Statistical Analysis Plan: IT001-303

Study Title:	A prospective Phase 3, double-blind, multicenter, randomized study of the efficacy and safety of sulopenem followed by sulopenem etzadroxil with probenecid versus ertapenem followed by ciprofloxacin and metronidazole or amoxicillin-clavulanate for treatment of complicated intra-abdominal infections in adults.
Study Number:	IT001-303
Study Phase:	Phase 3
Product Name:	Sulopenem (CP-70,429), Sulopenem-etzadroxil (PF-03709270)/Probenecid
Indication:	Complicated intra-abdominal infection (cIAI)
Study Statistician:	Michael Zelasky
Study Clinician:	Steven I. Aronin, M.D.
Sponsor:	Iterum Therapeutics International Limited 20 Research Parkway, Suite A Old Saybrook, CT 06475
Final SAP Date:	August 6, 2019 (Version 1)
Revised SAP Date:	October 17, 2019 (Version 2) December 6, 2019 (Version 2.1)
Protocol Version:	July 19, 2019 (Amendment 2)

SIGNATURE PAGE

Study Title:	A prospective Phase 3, double-blind, multicenter, randomized study of the efficacy and safety of sulopenem followed by sulopenem etzadroxil with probenecid versus ertapenem followed by ciprofloxacin and metronidazole or amoxicillin-clavulanate for treatment of complicated intra-abdominal infections in adults.
Study Number:	IT001-303

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

Prepared by: Michael Zelasky Date: 06DEC2019

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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
cIAI	Complicated Intra-Abdominal Infection
EOT	End of Treatment Visit
ESBL	Extended-Spectrum β-Lactamases
FDA	Food and Drug Administration
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
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 IT001-303, "A prospective Phase 3, double-blind, multicenter, randomized study of the efficacy and safety of sulopenem IV followed by sulopenem etzadroxil with probenecid versus ertapenem followed by ciprofloxacin and metronidazole or amoxicillin-clavulanate for treatment of complicated intra-abdominal 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 IT001-303 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 included in an addendum to the SAP and 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.

This version (2.1) of the SAP includes addendum 1 which contains changes in the SAP since version 2.0 was finalized. The addendum includes changes made prior to database lock, between database lock and creation of the unblinded SDTM datasets and after topline tables unblinded to treatment group were released but prior to unblinded listings and datasets were made available to the Sponsor.

2 STUDY DESIGN

This prospective Phase 3, double-blind, multicenter, randomized study compares sulopenem IV followed by sulopenem etzadroxil with probenecid versus ertapenem followed by ciprofloxacin and metronidazole or amoxicillin-clavulanate for treatment of complicated intra-abdominal infections in adults. Approximately 670 adults with cIAI will be randomized in a 1:1 fashion to receive either sulopenem IV 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 and metronidazole 500 mg or amoxicillin-clavulanate 875 mg twice daily to complete 7-10 total days of therapy. The duration of therapy in both treatment groups may be extended up to a total duration of 14 days if both (a) approved by the medical monitor, and (b) the patient has either multiple abscesses or non- appendix-related diffuse peritonitis AND has one of the following: fever or hypothermia (temperature ≥38°C or <35°C), leukocytosis defined as WBC ≥12,000/mm^3, or ileus.

Visits occur on Day 1, Day 5, Day 10 (± 1 day), Day 21 (± 1 day) and Day 28 (± 1 day). The Day 10 visit is the End of Therapy (**EOT**) visit, Day 21 is a phone call and Day 28 is the Test of Cure (**TOC**) visit. For patients requiring up to 14 days of therapy, 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 sulopenem etzadroxil with probenecid versus ertapenem followed by ciprofloxacin and metronidazole or amoxicillin-clavulanate for treatment of complicated intra-abdominal infection in adults, on Day 28 (TOC) post-randomization.

3.2 Secondary Objectives

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

4 DEFINITION OF ANALYSIS POPULATION

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 the ITT population who received at least a single dose of study medication and had the disease under study as defined as meeting inclusion criterion 3.

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

The micro-MITT population will include all MITT patients who have at least one gram-negative study pathogen (aerobe or anaerobe organisms) identified at study entry within 48 hours prior to first dose and up to 24 hours after the first dose, regardless of isolate susceptibilities and regardless of other organisms identified in the culture (see Section 6.4). Patients whose baseline cultures have ONLY gram-positive species will be excluded.

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-Day 21 and CE-TOC. The term "CE population" is used to refer to those patients who:

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 for EOT, Day 21 and TOC);
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 clinical response of cure or failure (and not indeterminate) at the visit in question (i.e., within the SAP defined allowed visit window), respectively;

e) Had not received more than 24 hours of a short acting antibiotic within the 72 hours prior of the initiation of study therapy. However, if a patient received more than 24 hours of an antibiotic for previous treatment failure, then this rule does not apply.
f) Did not receive any non-study systemic antibiotic therapy with potential activity against any of the pathogens collected at baseline between the time of the baseline culture and the visit being analyzed. 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 pathogen resistant to study drugs are allowed to receive agents with narrow spectrum gram-positive coverage (i.e., such as linezolid, daptomycin or vancomycin);
g) Site personnel involved in the assessment of efficacy parameters remained blinded to study treatment up to the time of the efficacy assessment,
h) Patients who receive study drug therapy beyond the protocol treatment period (up to 14 days) as a result of the investigator's assessment that additional drug therapy is needed for treatment of the underlying intra-abdominal 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)

The Microbiologically Evaluable populations will include those patients in both the micro-MITT and CE populations at the Day 5 (ME-Day 5), EOT (ME-EOT), Day 21 (ME-Day 21) and TOC visits (ME-TOC) who have a microbiologic response that is not indeterminate for the respective visit.

4.6 Safety

The safety population will include all patients in ITT population who received any amount of study drug.

4.7 Determination of Inclusion in Analysis Populations

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

Inclusion in 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 in the micro-MITT and ME populations will be determined programmatically and through a manual review conducted by the Sponsor.

5 DEFINITION OF ENDPOINTS

5.1 Clinical Response

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

A patient will be defined as a cure at a given visit (Day 5, EOT, Day 21 and TOC) if there is no reason for failure and the following criteria are met:

- The patient is alive
- Resolution of baseline signs and symptoms of the index infection and no new symptoms. Baseline signs and symptoms are further specified as follows:
  - Fever (defined as body temperature >38°C) or hypothermia with a core body temperature <35°C
  - Elevated white blood cell count (>12,000 cells/mm^3) or leukopenia (defined as white blood cell count <4,000 cells/mm^3). If WBC data is missing, then then this rule does not apply.
  - Systolic blood pressure <90 mm Hg
  - Oxygen saturation ≤90 percent. If oxygen saturation data is missing, then then this rule does not apply.
  - Abdominal pain and/or tenderness, with or without rebound
  - Localized or diffuse abdominal wall rigidity
  - Abdominal mass
  - Nausea and/or vomiting (can have nausea and/or vomiting due to AE but not due to failure)
  - Altered Mental Status
- No new non-study antibiotics taken as rescue therapy per the CRF or interventions for treatment failure are required nor a second course of study therapy

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

- Patient died due to cIAI
- Surgical site wound infection requiring non-study systemic antibiotic therapy
- Unplanned surgical procedures or percutaneous drainage procedures for complication as indicated on the Surgical Intervention CRF page or recurrence of cIAI based on documented worsening symptoms or signs of cIAI. If a patient has a surgical intervention, they will be a clinical failure for that visit and all subsequent

visits.

- Initiation of non-study antibacterial drug therapy taken as rescue therapy per the CRF or a second course of study therapy for treatment of cIAI based on documented worsening symptoms or signs of cIAI

Patients will be defined as having an indeterminate outcome if:

- Any data needed to determine whether the outcome is cure or failure are missing
- The cause of death is something other than the cIAI.

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, Day 21 and TOC). It is assessed for each pathogen present at baseline.

Per patient microbiologic response is a patient level response determined by the results of any cultures collected 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 Site Specimen	**Definition**
Eradication	A site specimen collected at a post-baseline visit deemed acceptable after manual review indicates absence of the baseline pathogen.
Presumed Eradication	There was no post-baseline site specimen for culture deemed acceptable after manual review and the patient was assessed as a clinical cure based on the programmatic determination of clinical response.
Persistence	A post-baseline site specimen deemed acceptable after manual review indicates presence of the baseline pathogen.
Presumed Persistence	There was no post-baseline site specimen for culture deemed acceptable after manual review and the patient was assessed as a clinical failure based on the programmatic determination of clinical response.
Persistence with increasing MIC	A post-baseline site specimen culture deemed acceptable after manual review for patients who have taken at least 2 full days of treatment indicates continued presence of the same baseline pathogen displaying ≥4 fold higher MIC to study drug therapy.

Indeterminate	Study data were not available for evaluation of efficacy, for any reason including: o Patient was lost to follow up or an assessment was not undertaken such that no culture was obtained (or culture results could not be interpreted for any reason) and the patient could not be assessed as a clinical cure or failure based on the programmatic determination of clinical response at the time of the visit o Death prior to the visit, where the underlying infection was clearly non-contributory o Circumstances that precluded classification as an eradication, presumed eradication, persistence, presumed persistence or persistence with increasing MIC

The data from unscheduled site specimen cultures will be used in the assessment of microbiologic response if the date of the unscheduled site specimen culture is on the same day of the analysis visit (day 5, day 10, day 28). If it occurs on another day, the normal microbiologic response algorithm will be used which will allow for the possibility of presumed eradication or presumed persistence.

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.
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 based on the programmatic determination of clinical response.
Persistence	The last follow-up blood culture prior to the visit or at the visit, after 72 hours of study treatment (3 days of IV infusions), 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 based on the programmatic determination of clinical response.
Persistence with increasing MIC	Follow-up blood cultures, after 72 hours of study treatment (3 days of IV infusions), show growth of the same baseline pathogen

	displaying ≥4 fold higher MIC to study drug therapy.
Indeterminate	Study data were not available for evaluation of efficacy, for any reason including: o Patient was lost to follow up or an assessment was not undertaken such that no culture was obtained (or culture results could not be interpreted for any reason) and the patient could not be assessed as a clinical cure or failure based on the programmatic determination of clinical response at the time of the visit o Death prior to the visit, where the underlying infection was clearly non-contributory o Circumstances that precluded classification as an eradication, presumed eradication, persistence, presumed persistence or persistence with increasing MIC

A per pathogen microbiologic success for pathogens from the site specimen is defined as eradication or presumed eradication. A per pathogen failure is persistence, presumed persistence or persistence with increasing MIC. A per pathogen microbiologic success for pathogens from the blood are defined in the same way.

When pathogens from the site specimen 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 for a patient are eradication or presumed eradication. A per patient microbiologic failure is one or more pathogens for a patient are persistence, presumed 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 pathogen that was not present at baseline is isolated from a site specimen or blood collected sometime following the first dose of study drug through EOT in the setting of

	recurrent/persistent/new cIAI symptoms requiring non-study systemic antibacterial treatment (clinical failure at EOT based on the programmatic determination of clinical response).
New Infection	Isolation of a non-baseline pathogen from a site specimen or blood culture post-EOT visit in a patient with one or more new cIAI signs/symptoms requiring new non-study systemic antibacterial treatment after the EOT visit (clinical failure post-EOT based on the programmatic determination of clinical response).
Recurrence	In a patient considered a clinical and microbiological success at EOT, isolation of the baseline pathogen from a site specimen or blood at a post-EOT visit, along with new or recurrent cIAI signs/symptoms requiring new non-study systemic antibacterial treatment after the EOT visit (clinical failure post-EOT based on the programmatic determination of clinical response).
Colonization	Isolation of a microorganism from a site specimen or blood culture after EOT in a patient without one or more signs and symptoms of cIAI and not requiring new non-study systemic antibiotic therapy (clinical cure post-EOT based on the programmatic determination of clinical response).

5.3 Investigator Assessment of Clinical Response:

Investigators will use the definitions below to document clinical response, irrespective of microbiologic findings, at EOT, Day 21 and TOC or premature discontinuation:

Clinical response	**Definition**
Clinical cure	Pre-therapy signs and symptoms of the index infection had resolved such that no additional antibiotics or interventions were required
Clinical failure	Patients who met any one of the criteria below were considered as failure: • Death related to cIAI prior to EOT, Day 21 or TOC for the EOT, Day 21

	or TOC assessments, respectively • Surgical site wound infection requiring non-study systemic antibiotic therapy • Unplanned surgical procedures or percutaneous drainage procedures for complication or recurrence of cIAI based on documented worsening symptoms or signs of cIAI • No apparent response to treatment defined as persistence or progression of most or all pre-therapy signs and symptoms or use of additional antibiotics or additional interventions for the current infection including additional unplanned surgical intervention • Patient previously met criteria for failure based on receipt of rescue antibiotics or death, as above
Indeterminate	Study data were not available for evaluation of efficacy for any reason, including: • Patient lost to follow-up or assessment not undertaken such that a determination of clinical response could not be made at either the EOT, Day 21 or TOC visit • Death prior to EOT, Day 21 or TOC for the EOT, Day 21 and TOC assessments, respectively, where cIAI was clearly noncontributory

5.4 Signs and Symptoms

The following signs and symptoms will be summarized at Day 5, EOT, Day 21 and TOC.

- Fever (defined as body temperature >38°C) or hypothermia with a core body temperature <35°C
- Elevated white blood cell count (>12,000 cells/mm^3) or leukopenia (defined as white

blood cell count <4,000 cells/mm^3)

- Drop in blood pressure (systolic BP must be <90 mmHg without pressor support)
- Oxygen saturation ≤90 percent
- Abdominal pain and/or tenderness, with or without rebound
- Localized or diffuse abdominal wall rigidity
- Abdominal mass
- Nausea and/or vomiting
- Altered Mental Status

5.5 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 sulopenem IV followed by sulopenem etzadroxil co-administered with probenecid is non-inferior (NI) to ertapenem followed by oral ciprofloxacin and metronidazole or amoxicillin-clavulanate on Day 28 for the outcome measure of clinical response, defined as resolution of the signs and symptoms of cIAI present at trial entry with no new symptoms such that no new antibiotics or interventions are required.

The expected clinical cure rate is estimated from numerous large randomized controlled trials in a similar cIAI patient population. In those studies, the estimated cure rate for the proposed primary efficacy outcome measure of clinical cure on Day 28 in the micro-MITT population was 85%.

The proposed sample size for the ITT population is 670 patients. This ITT sample size estimate is based on the assumption that 80%, or 536 patients, of this ITT population will be micro-MITT evaluable. The sample size of the micro-MITT population is 268 patients per arm based on a Z-test with unpooled variance. This micro-MITT sample size of 536 assumes a non-inferiority margin of 10%, a power of 90%, a one-sided alpha level of 0.025 and an 85% treatment response rate in both treatment groups.

The aggregate blinded clinical cure 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 <85%, the final ITT sample size may be increased based on the observed clinical cure rate at that blinded interim analysis, as well as the evaluability rate, to maintain a power of 90%. See Section 7.6.

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 and metronidazole 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. The proportion of patients who have cIAI caused by appendicitis with perforation or peri-appendiceal abscess will not exceed approximately 50 percent. 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 or TOC. If their assessments are out of window, they will not be included in that population.

For the ITT populations, including MITT and micro-MITT, 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 by-visit analyses of laboratory tests and vital signs, 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, the first value will be used.

Visit	Window
Day 5	No window
Day 10 - End of Treatment (EOT) or Day 11-14	± 1 day
Day 21 – Phone Call	± 1 day
Day 28 – Test of Cure (TOC)	± 1 day

6.4 Microbiology Data

The following organisms will always be considered a pathogen when isolated from an acceptable culture specimen:

- Monomicrobial or polymicrobial infections caused by:
  - Enterobacteriaceae
  - *Staphylococcus aureus*
  - Streptococci
  - Enterococci
  - Anaerobes
  - *Pseudomonas* spp.

Patients who have at least one Gram-negative pathogen, both aerobes and anaerobes, will

be included in the micro-MITT. These pathogens, specifically Enterobacteriaceae, anaerobes and *Pseudomonas* spp., will be called study pathogens.

- Even if the organism was isolated from an acceptable culture specimen, the following are never a pathogen:
  - *S. saprophyticus*
  - *Corynebacterium* spp.
  - *S. epidermidis*
  - *Bacillus* spp.
  - Diphtheroids
  - *Micrococcus* spp.
  - *Lactobacillus* spp.

All isolates not defined above will be assessed on a case-by-case basis via manual review by the Sponsor. If needed, patient clinical (e.g., type of infection, type of specimen, patient underlying conditions, etc.) and microbiological information (e.g., Gram stain) 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.

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 clinical response, patients will be assigned a response of indeterminate if any data needed to determine whether a patient is a cure or failure are missing unless 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:

- The window, within 48 hours prior to the first dose and up to 24 hours after the first dose, will be used for determining baseline microbiology pathogens and surgical intervention.

- For unscheduled surgical interventions, if the study day of the unscheduled visit is on or before the visit day for the day 5, EOT, Day 21 or TOC visit then the surgical intervention data will be used in the assessment of clinical response.

- For the analyses involving temperature, oral temperature will be used. If temperature is measured rectal, temporal or tympanic then the following formulas will be used to convert the data to oral:

  Oral temperature = rectal minus 1 degree
  Oral temperature = tympanic or temporal minus 0.5 degrees

- 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-EOT, CE-TOC, 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, BMI as a categorical variable: <25, 25-30, >30) and creatinine clearance (see Appendix C) as a categorical variable: <30, ≥30) and baseline characteristics (e.g., type of infection, pre-operative vs intra-operative, prior use of antibiotic for current cIAI episode, previous treatment failure, APACHE Scores, height, weight, BMI and creatinine clearance as a continuous variables). Differences between treatment groups will be analyzed using Fisher‘s Exact test for dichotomous variables (gender, ethnicity, race, geographic region) 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 will be summarized by treatment group and compared using the Fisher’s Exact test.

7.2.1 Baseline Microbiology

The microbiological assessment of the baseline infection site cultures and blood cultures 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 for the MITT population.

The bacterial pathogens identified from the baseline infection site cultures and blood cultures will be presented. The number and percentage of patients with isolated gram-positive pathogens (aerobic and anaerobic organisms) and with isolated gram-negative pathogens (aerobic and anaerobic organisms) will be presented by genus and species for the MITT, micro-MITT and ME populations. The same pathogen identified from both the infection site and blood cultures will be counted only once in the summary. In addition, the number and percentage of patients with monomicrobial and polymicrobial infections as well as ESBL positive and negative infections will be presented. If either the site specimen or blood culture is positive for an ESBL-producing pathogen, then the patient will be presented as ESBL positive.

A listing will present all baseline and post-baseline isolates obtained from the infection site specimens and blood 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 site specimens and blood cultures will be presented both separately and combined. All drugs for which MIC data are available will be presented. These tables include the following:

- The distribution of MIC to sulopenem, ertapenem, ciprofloxacin, amoxicillin-clavulanate and other drugs, including metronidazole (for anaerobic pathogens), 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 TOC 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 and metronidazole, one to three capsules taken is considered a half day of therapy and four to six capsules taken is considered a full day of dosing. For patients who step down to active amoxicillin-clavulanate, each capsule taken is considered a half day of therapy. See Appendix E for more details.

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 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:

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

By definition, patients in the CE and ME populations must have sufficient information for determination of clinical 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 clinical response at the Day 28 (TOC) visit in the micro-MITT population. The number and percentage of patients in each treatment group defined as a clinical cure, failure and indeterminate will tabulated. The observed difference in percentage of patients with a clinical cure at the Day 28 (TOC) visit (+/- 1 day) (sulopenem group minus the comparator group) will be determined. The null and alternative hypotheses are the following:

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

where p_1 is the primary efficacy endpoint rate in the sulopenem group, p_2 is the primary efficacy endpoint rate in the ciprofloxacin group, and Δ is the non-inferiority margin of 10%. A 95% confidence interval (CI) for the observed difference will be computed using a Z-statistic. The NI hypothesis test is a one-sided hypothesis test performed at the 2.5% level of significance. If the lower limit of the 95% CI for the difference in response rates in the m-MITT population is greater than -10% the NI of sulopenem to the comparator group will be concluded.

7.5.2 Additional Analyses of the Primary Efficacy Endpoint

- Subgroup Analyses
  - Infection Type (cIAI caused by appendicitis with perforation or peri-appendiceal abscess vs. all other cIAI diagnoses) and list of diagnoses
  - Geographic Region (U.S. vs. non-U.S.)
  - Prior Antibiotic Therapy
  - Hypoalbuminemia
  - Fed / Fasted State
- Sensitivity Analyses

Adjustment for Stratification Factor of Infection Type Missing Data / Indeterminates Equal Cure Multiple Imputation for Missing Data Covariate Analysis Analysis without Disease Under Study as an Exclusion Criterion

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

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

- The primary efficacy endpoint at TOC will be assessed within each baseline infection type strata by treatment group.
- The primary efficacy endpoint at TOC will also be assessed within each geographic region (U.S. vs. non-U.S.) by treatment group.
- The primary efficacy endpoint at TOC will also be assessed in the subgroups of patients who did and did not receive prior antibiotic therapy as indicated on the randomization CRF page.
- A subgroup analysis of the primary efficacy endpoint in those patients with and without hypoalbuminemia (serum albumin <2.5 g/dL) at baseline will be conducted.
- A subgroup analysis of the primary efficacy endpoint by fed / fasted state will be conducted. A patient will be considered fed if they took 80% or more 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 makes a difference.

Sensitivity analyses of the primary endpoint will be conducted and a 2-sided 95% CI will be computed for the difference in the cure 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 will consider all patients who have missing data for the primary endpoint (i.e., an indeterminate response) as cures.
- 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.
- A covariate exploratory analysis using logistic regression with the stepwise selection

method will be performed using baseline variables such as study drug, bacteremia at baseline, age, gender, race, infection type, *E. coli* at baseline, APACHE score, creatinine clearance, albumin, percentage of doses taken in fed state and other variables if imbalances exist at baseline. For the latter, baseline tables will be reviewed by Iterum prior to the covariate analysis. The alpha level for both entering and removing a covariate will be 0.10.

- A sensitivity analysis on a modified micro-MITT population where disease under study is not an exclusion criterion will be performed. If a patient does not have disease under study the patient is excluded from the MITT population. For this sensitivity analysis these patients will not be excluded from the MITT population. Since the Micro-MITT population is a subset of MITT population these patients will not be excluded from a modified micro-MITT population.

7.5.3 Secondary Efficacy Analysis

For clinical response the number and percentage of patients with a clinical cure, failure and indeterminate response at the EOT (+/- 1 day) visit will be determined in each treatment group in the micro-MITT population. The observed difference in percentage of patients with a clinical cure (sulopenem minus the comparator group) will be determined and a 95% CI for the observed difference will be computed using Z-test with unpooled variance.

7.5.4 Additional Efficacy Analyses

Analysis	Day 5	EOT (Day 10-14)	Day 21	TOC (Day 28)
Clinical Response	ITT MITT Micro-MITT CE ME	ITT MITT CE ME	ITT MITT Micro-MITT CE	ITT MITT CE ME
Clinical Response by Baseline Pathogen	Micro-MITT ME	Micro-MITT ME	Micro-MITT	MITT Micro-MITT ME
Clinical Response by MIC				Micro-MITT ME
Clinical Response Sensitivity Analysis Where patients not eligible to switch to oral therapy due to non-susceptibility to the oral agents are failures				ITT MITT Micro-MITT CE ME
Clinical Response with Multiple Treatment Groups		ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE	ITT MITT Micro-MITT CE ME
Clinical Response by Combination of Antibiotic Resistance Classes	Micro-MITT CE ME	Micro-MITT CE ME		Micro-MITT CE ME
Microbiologic Response	Micro-MITT ME	Micro-MITT ME		Micro-MITT ME
Per Pathogen Microbiologic Response from the Site Specimen,	Micro-MITT ME	Micro-MITT ME		MITT Micro-MITT

Blood and Combined				ME
Per Pathogen Microbiologic Response by MIC				Micro-MITT ME
Microbiologic Response for Post-Baseline Pathogens		Micro-MITT ME		Micro-MITT ME
Microbiologic Response by ESBL Positive and ESBL Negative	Micro-MITT ME	Micro-MITT ME		Micro-MITT ME
Investigator-Determined Clinical Response		ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE	ITT MITT Micro-MITT CE ME
Investigator-Determined Clinical Response by Baseline Pathogen		ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE	ITT MITT Micro-MITT CE ME
cIAI Symptoms	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE	ITT MITT Micro-MITT CE ME
cIAI Symptoms – Shift Table	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE ME	ITT MITT Micro-MITT CE	ITT MITT Micro-MITT CE ME

Clinical Response

The number and percentage of patients in each treatment group with a clinical response of cure and failure at Day 5, EOT, Day 21 and TOC will be presented for the ITT, MITT (will included indeterminates), CE and ME populations. Two-sided 95% unstratified CIs will be constructed for the observed difference in the overall cure rates between the treatment groups for descriptive purposes; no conclusion of NI will be made.

Clinical response at Day 5, EOT, Day 21 and TOC by baseline pathogen will be summarized by treatment group in the micro-MITT and ME populations.

Clinical response by ciprofloxacin MIC and sulopenem MIC for baseline pathogens will be provided for TOC visit.

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).

Clinical response with multiple treatment groups will display four treatment groups for patients: sulopenem, ertapenem followed by ciprofloxacin, ertapenem followed by

amoxicillin-clavulanate and ertapenem patients who stayed ertapenem the whole time. Differences with sulopenem and corresponding confidence intervals will be provided for each comparator.

Clinical response by combination of antibiotic resistance classes will be provided. The classes will be β-lactams (by ESBL status), quinolones (if non-susceptible to ciprofloxacin (QNS), TMP-SMX (if non-susceptible to TMP-SMX) and nitrofurantoin (if non-susceptible to NTF). The combinations of resistance will include non-susceptibility to both β-lactams and quinolones, at least 3 classes of antibacterials (quinolones, TMP-SMX and β-lactams), non-susceptibility to all four classes (quinolones, TMP-SMX, nitrofurantoin and β-lactams) and combinations of these resistant classes.

Microbiologic Response

The number and percentage of patients in each treatment group with a per patient microbiologic response of success, failure and indeterminate at Day 5, EOT and TOC will be presented for the micro-MITT population. Each category of success and failure will be included (e.g., eradication, presumed eradication). 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 populations. Two-sided 95% unstratified CIs will be constructed for the observed difference in the microbiologic success rates between the treatment groups for descriptive purposes; no conclusion of NI will be made.

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 the site specimen and blood, and then combined.

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

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.

Per pathogen microbiologic response by ESBL positive and negative will be presented at Day 5, EOT and TOC in the micro-MITT and ME populations. ESBL positive is defined as the baseline pathogen MIC for ceftriaxone > 1. For the purposes of the tables, if a patient is ESBL positive for 1 or more pathogens they will be reported in the ESBL positive group.

Investigator-Determined Clinical Response

Investigator-determined clinical response (clinical cure, failure and indeterminate) at the EOT, Day 21 and TOC visits will be presented by treatment group for the micro-MITT, CE and ME populations. Two-sided 95% unstratified CIs will be constructed for the observed difference in the clinical cure rates between the treatment groups for descriptive purposes.

Signs and Symptoms

A table containing the prevalence of each cIAI symptom at baseline, Day 5, EOT, Day 21 and TOC will be provided by treatment group.

A shift table of each cIAI symptom at Day 5, EOT, Day 21 and TOC compared to baseline will be provided.

7.6 Interim Analysis

In order to ensure that the point estimate of clinical cure used in the estimation of sample size is valid for this study, an interim analysis for sample size re-estimation will be performed when clinical response data at the TOC visit are available for approximately 60% of the patients (402 patients). The FDA Guidance "Non-inferiority Clinical Trials" [FDA Guidance 2010] notes that such a sample size re-estimation if based on the blinded clinical 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 sulopenem IV /sulopenem etzadroxil plus probenecid is NI to the comparator 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 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 endpoint, 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 the number of TEAEs and the 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. A total column (the sum of both treatment arms) will be presented.

The number of TEAEs and 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 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 TOC) 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. A total column (the sum of both treatment arms) will be presented.

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 include 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 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. A patient will be considered fed if they took 80% or more of their doses in a fed 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 over Percent of Subjects
- Number of Episodes of Diarrhea by Study Day
- Percent of Subjects with Diarrhea by Study Day
- Duration of Clinically Significant Diarrhea over Percent of Subjects
- 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 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. 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 for worst overall value post-baseline. Additionally, shift tables will be provided for elevated ALT and AST levels.

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 classified as major or minor. 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., endpoint 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 additional requirement of having to have baseline culture within 48 hours of first dose has been added to the definition of micro-MITT population.
- The following are additions or changes to the clinical evaluable definition:
    - The patient must meet all inclusion and exclusion criteria.
    - The patient must not have received prior antibiotic within 72 hours of first dose unless the duration is less than 24 hours. The protocol stated 48 hours.
    - 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 intra-abdominal 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.
- The patient must have a microbiologic response for the respective visit to be eligible for the micro evaluable populations.
- For microbiologic response, post baseline responses of superinfection, new infection, colonization and recurrence were added.
- For microbiologic response, patients with bacteremia at baseline must have cleared the bacteremia to be defined as an eradication.
- Several analyses were added for the primary endpoint: subgroup analyses for hypoalbuminemia and for fed/fast state, sensitivity analyses that set missing data or indeterminates to cure, a multiple imputation analysis and a covariate analysis.
- The analysis of diarrhea has been added.

9 REFERENCES

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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		END OF TREATMENT		FOLLOW-UP PERIOD		
Protocol Activity	**Screening/ Baseline (D-1 to D1)**	**Day 1**	**Day 5**	**Day 10 (+/- 1 day)**	**Day 11-14 (+/- 1 day)[7]**	**Day 21 Phone Call [8] (+/- 1 day)**	**Day 28 (TOC) (+/- 1 day)**	**Premature Discontinuation**
Informed consent	X							
Medical history and demographics	X							
Targeted physical examination[1]	X		X	X	X		X	X
Vital signs	X		X	X	X		X	X
cIAI signs and symptoms	X		X	X	X	X	X	X
Hematology	X		X	X	X		X[2]	X
Serum chemistry	X		X	X	X		X[2]	X
Pregnancy testing	X						X	X
FSH	X							
Banked serum sample	X							
Banked urine sample	X			X[3]	X[3]			
Urinalysis	X							
Intra-operative Gram stain and culture[4]	X							
Peripheral blood cultures[5]	X							
Plasma PK sampling for sulopenem[6]		X	X					
Previous drug and non-drug treatments	X							
Concomitant drug and non-drug treatments	X	X	X	X	X	X	X	X
Treatment		X (each day for a duration of 5-14 days)						
Compliance with oral therapy check				X	X			X
Adverse events	X	X	X	X	X	X	X	X
Investigator determined clinical response evaluation				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 or Day 11-14 visits

[3] Urine samples may be collected at EOT and banked if a need to document compliance with study drug therapy is identified

[4] Follow up cultures to be obtained if needed based upon clinical signs and symptoms

[5] Blood cultures (aerobic and anaerobic) 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

[6] In subset of patients enrolled in the PK substudy, 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.

[7] This visit applicable only to those patients who receive more than 10 days of study drug therapy, and should be conducted instead of the Day 10 visit
[8] Targeted physical examination can be performed if necessary based on symptoms

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
Albumin	<0.8 times the lower limit of the reference range
Total protein	<0.8 times the lower limit of the reference range
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

U.S. and Ex-U.S. Sites (Intra-abdominal sample)

1. Baseline intra-abdominal sample is submitted for culture to Local/Regional Lab
    a. If Local/Regional Lab's intra-abdominal sample culture fails to yield any pathogens, then the Local/Regional Lab's result is accepted as final
    b. If Local/Regional Lab's intra-abdominal sample culture yields a pathogen(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
        ii. If Local/Regional isolate(s) is lost or dies in transit, then Local/Regional Lab will be requested to send the back-up isolate(s) to IHMA for confirmation
            1. The result of IHMA's testing of this back-up isolate(s) will be accepted as the final result. However, if the backup isolate(s) sent by the Local/Regional Lab to IHMA are either lost in transit or non-viable, then the Local/Regional Lab's pathogen identification will be accepted as the final result.
2. Follow-up intra-abdominal sample is submitted for culture to Local/Regional Lab
    a. If the Local/Regional Lab's intra-abdominal sample culture fails to yield a pathogen(s), then the Local/Regional Lab's culture result will remain as the final result
    b. If the Local/Regional Lab's intra-abdominal sample culture yields a pathogen(s), then the Local/Regional Lab will send the isolate(s) to IHMA for confirmation
        i. The result of IHMA's testing of this isolate(s) will be accepted as the final result
        ii. If Local/Regional isolate(s) is lost or dies in transit, then Local/Regional Lab will be requested to send the back-up isolate(s) to IHMA for confirmation
            1. The result of IHMA's testing of this back-up isolate(s) will be accepted as the final result. However, if the backup isolate(s) sent by the Local/Regional Lab to IHMA are either lost in transit or non-viable, then the Local/Regional Lab's pathogen identification will be accepted as the final result.

U.S. and Ex-U.S. Sites (Blood)

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
        ii. If Local/Regional Lab's isolate(s) is lost or dies in transit, then Local/Regional Lab will be requested to send the back-up isolate(s) to IHMA for confirmation
            1. The result of IHMA's testing of this back-up isolate(s) will be accepted as the final result. However, if the backup isolate(s) sent by the Local/Regional Lab to IHMA are either lost in transit or non-viable, then the Local/Regional Lab's pathogen identification will be accepted as the final result.

2. Follow-up blood samples:

   When the Baseline blood sample yields an organism(s), follow-up blood samples are to be submitted for culture to Local/Regional Lab until the culture result is negative
   a. If the Local/Regional Lab's follow-up blood culture is "no growth", then the Local/Regional Lab's culture result will remain as the final result
   b. If the Local/Regional Lab's follow-up blood culture yields an organism(s), then the Local/Regional Lab will send the isolate(s) to IHMA for confirmation
      i. The result of IHMA's testing of this isolate(s) will be accepted as the final result
      ii. If Local/Regional Lab's isolate(s) is lost or dies in transit, then Local/Regional Lab'will be requested to send the back-up isolate(s) to IHMA for confirmation
         1. The result of IHMA's testing of this back-up isolate(s) will be accepted as the final result. However, if the backup isolate(s) sent by the Local/Regional Lab to IHMA are either lost in transit or non-viable, then the Local/Regional Lab's pathogen identification will be accepted as the final result.

Appendix E: Treatment Regimen and Duration of Exposure

		bl pathogen susceptible to ciprofloxacin	bl pathogen non-susceptible to ciprofloxacin, but susceptible to amoxicillin-clavulanate	bl pathogen non-susceptible to ciprofloxacin and amoxicillin-clavulanate
sulopenem treatment group	Patients with normal renal function	**Regimen A** (Ciprofloxacin susceptible and CrCl >= 30) **Treatment:** active oral sulopenem + placebo ciprofloxacin + placebo metronidazole **Duration of exposure:** we consider only number of pills taken from the bottle (sulopenem) - each tablet taken is considered a half day of therapy.	**Regimen B** (Ciprofloxacin non-susceptible but susceptible to amoxicillin-clavulanate and CrCl >= 30) **Treatment:** active oral sulopenem + placebo amoxicillin-clavulanate + placebo metronidazole **Duration of exposure:** we consider only number of pills taken from the bottle (sulopenem) - each tablet taken is considered a half day of therapy.	**Regimen C** (Non-susceptible to ciprofloxacin and amoxicillin-clavulanate OR ciprofloxacin non-susceptible and CrCl < 30) **Treatment:** active oral sulopenem + placebo infusion **Duration of exposure:** we consider only number of pills taken from the bottle (sulopenem) - each tablet taken is considered a half day of therapy.
	Patients with severe renal impairment (CrCl <30mL/min):	**Regimen D** (Ciprofloxacin susceptible and CrCl < 30) **Treatment:** active oral sulopenem + placebo ciprofloxacin (1 tablet each 18 hours) + placebo metronidazole **Duration of exposure:** we consider only number of pills taken from the bottle (sulopenem)- each tablet taken is considered a half day of therapy.	**Regimen C** (Non-susceptible to ciprofloxacin and amoxicillin-clavulanate OR ciprofloxacin non-susceptible and CrCl < 30) **Treatment:** active oral sulopenem + placebo infusion **Duration of exposure:** we consider only number of pills taken from the bottle (sulopenem) - each tablet taken is considered a half day of therapy.	**Regimen C** (Non-susceptible to ciprofloxacin and amoxicillin-clavulanate OR ciprofloxacin non-susceptible and CrCl < 30) **Treatment:** active oral sulopenem + placebo infusion **Duration of exposure:** we consider only number of pills taken from the bottle (sulopenem) - each tablet taken is considered a half day of therapy.
ertapenem treatment group	Patients with normal renal function	**Regimen A** (Ciprofloxacin susceptible and CrCl >= 30) **Treatment**: active ciprofloxacin + active metronidazole + placebo oral sulopenem **Duration of exposure:** we consider (i) number of pills from ciprofloxacin or amoxicillin blister pack (as ciprofloxacin) and (ii) number of pills from metronidazole blister pack; sum-up number of ciprofloxacin and metronidazole pills for a patient per day and compare the following rule: 1 to 3 pills on a given day equals ½ day of dosing and 4 to 6 or more pills equals 1 day of dosing	**Regimen B** (Ciprofloxacin non-susceptible but susceptible to amoxicillin-clavulanate and CrCl >= 30) **Treatment:** active amoxicillin-clavulanate + placebo metronidazole + placebo oral sulopenem **Duration of exposure:** we consider number of pills from ciprofloxacin or amoxicillin blister pack as amoxicillin - each capsule taken is considered a half day of therapy	**Regimen C** (Non-susceptible to ciprofloxacin and amoxicillin-clavulanate OR ciprofloxacin non-susceptible and CrCl < 30) **Treatment:** active IV ertapenem + placebo oral sulopenem **Duration of exposure:** we do not include such patients into oral duration of exposure.

	Patients with severe renal impairment (CrCl < 30mL/min):	**Regimen D** (Ciprofloxacin susceptible and CrCl < 30) **Treatment:** active ciprofloxacin (1 tablet each 18 hours) + active metronidazole + placebo oral sulopenem **Duration of exposure:** we consider (i) number of pills from ciprofloxacin or amoxicillin blister pack (as ciprofloxacin) and (ii) number of pills from metronidazole blister pack; sum-up number of ciprofloxacin and metronidazole pills for a patient per day and compare the following rule: 1 to 3 pills on a given day equals 0.5 days of dosing and 4, 5 or more pills equals 1 day of dosing.	**Regimen** C (Non-susceptible to ciprofloxacin and amoxicillin-clavulanate OR ciprofloxacin non-susceptible and CrCl < 30) **Treatment:** active IV ertapenem + placebo oral sulopenem **Duration of exposure:** we do not include such patients into oral duration of exposure.	**Regimen** C (Non-susceptible to ciprofloxacin and amoxicillin-clavulanate OR ciprofloxacin non-susceptible and CrCl < 30) **Treatment:** active IV ertapenem + placebo oral sulopenem **Duration of exposure:** we do not include such patients into oral duration of exposure.

Addendum 1:

This addendum documents contains changes made to the programming after version 2 of the SAP was finalized. The timing of when the changes were communicated to the CRO is included in the table.

SAP Section	Timing	Description
4.2	Prior to DB lock	Modified Intent-to-Treat Population • The MITT population includes the criterion of disease under study as defined as meeting inclusion criterion 3. To specify further this means a patient would be excluded from the MITT if "acute appendicitis" or "anterior abdominal wall abscess" was written in the Other field on the surgical intervention or pre-operative cIAI diagnosis CRF pages.
4.2	Prior to DB lock	Reasons for Exclusion from Populations Table • Only one reason for exclusion from the micro-MITT population in table 14.1.2 should be reported with the following hierarchy: 1.) Excluded from the MITT population, 2.) Did not have at least one gram-negative pathogen identified at study entry and 3.) Cultures not taken within the first 48 hours.
5.1	After blind was broken on topline tables but Sponsor still blinded at the subject level	Clinical Response – Surgical Intervention • To be a failure due to surgical intervention, the surgical procedure should have been on the Surgical Intervention page. However, information regarding surgical intervention also resides on the Prior and Concomitant Procedures page and the Post-Operative Radiologic Examination page. If the following procedures are listed on the Prior and Concomitant Procedures page after first dose of study drug, then the patient will be a failure due to surgical intervention. ○ LAPAROTOMY ○ SURGICAL INTERVENTION ○ LAPAROTOMY, ADHESIOLYSIS AND DRAINAGE OF PERITONEAL CAVITY ○ ABDOMINAL SURGERY ○ CT DRAINAGE FOR INTRAABDOMINAL ABSCESS

		○ ABDOMINAL CT WITH DRAINAGE ○ ULTRASOUND GUIDED DRAINAGE OF THE ABSCESS ○ RESECTIO SIGMATIS ○ DESCENDOSTOMY ○ PRIMARY CLOSURE OF THE ABDOMINAL WALL ○ ILEO-ILEO ANASTOMOSIS ○ ILEOSTOMY ○ SPLENECTOMY ○ RIGHT HEMICOLECTOMY ○ DIAGNOSTIC LAPAROSCOPY AND LYSIS OF ADHESIONS ○ RELAPARATOMY If a patient had a Post-Operative Radiologic Examination procedure with "Haemathoma in the abdominal cavity. Drainage of haemathoma under the US control" then the patient is a failure due to surgical intervention.
5.1	After blind was broken on topline tables but Sponsor still blinded at the subject level	Clinical Response – Antibiotic for Failure • To be a failure for rescue therapy, the rescue therapy box on the Antibiotic Therapy CRF page must be ticked. However, information regarding rescue therapy also resides in the Other field on the Antibiotic Therapy page. So, if the other field contains "*Subject withdrew study therapy and received non-antibiotics for cIAI*", the patient will be a failure for rescue therapy. However, other criteria may apply such as worsening of symptoms (see next bullet). • The definition from the protocol and SAP for a patient to be failure due to rescue medication is "*Initiation of non-trial antibacterial drug therapy for treatment of cIAI based on documented worsening symptoms or signs of cIAI*". "*Documented worsening of symptoms or signs of cIAI*" can be determined by checking the cIAI Signs and Symptoms page of the CRF. ○ If there are no signs and symptoms, then check the Post-Operative Radiologic Examination page on the day the antibiotic was given or the day before and if 'abnormal clinically significant' in the indication field then the patient is a failure due to rescue medication. If no such procedure is identified, then the patient is a not a failure due to rescue medication.

		○ If there is a single sign and symptom of abdominal pain/tenderness, then check the reason for the "investigator response for indeterminate" as "Received antibiotic for non cIAI infection" then the patient is not a failure due to rescue medication. Otherwise, check the abdominal physical exam. If the patient is normal or abnormal but not clinically significant for the abdomen, then check the Post-Operative Radiologic Examination page on the day the antibiotic was given or the day before and if 'abnormal clinically significant' in the indication field then the patient is a failure due to rescue medication. If no such procedure is identified, then the patient is a not a failure due to rescue medication. ○ If the patient has a wound infection while taking rescue medication at the analysis visit or at the subsequent visit, then the patient is a failure due to wound infection with rescue medication. The day 21 visit is a phone call so the evaluation of the wound will not be performed unless the patient comes into the clinic and the evaluation of the wound is performed. Thus, wound infection criterion will not be applied for day 21 unless the patient has data for that visit. ○ This assessment for failure should first be checked at the visit the antibiotic was given or if the antibiotic was given between visits, then check the preceding visit. If there are no assessments prior to the rescue therapy, then use the visit one day after the antibiotic therapy was given, if there is one. If there still aren't assessments, then consider the patient as having no signs and symptoms. ○ The next step for these patients is to run the existing program for clinical response (signs and symptoms, death, surgical intervention) at the visit.
5.1	After blind was broken on topline tables but Sponsor still blinded at the subject level	Clinical Response – Signs and Symptoms • If a patient has no other reason for failure except pain/tenderness and physical exam for abdomen is normal or abnormal but not clinically significant, then the patient is a cure. • If a patient's only reason for failure is tenderness and has a clinically significant physical finding for the abdomen and the specify field of the physical exam field is "site of umbilical hernia repair erythema and mild tenderness with palpation" then the patient is a cure.

		• If a patient has no other reason for failure except abdominal mass and physical exam for abdomen is normal or abnormal but not clinically significant, then the patient is a cure. • If a patient has no other reason for failure except nausea/vomiting, then the patient is a cure.
5.1	After DB lock but prior to creation of SDTM datasets	Clinical Response – Signs and Symptoms • For the oxygen saturation component of clinical response, oxygen saturation must be less than 90% to be an unresolved symptom.
5.1	Prior to DB lock	Clinical Response – Signs and Symptoms • Signs and symptoms to assess for clinical response at Day 21 are abdominal pain, nausea, vomiting, and altered mental status since Day 21 is a phone call.
5.1	Prior to DB lock	Clinical Response – Signs and Symptoms • The new WBC algorithm for clinical response is for patients who have <4000 at BL to be a success WBC must be >=4000 at the post-BL visit. For patients who have >12,000 at BL to be a success WBC must be <=12,000 at the post-BL visit.
6.4	Prior to DB lock	Microbiology Data • For classification of organisms from the local lab to aerobes/anaerobes and gram negative/gram positive, the PATHS dataset will include a variable for each category specifying which it is.
6.6	Prior to DB lock	Comments on Statistical Analysis – Temperature • For analyses involving temperature do not convert rectal, temporal, tympanic temperatures to oral. For tables, just report them without respect to method.

7.2	Prior to DB lock	Demographics and Baseline Characteristics – Creatinine Clearance • The creatinine clearance categories for the demographics table are <30, 30-60 and > 60.
7.2.1	Prior to DB lock	Baseline Microbiology • For the 14.1.12.x tables, add a third row for Mixed Polymicrobial as defined as a patient having one gram negative and one gram positive pathogen. The three rows are mutually exclusive.
7.5.4	After DB lock but prior to creation of SDTM datasets	Additional Efficacy Analyses – Clinical Response Table • The clinical response by combination of antibiotic resistance classes table will only include two resistance classes, β-lactams (by ESBL status) and quinolones (i.e., ciprofloxacin), and resistant to both. The table should contain the following resistance classes: ESBL Status, Quinolone Resistance Class and Resistance to Quinolone/Beta-lactams. The beta-lactams to use are: Amoxicillin/Clavulanate, Ampicillin/Sulbactam, Aztreonam, Ceftazidime/Avibactam, Ceftriaxone and Piperacillin/Tazobactam. All of these drugs have to be resistant to qualify beta-lactams as resistant.
7.5.4	Prior to DB lock	Additional Efficacy Analyses – Clinical Response by MIC Table • MIC50 values are derived by ordering the MIC values from lowest to highest with a greater than value next in order after the value (e.g., 8 is first then > 8 is next then 16 then >16) then determining the cumulative percentage from lowest to highest then selecting the first value equal to or greater than 50%. There is no rounding in this process. MIC90 is derived the same way but uses the threshold of 90%.
7.5.4	Prior to DB lock	Additional Efficacy Analyses – Clinical Response with Multiple Treatment Groups Table • Clinical response with multiple treatment groups by stepdown category will display five (instead of 4) treatment groups for patients: sulopenem IV only, sulopenem IV followed by sulopenem oral, ertapenem followed by ciprofloxacin, ertapenem followed by amoxicillin-clavulanate and ertapenem patients who stayed ertapenem the whole time. Confidence intervals are not needed for this analysis.

7.5.4	Prior to DB lock	Additional Efficacy Analyses – Investigator Clinical Response • Investigator determined clinical response by baseline pathogens tables do not need to be produced.
7.5.4	Prior to DB lock	Additional Efficacy Analyses – Micro Tables • For tables 14.2.5.2.3, 14.2.6.2.3, 14.2.7.2.3, 14.2.8.2.3, the blood contaminants, as specified in the PATHs dataset, should be removed.
7.5.4	Prior to DB lock	Additional Efficacy Analyses – Micro Tables by ESBL Status • For the ESBL analyses, if a patient is ESBL positive for 1 or more pathogens they will be reported in the ESBL positive group for the per patient tables. For the per pathogen tables, the ESBL status for that pathogen will be used. • For the microbiologic response by ESBL status tables, only Enterobacteriaceae pathogens should be included in the table.
7.7.1	Prior to DB lock	Adverse Events – Censoring • When censoring for the AE duration table, which is needed when there isn't a stop date, use the last date the patient was involved with the study by checking visit date across all SDTM domains.
7.7.1	Prior to DB lock	Adverse Events – Age Categories • The adverse event by age group table will be done twice: once with the categories of <65 and >=65 and once with the categories of <65, 65-74, 75-84 and >=85.
7.7.1	Prior to DB lock	Adverse Events – Relationship to Study Drug • For the adverse event tables by relationship to IV study drug and relationship to Oral study drug, only AEs that begin while on IV will be displayed for the former and only AEs that begin while on oral dosing will be displayed in the latter. For AEs that begin after last IV dose but before first oral dose will be attributed to IV dosing.

7.7.2	Prior to DB lock	Laboratory Values – Elevated ALT, AST and Bilirubin Table • Elevated ALT, AST and Bilirubin levels will be summarized not only by-study visit but also by worst value across all assessments per patient. The denominator will be the number of patients that have had the test performed.