Statistical Analysis Plan: IT001-302

Study Title:	A prospective, Phase 3, randomized, multi-center, double-blind, double dummy study of the efficacy, tolerability and safety of intravenous sulopenem followed by oral sulopenem-etzadroxil with probenecid versus intravenous ertapenem followed by oral ciprofloxacin or amoxicillin-clavulanate for treatment of complicated urinary tract infections in adults.
Study Number:	IT001-302
Study Phase:	Phase 3
Product Name:	Sulopenem (CP-70,429), Sulopenem-etzadroxil (PF-03709270)/Probenecid
Indication:	Complicated urinary tract infection
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Final SAP Date:	September 25, 2019
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SIGNATURE PAGE

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Study Number:	IT001-302

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
cUTI	Complicated Urinary Tract Infection
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
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
WHODRUG	World Health Organization (WHO) Drug Dictionary

1 INTRODUCTION

This document presents the Statistical Analysis Plan (SAP) for the protocol IT001-302, "A prospective, Phase 3, randomized, multi-center, double-blind, double dummy study of the efficacy, tolerability and safety of intravenous sulopenem followed by oral sulopenem-etzadroxil with probenecid versus intravenous ertapenem followed by oral ciprofloxacin or amoxicillin-clavulanate for treatment of complicated urinary tract infections in adults." 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 IT001-302 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 final study protocol as noted on Page 1.

2 STUDY DESIGN

This prospective Phase 3, randomized, multicenter, double-blind, double dummy, controlled study compares intravenous sulopenem followed by oral sulopenem-etzadroxil with probenecid to intravenous ertapenem followed by oral ciprofloxacin or amoxicillin-clavulanate for the treatment of patients with complicated urinary tract infection (cUTI). Approximately 1156 adults with cUTI will be randomized in a 1:1 fashion to receive either IV sulopenem 1000 mg once daily for at least 5 days (5 doses) followed by sulopenem-etzadroxil 500 mg co-administered with oral probenecid 500 mg twice daily to complete 7-10 total days of treatment or ertapenem IV 1000 mg once daily for at least 5 days (5 doses) followed by oral ciprofloxacin 500 mg or amoxicillin-clavulanate 875 mg twice daily to complete 7-10 total days of therapy. The duration of treatment may be extended up to a total duration of 14 days for patients with bacteremia at baseline.

Visits occur on Day 1, Day 5, Day 10 (± 1 day), Day 21 (± 1 day) and Day 28 (± 3 days). The Day 10 visit is the End of Therapy (**EOT**) visit, Day 21 is the Test of Cure (**TOC**) visit and Day 28 is the Final Visit (**FV**) which is a phone call. For patients with bacteremia at baseline whose duration of therapy is extended up to 14 days, the EOT visit should occur on Day 11-14 (± 1 day) correlating with their EOT, instead of on Day 10.

3 STUDY OBJECTIVES

3.1 Primary Objective

To compare the efficacy of sulopenem IV followed by oral sulopenem-etzadroxil plus probenecid with ertapenem IV followed by oral ciprofloxacin or amoxicillin-clavulanate for the treatment of complicated urinary tract infection at the TOC visit.

3.2 Secondary Objectives

- To compare the per-patient microbiologic response across treatment groups.

- To compare the efficacy outcomes at relevant time points
- To assess the safety profile of treatment with each regimen.
- To assess the population PK profile of sulopenem IV and/or sulopenem-etzadroxil co-administered with probenecid.

4 DEFINITION OF ANALYSIS POPULATIONS

4.1 Intent-to-Treat (ITT)

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

4.2 Modified Intent-to-Treat (MITT)

The MITT population 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 five baseline cUTI symptoms listed in inclusion criteria #4.

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 only, susceptible to sulopenem (MIC $\leq$ 1) and ertapenem (MIC $\leq$ 0.5)] and no more than 2 species of microorganisms identified in the study entry urine culture 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) except in the situation where one of the organisms cultured from the urine is also isolated from blood cultures drawn at baseline. Patients with a study pathogen isolated from baseline blood cultures will be included in the m-MITT population regardless of the patient's baseline urine culture result. _See section 6.4 for further details on the use of lab results for determining eligibility for inclusion in the micro-MITT.

4.4 Clinical Evaluable (CE)

Four CE populations will be defined based on the timing of the outcome assessment, CE-Day 5, CE-EOT, CE-TOC and CE-FV. The term "CE population" is used to refer to all. The CE population is a subset of the MITT population and follows the rules below.

a) Received all their protocol defined active study medication up to the timepoint of assessment (i.e., 5 days of IV for the day 5 visit and at least 7 days of therapy in a row for EOT, TOC and FV)

b) Met all inclusion and no exclusion criteria

c) Had no important 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 Day 5, EOT or TOC visits (i.e., within the SAP defined allowed visit window), respectively.

e) Did not receive effective antibacterial drug therapy for cUTI for a continuous duration of more than 24 hours during the previous 72 hours prior to the initiation of study therapy. Patients who have objective documentation of clinical progression of cUTI while on antibacterial drug therapy, or patients who received antibacterial drugs for surgical prophylaxis and then develop cUTI, may be appropriate for inclusion.

f) Did not receive any systemic antibiotic therapy (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) with potential activity against any of the uropathogens collected at baseline between the time of the baseline culture and the Day 5, 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, but not limited to, linezolid, daptomycin or vancomycin).

g) Received appropriate adjunctive antibacterial coverage (i.e., such as, but not limited to, 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 (PSAQ) 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 (up to 14 days) for patients with bacteremia at baseline) 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 5 (ME-Day 5), Day 10 visit (ME-EOT; or Day 11-14 (± 1 day) for patients with bacteremia at baseline) and Day 21 visit (ME-TOC) and have an appropriately collected urine culture specimen and interpretable urine culture (lab culture result reportable by the lab) result at the Day 5, Day 10 (or Day 11-14 (± 1 day) for patients with bacteremia at baseline) and Day 21 visits (i.e., within the SAP defined allowed visit window), respectively.

4.6 Safety

The safety population is comprised of all patients in ITT population who received any amount of study drug.

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 by the sponsor.

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 and ME populations will be determined programmatically and through a manual review conducted by the Sponsor.

5 DEFINITION OF OUTCOMES

5.1 Overall Response

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

A patient will be defined as a success at a given visit (Day 5, EOT and TOC) if the following criteria are met:

- The patient is alive
- Resolution of dysuria, urinary frequency, urinary urgency, suprapubic pain, and flank pain or pelvic pain if present at trial entry and no new symptoms per the patient's questionnaire.
  - Baseline symptoms associated with anatomic abnormalities that predispose to cUTI (e.g., symptoms associated with the presence of an indwelling urinary catheter, benign prostatic hypertrophy, urethral stricture, chronic hydronephrosis, overactive bladder or certain other symptoms that were present before the cUTI event such as flank pain related to a recent procedure) do not need to be resolved.
  - For certain patients PSAQ symptoms may not be relevant and therefore if missing will not be counted as an indeterminate outcome (e.g., patients with an indwelling urinary catheter or suprapubic catheter may not have symptoms of frequency, urgency or dysuria)
- The patient has not received any non-study rescue antibacterial for cUTI (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 is given for other reasons then the patient will not be considered a non-responder for cUTI
- The bacterial pathogen found at $\geq 10^5$ CFU/ml in the trial entry urine cultures are reduced to $<10^3$ CFU/mL in the urine culture taken at the specified study visit and the blood culture is eradicated or was presumed eradicated if one was present at baseline

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

- Patient died due to cUTI
- Patient received non-study antibacterial therapy for cUTI (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 does not have resolution or experiences worsening of symptoms of cUTI (dysuria, urinary frequency, urinary urgency, suprapubic pain, and flank pain or pelvic pain) present at trial entry and/or has new cUTI symptoms.
  - Baseline symptoms associated with anatomic abnormalities that predispose to cUTI (e.g., symptoms associated with the presence of an indwelling urinary catheter, benign prostatic hypertrophy, urethral stricture, chronic hydronephrosis, overactive bladder or certain other symptoms that were present before the cUTI event such as flank pain related to a recent procedure) do not need to be resolved.
  - For certain patients PSAQ symptoms may not be relevant and therefore if missing will not be counted as an indeterminate outcome (e.g., patients with an indwelling urinary catheter or suprapubic catheter may not have symptoms of frequency, urgency or dysuria)
- The bacterial pathogen found at $\geq 10^5$ CFU/ml in the trial entry urine culture is not reduced to $<10^3$ CFU/mL in the urine culture taken at the specified study visit or the blood culture is not eradicated if one was present at baseline

Patients will 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 or the blood pathogen is not eradicated if one was present at baseline in which case the patient is a failure). Patients who died due to other reasons than the cUTI 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 5, EOT and TOC). 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 all 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

Per Pathogen Microbiological Response for Pathogens from Urine	Definition
Eradication	A urine culture taken within 48 hours prior to randomization (baseline) and compared with the culture from the timepoint of analysis showed that the urine culture obtained at the relevant visit demonstrated $<10^3$ CFU/mL of the baseline uropathogen (contaminated results are considered an eradication).
Persistence	A uropathogen from urine present at baseline 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 circumstances that precluded classification as an eradication, presumed eradication, persistence, presumed persistence or persistence with increasing MIC.

* The genus/species and susceptibility profiles need to match. For the baseline and TOC visits, additional molecular testing by pulsed field gel electrophoresis (PFGE) or whole genome sequencing (WGS) may be performed for confirmation.

Per Pathogen Microbiological Response for Pathogens from Blood	Definition
Eradication	The last follow-up blood culture prior to the visit or at the visit is sterile (no growth).
Presumed Eradication	If follow-up blood cultures were not done for patients with bacteremia at baseline, and the patient was assessed as a clinical cure at that visit based on the programmatic determination of clinical response.
Persistence	The last follow-up blood culture prior to the visit or at the visit shows growth of the baseline pathogen.*
Presumed Persistence	If follow-up blood cultures were not done for patients with bacteremia at baseline, and the patient was assessed as a clinical failure at that visit based on the programmatic determination of clinical response.

Persistence with increasing MIC	Follow-up blood cultures taken after at least 2 full days of treatment show growth of the same baseline pathogen displaying ≥4-fold higher MIC to study drug therapy.
Indeterminate	Patient was lost to follow-up or circumstances that precluded classification as an eradication, presumed eradication, persistence, presumed persistence or persistence with increasing MIC.

* The genus/species and susceptibility profiles need to match. For the baseline and TOC visits, additional molecular testing by pulsed field gel electrophoresis (PFGE) or whole genome sequencing (WGS) may be performed for confirmation.

A per pathogen microbiologic success for pathogens from the urine is defined as Eradication (or presumed eradication, if applicable). A pathogen failure is Persistence (or presumed persistence, if applicable) or Persistence with Increasing MIC. A per pathogen microbiologic success for pathogens from the blood are defined in the same way.

When pathogens from urine or blood are presented in the same table the individual per pathogen outcomes are combined into a single outcome where the worst outcome from urine or blood is used. The order from worst to best is Persistence with increasing MIC, Persistence, Presumed Persistence, Indeterminate, Presumed Eradication and then Eradication.

A per patient microbiologic success is defined as all pathogen responses (both urine and blood) for a patient are Eradication (or presumed eradication, if applicable). A per patient microbiologic failure is one or more pathogens for a patient are Persistence (or presumed persistence, if applicable) 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 pathogen in the urine or blood 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 cUTI symptoms requiring non-study systemic antibacterial treatment* (patient-determined clinical failure at EOT).
New Infection	Isolation of a non-baseline pathogen in the urine or blood from a culture post-EOT visit with $\geq 10^5$ CFU/mL in a patient with one or more cUTI 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 in the urine or blood from a culture specimen with $\geq 10^5$ CFU/mL post-EOT visit, along with new or recurrence of one or more cUTI signs/symptoms requiring new systemic antibacterial treatment* after the EOT visit (patient-determined clinical failure post-EOT).
Colonization	Isolation of a micro-organism in the urine or blood after EOT in a patient without one or more signs and symptoms of cUTI 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 5, EOT, TOC and FV) if the following criteria are met (programmatically, based on the data on the eCRF):

- The patient is alive
- Resolution of dysuria, urinary frequency, urinary urgency, suprapubic pain, and flank pain or pelvic pain if present at trial entry and no new symptoms per the patient's questionnaire.
  - Baseline symptoms associated with anatomic abnormalities that predispose to cUTI (e.g., symptoms associated with the presence of an indwelling urinary catheter, benign prostatic hypertrophy, urethral stricture, chronic hydronephrosis, overactive bladder or certain other symptoms that were present before the cUTI event such as flank pain related to a recent procedure) do not need to be resolved.

  - For certain patients PSAQ symptoms may not be relevant and therefore if missing will not be counted as an indeterminate outcome (e.g., patients with an indwelling urinary catheter or suprapubic catheter may not have symptoms of frequency, urgency or dysuria)
- The patient has not received any non-study rescue antibacterial therapy for cUTI (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

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 cUTI 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 Day 5, EOT, TOC and 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 cUTI prior to Day 5, EOT, TOC and FV, respectively • Persistence or progression of any pre-therapy cUTI signs and symptoms or use of additional antibiotics for the current infection • Patient previously met criteria for failure and received rescue antibiotics
Indeterminate	Data not available for evaluation of efficacy for any reason, including but not limited to: • Patient lost to follow-up or assessment not undertaken such that a determination of clinical response could not be made at either the Day 5, EOT, TOC, or FV, respectively • Death prior to Day 5, EOT, TOC, or FV respectively, where cUTI 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:

- 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
- Suprapubic pain (uncomfortable pressure) in the lower abdomen
- Lower back/flank pain
- Pelvic pain (uncomfortable pressure) in the pelvic area

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 Other Signs and Symptoms

In addition to the signs and symptoms collected on the PSAQ, the following will be collected:

- Rigors, chills or fever/hypothermia with temperature (oral, rectal, tympanic, temporal) >100.4ºF or 38ºC, or <95ºF or 35ºC
- Nausea or vomiting
- Costovertebral angle tenderness on physical examination

These symptoms plus the ones collected on the PSAQ will be used to create a supplementary clinical response which will be the same as patient-determined clinical response but with the added signs and symptoms. The supplementary clinical response will use nine symptoms, six from the PSAQ plus these three.

5.7 Safety Outcome 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 sulopenem IV followed by sulopenem-etzadroxil co-administered with probenecid is NI to IV ertapenem followed by oral ciprofloxacin or amoxicillin-clavulanate for the outcome measure of overall response, defined as resolution of the symptoms of cUTI present at trial entry (and no new symptoms) such that no new antibiotics are required (clinical success), and the demonstration that the bacterial pathogen found at trial entry is reduced to $<10^3$ CFU/mL on urine culture (microbiological success).

The proposed sample size for the ITT population is 1156 patients. This ITT sample size estimate is based on the assumption that 80%, or 924 patients, of this ITT population will be m-MITT evaluable. The original sample size of the m-MITT population is 462 patients per arm based on a continuity-corrected Z-test with unpooled variance. This 924 m-MITT sample size assumes a non-inferiority margin of 10%, a power of 90%, a one-sided alpha level of 0.025 and a 70% overall responder rate in both treatment groups.

The expected overall response rate is estimated from large randomized controlled trials in a

similar cUTI patient population [Wagenlehner 2015, Wagenlehner 2016]. In those studies, the estimated response rate for the proposed primary efficacy outcome measure of overall response (combined clinical and microbiologic response) at TOC in the m-MITT population was 70%. The aggregate blinded response rate will be assessed when approximately 60% of the subjects have been randomized and have efficacy outcome data at TOC available. If the aggregate response rate at that point is <70%, or if the evaluability rate (proportion of ITT subjects included in the m-MITT population) is <80%, the sample size may be increased to maintain a power of 90% (see section 7.6); the sample size methodology used at this interim assessment may or may not include a continuity correction.

6.2 Randomization

Patients will be randomized in a 1:1 ratio to sulopenem IV followed by oral sulopenem-etzadroxil plus probenecid or ertapenem IV followed by oral ciprofloxacin or amoxicillin-clavulanate using an Interactive Web Randomization System (IWRS), provided they have satisfied all patient selection criteria. The randomization schedule will be stratified by the type of infection (pyelonephritis vs cUTI without pyelonephritis). No more than 25% of patients may have received prior antibiotic therapy, and at least 30%, but no more than 70% of patients may have acute pyelonephritis. 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 and TOC. If their assessments are out of window, they will not be included in that population.

For the ITT, MITT and micro-MITT 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 efficacy.

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 5	No window
Day 10 - End of Treatment (EOT) or Day 11-14 for patients with bacteremia at baseline	± 1 day
Day 21 - Test of Cure (TOC)	± 1 day
Day 28 - Final Visit (FV)	± 3 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*
- The micro-MITT population will only include patients with UTIs caused by Enterobacteriaceae (study uropathogens), susceptible to ertapenem with an MIC ≤0.5 µg/mL and susceptible to sulopenem with an MIC ≤1.0 µg/mL. Patients may have other non-Enterobacteriaceae uropathogens

The following normal flora are never a pathogen:

- Corynebacterium spp.
- *S. epidermidis*
- *S. aureus*
- *S. saprophyticus*
- 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. All organisms isolated from a blood culture will be reviewed by the Sponsor to determine if the organism is a pathogen.

Blood cultures should be drawn at Baseline (prior to study drug treatment) from 2 different anatomical sites and not through an existing intravascular line. If positive, blood cultures should be repeated immediately (no later than 24 hours after notification) until negative.

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 outcome, 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

7.1 Patient Disposition

The number of patients included in each of the study populations (i.e., ITT, Safety, MITT, Micro-MITT, CE-Day 5, CE-EOT, CE-TOC, ME-Day 5, ME-EOT and ME-TOC) 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 and CRF (rigors / chills / temperature, nausea / vomiting, costovertebral angle tenderness) will be summarized by treatment group and compared using the Wilcoxon Rank Sum test for ordinal data.

The factors defining complicated UTI will be summarized by treatment group:

i. The presence of an indwelling urethral catheter
ii. >100 mL of residual urine after voiding
iii. Neurogenic bladder
iv. Obstructive uropathy due to nephrolithiasis, tumor or fibrosis
v. Azotemia (blood urea nitrogen [BUN] > 20 mg/dL and BUN/creatinine ratio <15) due to intrinsic renal disease
vi. Urinary retention in men possibly due to benign prostatic hypertrophy

vii. Surgically modified or abnormal urinary tract anatomy

7.2.1 Baseline Microbiology

The microbiological assessment of the baseline urine and blood samples will be summarized by treatment group for the micro-MITT and ME 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 at $\geq 10^5$ CFU/ml and $>10^3$-$<10^5$ CFU/ml will also be presented.

The bacterial pathogens identified from the baseline urine cultures and blood cultures will be presented. The number and percentage of patients with a gram-positive pathogen and with a gram-negative pathogen will be presented by genus and species for the MITT, micro-MITT and ME populations. The same pathogen identified from both the blood and the culture of the infection site will be counted only once in the summary. In addition, the number and percentage of patients with infections that are mono-microbial, poly-microbial, ESBL positive, ESBL negative, quinolone positive, quinolone negative and ESBL+ and quinolone non-susceptible pathogens (subjects with a resistant baseline pathogen that precludes oral step down). If either the urine specimen or blood culture is ESBL positive, then the patient will be presented as ESBL positive; same for quinolone resistance.

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. Pathogens from urine specimen and blood cultures will be presented separately and combined. All drugs in which MIC data is available will be presented. These include the following.

- The distribution of MIC to sulopenem, ertapenem, ciprofloxacin, amoxicillin-clavulanate 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.

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

A dosing summary by treatment group will be presented for all study populations. The distribution of patients by the number of days on study drug therapy in each treatment group will be presented for overall dosing and separately by oral dosing only and IV dosing only. For patients who step down to active sulopenem etzadroxil/probenecid, each tablet taken is considered a half day of therapy. For patients who step down to active ciprofloxacin, each capsule taken is considered a half day of therapy. For patients who step down to active amoxicillin-clavulanate, each capsule taken is considered a half day of therapy.

7.5 Efficacy Analyses

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

Unless otherwise stated, patients who were randomized to the wrong infection type (pyelonephritis vs cUTI without pyelonephritis) stratum will be analyzed in the stratum to which they were randomized.

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 outcome is based on overall response at the Day 21 (± 1 day; TOC) visit in the micro-MITT population. Patients will be programmatically categorized as a responder, non-responder, or indeterminate response. Patients with missing data or who are lost to follow-up are defined as indeterminate for the primary analysis and are included in the denominator for the calculation of overall response rate. Thus, patients with an indeterminate outcome are considered non-responders for the primary analysis. The number and percentage of patients in

each treatment group in each response category will be reported. The null and alternative hypothesis are the following:

H_0: $P_1 - P_2 \leq -\Delta$

H_1: $P_1 - P_2 > -\Delta$

Where:

P_1 = the primary efficacy outcome in the sulopenem IV/sulopenem-etzadroxil group,

P_2 = the primary efficacy outcome in the ertapenem/oral ciprofloxacin or amoxicillin-clavulanate group,

Δ = the non-inferiority margin.

The non-inferiority 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% confidence interval (CI) for the observed difference in the overall success rate (sulopenem treatment group minus the ertapenem treatment group). The primary analysis is based on a CI computed using a Z-statistic. If the lower limit of the 95% CI for the difference in the micro-MITT population is greater than - 10%, the null hypothesis will be rejected and the non-inferiority of sulopenem IV/sulopenem-etzadroxil to ertapenem/oral ciprofloxacin or amoxicillin-clavulanate will be concluded.

7.5.2 Additional Analyses of the Primary Efficacy Outcome

- Subgroup Analyses
  - Infection Type (pyelonephritis vs cUTI without pyelonephritis)
  - Geographic Region (U.S. vs. non-U.S.)
  - Fed / Fasted State
  - Hypoalbuminemia
  - cUTI Diagnoses
- Sensitivity Analyses
  - Adjustment for Stratification Factor of Infection Type
  - Patients not eligible to switch to oral therapy due to resistance to the oral agents (sulopenem, ciprofloxacin, amoxicillin/clavulanate) will be considered as failures
  - 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 cUTI symptoms
  - Overall response defined by urgency and frequency are improved and no worse than mild and all other symptoms are resolved and no new cUTI 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

A LOCF analysis will be conducted where overall response will be carried forward for patients who died, if there are enough deaths to justify the analysis.

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

A two-sided 95% CI for the observed difference in the overall response rates will be calculated for each subgroup in the below subgroup analyses.

- The primary efficacy outcome at TOC will be assessed within each baseline infection type (pyelonephritis vs cUTI without pyelonephritis) strata by treatment group.
- The primary efficacy outcome at TOC will also be assessed within each geographic region (U.S. vs. non-U.S.) by treatment group.
- A subgroup analysis of the primary efficacy outcome by fed / fasted state will be conducted. A patient will be considered fed if they took 100% of their doses in a fed state. If the patient did not take oral dosing they will be excluded from this analysis. Different proportions of doses taken in a fed state may be explored if the analysis suggests that the fed state is associated with outcome.
- A subgroup analysis of the primary efficacy endpoint in those patients with and without hypoalbuminemia (serum albumin <2.0 g/dL) at baseline will be conducted.
- As presently defined in the study protocol and case report form, 'cUTI without pyelonephritis' patients can have 'flank pain or pelvic pain' and 'costovertebral angle tenderness'. An analysis of the primary endpoint will be performed with mutually exclusive subgroups of cUTI, specifically 'pyelonephritis', 'cUTI without pyelonephritis' and 'cUTI without pyelonephritis' but with evidence of pyelonephritis (i.e., 'flank pain or pelvic pain' and 'costovertebral angle tenderness').

Sensitivity analyses of the primary outcome will be conducted and a 2-sided 95% CI will be computed for the difference in the success rates between the treatment groups, unless stated otherwise.

- An adjusted analysis (95% CI will be adjusted for the stratification factor of infection type using the stratified method of Miettinen and Nurminen) will be provided for the difference in the overall response rate between the two treatment groups. Cochran-Mantel-Haenszel weights will be used for the stratum weights in the calculation of the CI.
- A sensitivity analysis of the primary outcome at TOC will be conducted where patients not eligible to switch to oral therapy due to non-susceptibility to the oral agents (ertapenem, ciprofloxacin, amoxicillin/clavulanate) will be considered as failures (patients treated with sulopenem who are non-susceptible to ertapenem and patients treated with ertapenem who are non-susceptible to both ciprofloxacin and amoxicillin/clavulanate will be considered failures).
- A sensitivity analysis will consider all patients who have missing data for the primary outcome (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 microbiological eradication contributing to the overall response requires complete eradication defined as no growth (<100 CFU/mL) of baseline pathogen on a follow-up urine culture at TOC.
- An analysis will consider the primary outcome at TOC defined in section 5.1 except, improvement of symptoms (instead of resolution) from baseline and no worse than mild and no new cUTI symptoms.
- An analysis will consider the primary outcome 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 cUTI symptoms.
- An optional analysis of the primary efficacy outcome measure will be conducted in an adjusted micro-MITT population utilizing results from both culture and rapid diagnostic testing. In addition to patients with $\geq 10^5$ CFU/ml by culture, patients with baseline urine samples in which a study uropathogen is identified by rapid diagnostic testing and a quantity consistent with $\geq 10^5$ CFU/ml by culture will be included in the micro-MITT population. These patients may include those with a study uropathogen identified by culture with an organism burden of $>10^3$ - $<10^5$ CFU/ml or patients whose urine culture was missing at baseline but for whom a banked urine specimen was available for analysis.
- 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.

7.5.3 Secondary Efficacy Analysis

The number and percentage of patients with a per-patient microbiologic response of eradication, persistence, persistence with increasing MIC, and indeterminate at the Day 21 (± 1 day; TOC) visit will be determined in each treatment group in the m-MITT population. The observed difference in percentage of patients with a microbiologic eradication (sulopenem group minus ertapenem group) will be determined and a 95% CI for the observed difference will be computed using a Z-statistic.

7.5.4 Additional Efficacy Analyses

Analysis	Day 5	EOT (Day 10)	TOC (Day 21)	FV (Day 28)

Overall Response	Micro-MITT ME	Micro-MITT ME	Micro-MITT[#] ME	
Overall Response by Baseline Pathogens	Micro-MITT ME	Micro-MITT ME	Micro-MITT ME	
Overall Response by MIC			Micro-MITT ME	
Overall Response by Combination of Antibiotic Resistance Classes	Micro-MITT ME	Micro-MITT ME	Micro-MITT ME	
Overall Response by 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	
Overall Response by Step Down Category	Micro-MITT ME	Micro-MITT ME	Micro-MITT ME	
Microbiologic Response	Micro-MITT ME	Micro-MITT ME	Micro-MITT[##] ME	
Per Pathogen Microbiologic Response from Urine, Blood and Combined	Micro-MITT ME	Micro-MITT ME	MITT Micro-MITT ME	
Microbiologic Response by ESBL Positive and ESBL Negative	Micro-MITT ME	Micro-MITT ME	Micro-MITT ME	
Per Pathogen Microbiologic Response by MIC			Micro-MITT ME	
Microbiologic Response for Complete Eradication	Micro-MITT ME	Micro-MITT ME	Micro-MITT ME	
Microbiologic Response for Complete Eradication by Baseline Pathogens	Micro-MITT ME	Micro-MITT ME	Micro-MITT ME	
Microbiologic Response for Post-Baseline Pathogens		Micro-MITT ME	Micro-MITT ME	
Patient Determined Clinical Response	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE
Patient Determined Clinical Response by Baseline Pathogen	Micro-MITT ME	Micro-MITT ME	Micro-MITT ME	Micro-MITT
Patient Determined Clinical Response by ESBL Positive and ESBL Negative	Micro-MITT ME	Micro-MITT ME	Micro-MITT ME	Micro-MITT
Patient Determined Clinical Response defined by improvement of symptoms (instead of resolution) from baseline and no worse than mild and no new cUTI symptoms			ITT MITT Micro-MITT CE ME	
Patient Determined Clinical Response defined by urgency and frequency are improved and no worse than mild and all other symptoms are resolved and no new cUTI symptoms			ITT MITT Micro-MITT CE ME	
Investigator-Determined Clinical Response	ITT MITT Micro-MITT CE	ITT MITT Micro-MITT CE	ITT MITT Micro-MITT CE	ITT MITT Micro-MITT CE

	ME	ME	ME	
Patient Symptom Assessment Questionnaire	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE
Patient Symptom Assessment Questionnaire – Shift Table of Severity	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE
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 CE ME	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE
Patient Symptom Assessment Questionnaire – Sensitivity Analysis using bothersome questions	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE
Other Signs & Symptoms (rigors / chills / temperature, nausea / vomiting, costovertebral angle tenderness)	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME	
Supplementary Clinical Response	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME	

Primary Endpoint
Secondary 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 MITT and micro-MITT populations.

Overall Response

The number and percentage of patients in each treatment group with an overall response of success, failure and indeterminate at Day 5 and EOT will be presented for the micro-MITT population (note, overall response at TOC in the micro-MITT population is the primary endpoint). The number and percentage of patients in each treatment group with an overall response of success and failure at Day 5, EOT and TOC 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.

Overall response at Day 5, EOT and TOC by baseline pathogen (key pathogens and species such as *E. coli*, Klebsiella species and Proteus species) will be summarized by treatment group

in the micro-MITT and ME populations. Confidence intervals at the genus level will be provided.

Overall response by ertapenem MIC and sulopenem MIC for baseline pathogens will be provided for TOC visit.

Overall response by combination of antibiotic resistance classes will be provided. The classes will be ESBL status, quinolone non-susceptible (QNS), TMP-SMX resistant, non-susceptible to at least 2 classes of antibacterials (MDR – quinolones, TMP-SMX and beta-lactams), resistance to all three classes (quinolones, TMP-SMX 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 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.

Overall response by the IV/Oral treatment regimen they took (e.g., ertapenem IV only, ertapenem IV followed by ciprofloxacin, etc.) and what they were supposed to take per susceptibility data (e.g., ciprofloxacin susceptible, ciprofloxacin resistant/intermediate and amoxicillin/clavulanate, etc.) will be provided.

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 5 and EOT will be presented for the micro-MITT population (note, microbiologic response at TOC in the micro-MITT population is the secondary endpoint). The number and percentage of patients in each treatment group with a per patient microbiologic response of success and failure at Day 5, EOT and TOC 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.

Per pathogen microbiologic response at Day 5, EOT and TOC by baseline pathogen will be summarized by treatment group in the micro-MITT and ME populations separately for urine and blood, and then combined. Confidence intervals at the genus level will be provided.

Microbiologic response by ESBL positive and ESBL negative at Day 5, EOT and TOC will be summarized by treatment group in the micro-MITT and ME populations.

Per pathogen microbiologic response by ertapenem MIC and sulopenem MIC for individual pathogens will be provided for TOC visit.

The number and percentage of patients in each treatment group with a microbiologic response of complete eradication defined as no growth ($<10^2$ CFU/mL) of baseline pathogen on a follow-up culture at Day 5, EOT and TOC will also be presented for the micro-MITT and ME populations and by baseline pathogen. The EMA analysis dataset will include a supportive analysis in which $<10^2$ CFU/mL at TOC are required in the micro-MITT population. 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 5, EOT, TOC and FV will be presented for the micro-MITT, MITT and ITT populations. The number and percentage of patients in each treatment group with a patient-determined clinical response of success and failure at Day 5, EOT, TOC and FV will be presented for the CE and ME populations (there isn't an ME population for FV since it was a phone call visit). Two-sided 95% unstratified CIs will be constructed for the observed difference in the overall success rates between the treatment groups for descriptive purposes; no conclusion of NI will be made.

Patient determined clinical response will also be presented by baseline pathogen and by ESBL positive/negative for Day 5, 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 cUTI symptoms will also be presented for Day 5, EOT and TOC in each treatment group for all populations.

Patient determined clinical response defined by urgency and frequency are improved and no worse than mild and all other symptoms are resolved and no new cUTI symptoms will also be presented for Day 5, EOT and TOC in each treatment group for all populations.

Investigator-Determined Clinical Response

Investigator-determined clinical response (clinical success, failure and indeterminate) at the Day 5, EOT, TOC and FV visits will be presented by treatment group for the micro-MITT, MITT, ITT, 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 cUTI symptom based on the PSAQ to Day 5, EOT, TOC and FV will be provided by treatment group for all populations.

A shift table of the severity of each cUTI symptom based on the PSAQ from baseline to Day 5, EOT, TOC and FV will be presented by treatment group for the micro-MITT, MITT, ITT,

CE and ME populations.

Kaplan-Meier plots for time to resolution of all PSAQ symptoms will be provided for the MITT and micro-MITT populations. Patients will be censored at time of taking non-study antibacterial therapy for cUTI, lost to follow-up or at the end of the study if the symptoms have not resolved.

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 Day 5, EOT and TOC in the micro-MITT, MITT, ITT, CE and ME 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. These negative symptoms will be counted as 'no symptom'.

Supplementary Clinical Response

The other signs and symptoms (rigors / chills / temperature, nausea / vomiting, costovertebral angle tenderness) will be added to the PSAQ signs and symptoms to create a supplementary clinical response which will be the same as patient-determined clinical response but with the added signs and symptoms.

The number and percentage of patients in each treatment group with a supplementary clinical response of success, failure and indeterminate at Day 5, EOT and TOC will be presented for the micro-MITT, MITT and ITT populations. The number and percentage of patients in each treatment group with a supplementary clinical response of success and failure at Day 5, EOT and TOC 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.

7.6 Interim Analysis

In order to ensure that the point estimate of overall response (combined clinical and microbiologic response) used in the estimation of sample size is valid for this study, an interim analysis for sample size re-estimation will be performed when response data at Day 21 (± 1 day; TOC) are available for approximately 60% of the patients (692 patients). 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 the sulopenem regimen is NI to the comparator treatment regimen for the primary outcome measure. In addition, the sample size may be increased based on a lower than expected evaluability rate. The sample size re-estimation will be based on the blinded overall (not by treatment group) outcome rate and evaluability rate and will be conducted by an independent, blinded statistician. A Data Monitoring Committee (DMC) will be provided the results of the interim analysis by the independent, blinded 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 [unrelated (unrelated or unlikely) or related (possibly or probably)] to IV and oral 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 (list all categories collected) and age (<65 and ≥ 65).

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 include verbatim terms 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. If the patient did not take oral dosing they will be excluded from this analysis. Only AEs that occur while taking oral dosing will be analyzed.

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 the 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 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 current protocol and the SAP:

- The following are additions or changes to the clinical evaluable definition:
    - The patient must meet all inclusion and none of exclusion criteria.
    - Received appropriate adjunctive antibacterial coverage (i.e., such as, but not limited to, 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 (PSAQ) at the post-baseline visit.
    - Site personnel involved in the assessment of efficacy parameters must have remained blinded to study treatment up to the time of the efficacy assessment.
    - Patients who receive study drug therapy beyond the protocol treatment period as a result of the investigator's assessment that additional drug therapy is needed for treatment of the underlying cUTI 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 microbiologic response, post baseline responses of superinfection, new infection, colonization and recurrence were added.
- The analysis of diarrhea 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 cUTI symptoms
    - Overall response defined by urgency and frequency are improved and no worse than mild and all other symptoms are resolved and no new cUTI symptoms
    - Missing Data / Indeterminates Equal Success
    - Multiple Imputation for Missing Data
    - Overall response defined by both urine and blood cultures
    - Patients with baseline urine samples in which a study uropathogen is identified by rapid diagnostic testing and a quantity consistent with $\geq 10^5$ CFU/ml by culture will be included in the micro-MITT population. These patients may include those with a study uropathogen identified by culture with an organism burden of $>10^3$- $<10^5$ CFU/ml or patients whose urine culture was missing at baseline but for whom a banked urine specimen was available for analysis.
    - A LOCF analysis will be conducted where overall response will be carried forward for patients who died, if there are enough deaths to justify the analysis.
    - Covariate Analysis
    - cUTI baseline factors
    - Hypoalbuminemia

9 REFERENCES

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3. Guidance for Industry: Non-Inferiority Clinical Trials. Draft. March 2010.

4. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July 2009.

5. Guidance for Industry: Adaptive Design and Clinical Trials for Drugs and Biologics. Draft. March 2010.

6. Karvanen J. The Statistical Basis of Laboratory Data Normalization. Drug Information Journal, Vol. 37, pp. 101–107, 2003.

Appendix A: Schedule of Activities

	SCREENING	TREATMENT PERIOD			FOLLOW-UP PERIOD			
Protocol Activity	**D-1 to D1** **Baseline**	**D1**	**D5** **On Treatment**	**D10[5] (± 1 day)**	**D21 (± 1 day) TOC**	**D28[6] (± 3 days) FV (phone call)**	**Premature Discontinuation**	
							Study Drug[7]	**Study**
Informed Consent	X							
Medical History and Demographics	X							
Targeted Physical Examination[1]	X		X[1]	X[1]	X[1]		X[1]	X[1]
Vital Signs	X		X	X	X		X	X
Hematology	X		X	X	X[2]			X
Serum Chemistry	X		X*	X	X[2]			X
Pregnancy testing	X							X
Banked serum sample	X			X				
Banked urine sample	X			X				
Urinalysis	X		X	X	X		X	X
Urine Gram stain	X							
Urine Culture	X		X	X	X		X	X
Peripheral Blood cultures[3]	X							
Plasma and urine PK sampling for sulopenem[4]		X[4]						
Previous Drug and Non-drug Treatments	X							
Concomitant Medications		X	X	X	X	X	X	X
Treatment		X (each day for 7-10 days; may be extended to 14 days for patients with bacteremia at baseline)						
Compliance check with oral therapy				X			X	
Adverse Events	X	X	X	X	X	X	X	X
Patient Symptom Assessment Questionnaire	X		X	X	X	X	X	X
Investigator assessment of clinical response			X	X	X	X	X	X

Schedule of Activities Footnotes:

1 Post-baseline, to be done if needed, based on symptoms

2 As needed to follow up on abnormal labs from Day 10 (± 1 day; or Day 11-14 (± 1 day) for patients with bacteremia at Baseline)

3 Blood cultures should be drawn at Baseline (prior to study drug treatment) from 2 different anatomical sites and not through an existing intravascular line. If positive, blood cultures should be repeated immediately (no later than 24 hours after notification) until negative.

4 In the subset of patients enrolled in the PK sub-study, collect plasma for PK analysis 2 hours and 4 hours post-

dose on Day 1; collect plasma for PK analysis 2 hours, 4 hours and 6 hours post-dose after first oral dose. Analysis to be performed only on samples collected from patients in the sulopenem treatment group. Patients will empty their bladder just prior to initiation of oral dosing on the day of the oral switch and a 1 ml aliquot from this urine will be frozen. 1 ml aliquots of urine from the following intervals after administration of the first dose of oral study drug after IV to oral switch: 0-2 hours, 2-4 hours, 4-6 hours, 6-8 hours, and 8-12 hours, may be collected and frozen for PKPD assessments.

5 For patients with bacteremia at baseline whose duration of therapy is extended up to 14 days, the EOT visit should occur on Day 11-14 (± 1 day) correlating with their EOT, instead of on Day 10. This visit should include collection of a urine specimen for urinalysis and urine culture, review of concomitant medications, compliance check with oral therapy, adverse events, PSAQ, and investigator assessment.

6 Patients should return to provide a urine specimen for urinalysis, urine culture and susceptibility in case of relapse of urinary symptoms

7 Visit to be completed within 3 days of discontinuation from study drug therapy

* If estimated CrCl is abnormal at Baseline, a repeat serum creatinine must be obtained at Day 5 in order to re-evaluate the CrCl and determine the appropriate oral or IV therapy.

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

Urine Culture

1. Baseline urine sample is submitted for culture to Local/Regional Lab
2. All pathogens identified at the local/regional lab will be considered as part of the baseline urine culture result.
   a. Uropathogens as defined in section 6.4 will be sent 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 lab.
3. If Local/Regional Lab's urine culture yields >2 micro-organisms in a quantity of >105 CFU/mL, this will be considered as "contaminated."

Blood Culture

1. Baseline blood sample is submitted for culture to Local/Regional Lab
   a. If Local/Regional Lab's blood culture is "no growth", then the Local/Regional Lab's result is accepted as final
   b. If Local/Regional Lab's blood culture yields an organism(s), the isolate(s) is forwarded to IHMA for confirmation
      i. The result of IHMA's testing of this isolate(s) will be accepted as the final result
   c. If Local/Regional Lab's isolate(s) is lost or dies in transit then the Local/Regional Lab's pathogen identification will be accepted as the final result.