pathogen Microbiologic Response		Micro-MITT Micro-MITTS Micro-MITTR ME	MITT Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS Micro-MITTR ME
Microbiologic Response by ESBL Positive and ESBL Negative		Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS Micro-MITTR ME
Per Pathogen Microbiologic Response by MIC			Micro-MITT Micro-MITTS	

			Micro-MITTR ME	
Microbiologic Response for Complete Eradication		Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS Micro-MITTR ME
Microbiologic Response for Complete Eradication by Baseline Pathogens		Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS Micro-MITTR ME
Microbiologic Response for Post-Baseline Pathogens		Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS Micro-MITTR ME
Patient Determined Clinical Response	ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME	ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME	ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME	ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME
Patient Determined Clinical Response by Baseline Pathogen		Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS Micro-MITTR ME
Patient Determined Clinical Response by ESBL Positive and ESBL Negative		Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS Micro-MITTR ME	Micro-MITT Micro-MITTS Micro-MITTR ME
Patient Determined Clinical Response by Baseline Culture Density		MITT	MITT	MITT
Patient Determined Clinical Response defined by improvement of symptoms (instead of resolution) from baseline and no worse than mild and no new uUTI symptoms			ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME	
Patient Determined Clinical Response defined by urgency and frequency are improved and no worse than mild and all other symptoms are resolved and no new uUTI symptoms			ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME	
Patient Determined Clinical Response Failure by Symptoms and Bothersome Questions		ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME	ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME	ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME
Investigator-Determined Clinical Response		ITT MITT Micro-MITT	ITT MITT Micro-MITT	ITT MITT Micro-MITT

		Micro-MITTS Micro-MITTR CE ME	Micro-MITTS Micro-MITTR CE ME	Micro-MITTS Micro-MITTR CE ME
Patient Symptom Assessment Questionnaire		ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME	ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME	ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME
Patient Symptom Assessment Questionnaire – Shift Table of Severity		ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME	ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME	ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME
Patient Symptom Assessment Questionnaire – Kaplan-Meier Plot for Time to Resolution of All Symptoms*				
Patient Symptom Assessment Questionnaire – Severity by Bothersome Questions		ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME	ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME	ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME
Patient Symptom Assessment Questionnaire – Sensitivity Analysis using bothersome questions		ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME	ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME	ITT MITT Micro-MITT Micro-MITTS Micro-MITTR CE ME

[#] Primary Endpoint
* Overall response by assessment day (not grouped by visit) and Kaplan-Meier Plot of time to resolution of all PSAQ symptoms are not done at individual visits and will be done in the micro-MITT, micro-MITTS and micro-MITTR populations.

Overall Response

The number and percentage of patients in each treatment group with an overall response of success, failure and indeterminate at Day 3, EOT, and FV will be presented for the micro-MITT, micro-MITTS and micro-MITTR populations (note, overall response at TOC in the micro-MITTS and micro-MITTR populations are the primary endpoints). The number and percentage of patients in each treatment group with an overall response of success and failure at Day 3, EOT, TOC and FV will be presented for the ME population. Two-sided 95% unstratified CIs will be constructed for the observed difference in the overall success rates between the treatment groups for descriptive purposes; no conclusion of NI will be made. Note, overall response is not analyzed in the ITT, MITT and CE populations because these populations do not require a baseline pathogen. For the day 3 analysis, overall response will

also be presented where clinical success contributing to the overall response requires at least one symptom improved from BL with no symptoms worsening and no new symptoms.

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

Overall response by ciprofloxacin MIC and sulopenem MIC for baseline pathogens will be provided for TOC visit in the micro-MITT, micro-MITTS, micro-MITTR and ME populations.

Overall Response by combination of antibiotic resistance classes will be provided. The classes will be ESBL status, quinolone non-susceptible (QNS), TMP-SMX resistant, nitrofurantoin (NTF), non-susceptible to at least 3 classes of antibacterials (MDR – quinolones, TMP-SMX and beta-lactams), resistance to all four classes (quinolones, TMP-SMX, nitrofurantoin and beta-lactams) and combinations of these resistant classes. Ceftriaxone will serve as the reference drug for ESBL status, ciprofloxacin will serve as the reference drug for the quinolone class, and ampicillin will serve as the reference drug for the beta-lactam class. Resistance to a class means resistance to the reference drug in that class. A second table will be provided for resistance to oral drugs (ciprofloxacin, TMP-SMX, nitrofurantoin, ampicillin, amoxicillin-clavulanate, tetracycline and fosfomycin). Multi-drug resistance will not be included in this table. However, multi-drug resistance will be explored for the primary endpoint in other ways.

Summary tables will be provided comparing the treatment groups by day the overall assessment was made. For example, if patient's EOT assessment was conducted on day 4 then they would be analyzed in the day 4 table. A figure of overall response by day of assessment will be provided too.

Overall response with failure defined as the patient has both symptoms and a pathogen ≥ 1000 CFU/mL will be presented for micro-MITT and ME.

Microbiologic Response

The number and percentage of patients in each treatment group with a per patient microbiologic response of success, failure (persistence and persistence with increasing MIC) and indeterminate at Day 3, EOT, TOC and FV will be presented for the micro-MITT, micro-MITTS and micro-MITTR populations. The number and percentage of patients in each treatment group with a per patient microbiologic response of success and failure at Day 3, EOT and FV will be presented for the ME population (note, microbiologic response at TOC in the ME-S and ME-R populations are the secondary endpoints). 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.

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

Per pathogen microbiologic response by ciprofloxacin MIC and sulopenem MIC for

individual pathogens will be provided for TOC visit in the micro-MITT, micro-MITTS, micro-MITTR and ME populations.

The number and percentage of patients in each treatment group with a microbiologic response of complete eradication defined as no growth (<100 CFU/mL) of baseline pathogen on a follow-up urine culture at TOC will also be presented for the micro-MITT, micro-MITTS, micro-MITTR and ME populations and by baseline pathogen. The EMA endpoint requires $<10^2$ CFU/mL at TOC for micro-MITT. Additionally, rows for microbiologic response $<10^3$, $<10^4$ and $<10^5$ will be displayed.

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

Patient Determined Clinical Response

The number and percentage of patients in each treatment group with a patient-determined clinical response of success, failure and indeterminate at Day 3, EOT, TOC and FV will be presented for the micro-MITT, micro-MITTS, micro-MITTR, MITT and ITT populations. The number and percentage of patients in each treatment group with a patient-determined clinical response of success and failure at Day 3, EOT, TOC and FV will be presented for the CE and ME populations. Two-sided 95% unstratified CIs will be constructed for the observed difference in the overall success rates between the treatment groups for descriptive purposes; no conclusion of NI will be made. For the day 3 analysis, patient determined clinical response will also be presented where the definition of success is at least one symptom improved from BL with no symptoms worsening and no new symptoms.

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

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

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

Patient determined clinical response failure by symptoms and bothersome questions will be presented for EOT, TOC and FV in each treatment group for all populations. For patients with clinical failure, the worst severity of symptoms will be tabulated and if two symptoms have the same worse severity (e.g., the worst severity is moderate and two symptoms are moderate) then the worst bothersome category will be used for the two symptoms.

Investigator-Determined Clinical Response

Investigator-determined clinical response (clinical success, failure and indeterminate) at the

EOT, TOC and FV visits will be presented by treatment group for the micro-MITT, micro-MITTS, micro-MITTR, CE and ME populations. Two-sided 95% unstratified CIs will be constructed for the observed difference in the clinical cure rates between the treatment groups for descriptive purposes.

Patient Symptom Assessment Questionnaire

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

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

Kaplan-Meier plots for time to resolution of all PSAQ symptoms will be provided for the micro-MITT, micro-MITTS and micro-MITTR populations. Patients will be censored at time of taking non-study antibacterial therapy for uUTI.

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

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

7.6 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 TOC are available for approximately 33% and 66% of the patients (approximately 450 and 900 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 patients 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.

In addition, the micro-MITT rate (i.e. evaluability rate) and proportion of patients with a susceptible pathogen (micro-MITTS evaluability rate) will be used to determine the total number of patients 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 (unblinded interim analysis). 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%, no change to the sample size will be made. 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 patients in the micro-MITT population and the micro-MITTR population. No adjustment to the overall alpha level is needed.

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.

7.7 Safety Analyses

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

7.7.1 Adverse Events

Verbatim descriptions of AEs will be coded using Version 21.0 or higher of MedDRA. Summary tables will be provided for all treatment-emergent AEs (TEAEs). An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a product or medical device, unless the event is captured in the study outcome, as defined below; the event need not necessarily have a causal relationship with the treatment or usage. A TEAE is any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug (on or after start date and time of first dose). All AEs (including non-TEAEs), serious TEAEs, and TEAEs leading to study drug discontinuation will be provided in listings by treatment group, site, patient, verbatim term, MedDRA system organ class and preferred terms, onset and resolution date, seriousness flag, intensity, relationship to study drug, action taken and outcome.

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

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

The incidence of treatment emergent adverse events by system organ class, preferred term will also be presented by gender, race and age.

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

If an AE starts on the same day that dosing is initiated, and the start time of the AE is missing then the AE is considered TEAE.

7.7.1.1 Diarrhea Episodes

Diarrhea episodes will be collected on the adverse event page and will include verbatim terms of diarrhea and loose or watery stools. An AE event will be captured each day there is an episode. If there are multiple episodes on a day, the number of episodes will be captured in the verbatim term with an 'X' followed by the number of episodes (e.g., X3).

Clinically significant diarrhea is defined as having three or more episodes of diarrhea (preferred term which will included loose or watery stools verbatim terms) in one day or having two or more episodes of diarrhea per day for two consecutive days.

The number and percentage of treatment emergent episodes of clinically significant diarrhea

and number and percentage of subjects with treatment emergent clinically significant episodes of diarrhea will be summarized by severity level and drug relatedness. If severity level differs or drug relatedness differs across days, then the worst severity or the worst drug-relatedness will be used. The duration of treatment emergent clinically significant episodes (i.e., the number of days that diarrhea lasts) will also be summarized. The number of treatment emergent clinically significant episodes and the number of subjects with clinically significant episodes of diarrhea will be analyzed by fed / fasted state.

The following bar charts will be provided for diarrhea episodes:

- Duration of Diarrhea
- Number of Episodes of Diarrhea by Study Day
- Percent of Subjects with Diarrhea by Study Day
- Duration of Clinically Significant Diarrhea
- Number of Episodes of Clinically Significant Diarrhea by Study Day
- Percent of Subjects with Clinically Significant Diarrhea by Study Day

7.7.2 Laboratory Values

Several analyses of the laboratory data will be presented. Both local and central labs were performed. Only the central lab data will be summarized. However, if a central lab value is missing the local lab value will be used for the summary table. A listing will contain all lab data from both local and central labs.

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

$$s = x\frac{U_S}{U_X}$$

where s = the individual local laboratory value normalized against the central laboratory normal range; x = the original individual laboratory value; U_X is the upper limit of the normal range for an individual laboratory parameter; U_s is the upper limit of the laboratory normal range for that laboratory parameter from the common source.

Descriptive statistics for chemistry and hematology values and the change from baseline will be summarized for all study visits. The change from baseline to each post-baseline visit will also be summarized by treatment group and it will be calculated for each patient at the specified visit as the value at the specified visit minus the baseline value.

Laboratory values will also be classified as of potential clinical concern. The number and percentage of patients with a laboratory value of potential clinical concern will be summarized by visit and treatment group and broken out by patients with normal and abnormal at baseline. Worst overall value for each test will be used for this table. For a few tests, worst value can have both a low and a high value. When calculating the worst overall

value, use the highest value when dealing with ULN or a > sign or a >= sign and use the lowest value when dealing with LLN or a < sign or a <= sign. See appendix B.

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

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

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

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

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

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

7.7.3 Physical Examinations

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

7.7.4 Vital Signs

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

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

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

7.8 Protocol Deviations

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

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

8 DIFFERENCES WITH ANALYSES SPECIFIED IN THE PROTOCOL

The following is the list of differences between the protocol and the SAP:

- The additional requirement of having the disease under study has been added to the definition of the MITT population.
- The following are additions or changes to the clinical evaluable definition:
    - The patient must meet certain inclusion and exclusion criteria.
    - The patient must have received appropriate adjunctive antibacterial coverage if the patient had a culture-documented Enterococcus spp. or other gram-positive pathogens at baseline and symptoms.
    - Site personnel involved in the assessment of efficacy parameters must have remained blinded to study treatment up to the time of the efficacy assessment,
    - Patients who receive study drug therapy beyond the protocol treatment period as a result of the investigator's assessment that additional drug therapy is needed for treatment of the underlying infection will be defined as failures for patient determined clinical response at TOC. Thus, these patients will be included in the CE populations, if all other criteria are met.
    - For CE-FV, the protocol states that a patient must be in the CE-TOC population. This rule has been eliminated to include patients with assessment outside of the TOC window.
- Only one micro-evaluable population is defined in the protocol. The SAP defines two: ME-S for micro-evaluable ciprofloxacin susceptible patients and ME-R for micro-evaluable ciprofloxacin resistant patients.
- For microbiologic response, post baseline responses of superinfection, new infection, colonization and recurrence were added.
- The analysis of diarrhea has been added.

- In the Additional Hypothesis Testing of the Primary Efficacy Endpoint section, the analysis within the MITT population has been added.
- The following sensitivity analyses of the primary endpoint have been added:
    - Overall response defined by improvement of symptoms (instead of resolution) from baseline and no worse than mild and no new uUTI symptoms
    - Overall response defined by urgency and frequency are improved and no worse than mild and all other symptoms are resolved and no new uUTI symptoms
    - Patients with positive cultures identified by rapid diagnostic testing will be included in the micro-MITT population
    - Covariate Analysis
    - Hypoalbuminemia

9 REFERENCES

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Appendix A: 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		X		
Urinalysis	X		X	X	X	X	X
Urine Gram stain	X						
Urine Culture and sensitivity	X		X	X	X	X	X
Plasma & Urine 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 sub-study, collect plasma for PK analysis 2 hours, 4 hours, and 6 hours post-dose after first oral dose, and collect urine for PK analysis at the following time intervals: 0-2 hours, 2-4 hours and 4-6 hours

Appendix B: 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 C: Method for Determination of Creatinine Clearance

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

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 D: Microbiology Rules for Determination of Final Pathogen

Baseline

1. Baseline urine sample is submitted for culture to:
    a. Local/Regional Lab (non-U.S.), local lab (a few U.S. sites) or Covance (all U.S. sites)
    b. IHMA (U.S. only)
2. All baseline pathogens identified at the Local/Regional lab (non-U.S.), local lab (U.S.), Covance and IHMA (U.S. only) will be considered as part of the baseline urine culture result.
    a. Uropathogens as defined in section 6.4 will be sent from the Local/Regional Lab (non-U.S.) or Covance (U.S.) to IHMA for confirmation of genus/species and IHMA confirmation will be final
    b. Non-uropathogens not sent to IHMA or isolates not available for confirmation at IHMA will remain as identified by the Local/Regional Lab (non-U.S.), local lab (U.S.) or Covance.
3. If Local/Regional Lab's (non-U.S.), local lab (U.S.) or Covance's urine culture yields >2 micro-organisms in a quantity of $>10^5$ CFU/mL, this will be considered as "contaminated."
4. When the susceptibility status (susceptible, non-susceptible) is inconsistent between the Local/Regional lab (non-U.S.), local lab (U.S.), Covance, IHMA (confirmation) and IHMA (baseline urine culture, U.S. only) for a pathogen, PCR testing will be used to determine if the pathogen is gyrase positive or negative. If it is gyrase positive then there will be two final baseline pathogens, one susceptible and one non-susceptible. If it is gyrase negative, then there is one final baseline pathogen which is susceptible.

Post-Baseline Visits

1. Post-baseline urine sample is submitted for culture to Local/Regional Lab (non-U.S.) or Covance (U.S.)
2. All pathogens identified at the local/regional lab and Covance will be considered as part of the post-baseline urine culture result (in the case of missing culture data PCR may be used to confirm the presence or absence of the baseline pathogen)
    a. Uropathogens as defined in section 6.4 will be sent from the Local/Regional Lab (non-U.S.) or Covance (U.S.) to IHMA for confirmation and IHMA confirmation will be final
    b. Non-uropathogens not sent to IHMA or isolates not available for confirmation at IHMA will remain as identified by the Local/Regional Lab or Covance.
3. If Local/Regional Lab's or Covance's urine culture yields >2 micro-organisms in a quantity of $>10^5$ CFU/mL, this will be considered as "contaminated."
4. When the susceptibility status (susceptible, non-susceptible) is inconsistent between the Local/Regional lab, Covance and IHMA confirmation for a pathogen, PCR testing will be used to determine if the pathogen is gyrase positive or negative. If it is gyrase positive then there will be two final post-baseline pathogens, one susceptible and one non-susceptible. If it is gyrase negative, then there is one final post-baseline pathogen which is susceptible.

Appendix E: Inclusion of OpGen (PCR) Data for Exploratory Analysis

Patients that do not qualify for the micro-MITT population will have their baseline urine sample analyzed by PCR technology. The results of the PCR analysis may be used in an optional analysis to determine if these patients will be included in the adjusted micro-MITT population.

The PCR analysis detects the following pathogens: Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis, Pseudomonas aeruginosa and Proteus mirabilis. The test also reports on the presence/absence of a variety of antibiotic resistance gene mutations, including the DNA Gyrase gene mutation associated with quinolone resistance for E. coli, K. pneumoniae, and P. aeruginosa.

If the PCR analysis detects a E. coli, K. pneumoniae, or P. mirabilis in a quantity ≥ 100,000 CFU/ml, then the patient will qualify for the adjusted micro-MITT population. When available, the results of standard antimicrobial susceptibility testing from the baseline urine culture will be used to define the quinolone-susceptibility group. When this information is not available, the presence/absence of DNA Gyrase gene mutation by OpGen will be used. If the E. coli and/or K. pneumoniae DNA Gyrase gene mutation is detected, then the corresponding organism(s) is considered non-susceptible to ciprofloxacin. If the DNA Gyrase gene mutation is not detected, then the corresponding organism(s) is considered susceptible to ciprofloxacin.

If the OpGen test identifies 3 or more organisms in a quantity ≥ 100,000 CFU/ml in the sample, then the sample is considered contaminated.