Clinical Trial Protocol: 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-70429), Sulopenem etzadroxil (PF-03709270)/Probenecid
IND Number:	129,849; 129,834
EudraCT Number	2017-003773-34
Indication:	Complicated intra-abdominal infection
Investigators:	Multicenter
Sponsor:	Iterum Therapeutics International Limited Block 2 Floor 3, Harcourt Centre, Harcourt Street, Dublin 2, Ireland
Sponsor Contact:	Sailaja Puttagunta
Sponsor's US Agent:	Iterum Therapeutics US Limited 20 Research Parkway, Suite A Old Saybrook, CT 06475
Medical Monitor:	Bernard Brownstein Office phone number: +1 (267) 464 2572 ext:2172 Cell phone number: +1 (267) 858 0655 Email address: Bernard.Brownstein@psi-cro.com
Pharmacovigilance	PSI Pharmacovigilance
Pharmacovigilance Contact	Email: SafetyDesk@psi-cro.com Fax numbers: 1-800-361-9714; +7 (812) 320 3850

	Date
Original Draft Protocol	August 23, 2017
Revised Draft Protoco	October 04, 2017
Final Protocol	May 29, 2018

Throughout this document, symbols indicating proprietary names (®, ™) are not displayed. The appearance of product names without these symbols does not imply that these names are not protected.

SYNOPSIS

Sponsor:

Iterum Therapeutics International Limited

Name of Finished Product:

Sulopenem; Sulopenem etzadroxil/probenecid

Name of Active Ingredient:

Sulopenem (CP-70429); Sulopenem etzadroxil (PF-03709270)/probenecid

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

Primary Objective(s):

To compare the efficacy of sulopenem 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 (test of cure [TOC]) post randomization.

Secondary Objective(s):

To compare the efficacy outcomes at other relevant time points as well as the safety profile of treatment with sulopenem followed by sulopenem etzadroxil plus probenecid versus ertapenem followed by ciprofloxacin and metronidazole or amoxicillin-clavulanate for treatment of complicated intra-abdominal infection in adults.

To assess the population PK profile of sulopenem when administered either intravenously or as the prodrug, sulopenem etzadroxil, co-administered with probenecid.

Study Design:

Sulopenem is an investigational penem antibiotic being developed for treatment of uncomplicated urinary tract infections (uUTI), complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI). Sulopenem etzadroxil is an oral pro-drug of sulopenem. Upon oral absorption, sulopenem etzadroxil is expected to be rapidly hydrolyzed to yield sulopenem, the active moiety, as well as the non-active moieties, formaldehyde and 2-ethylbutyric acid (2-EBA).

Sulopenem possesses potent activity against species of the Enterobacteriaceae that encode ESBLs or AmpC-type β-lactamases that confer resistance to third generation cephalosporins. Sulopenem etzadroxil is expected to be the first oral penem on the market in the United States

or Europe and will offer the option of treatment in the outpatient setting as well as IV to oral switch therapy for early discharge of patients hospitalized with serious complicated infections. Probenecid, co-administered with the oral prodrug, will reduce renal clearance and increase systemic exposure of the active moiety, sulopenem.

This Phase 3, multicenter, double-blind, randomized, controlled study compares IV sulopenem followed by sulopenem etzadroxil with probenecid and ertapenem IV followed by oral ciprofloxacin and metronidazole or amoxicillin-clavulanate for treatment of cIAI. The site pharmacist will be unblinded in order to prepare the intravenous study medications and select the appropriate oral follow on therapy for patients randomized to the ertapenem regimen. Approximately 670 adults with cIAI will be randomized in a 1:1 fashion to receive either IV sulopenem 1000 mg once daily for at least 5 days followed by sulopenem etzadroxil 500 mg co-administered with oral probenecid 500 mg twice daily to complete 7-10 days of treatment or ertapenem IV 1000 mg once daily for at least 5 days followed by ciprofloxacin and metronidazole or amoxicillin-clavulanate to complete 7-10 days of therapy. 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.

The primary outcome measure (clinical response) for the efficacy evaluation will be assessed programmatically on Day 28 (TOC) as either:

Clinical cure, defined as:

- Patient is alive
- Resolution in baseline signs and symptoms of the index infection
    - No new symptoms
- No new antibiotics or interventions for treatment failure are required

Clinical failure, defined as:

- death due to cIAI
- 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
- Initiation of non-trial antibacterial drug therapy for treatment of cIAI based on documented worsening symptoms or signs of cIAI

If data are unavailable to determine if the patient is a cure or a failure, the patient outcome will be considered an indeterminate response.

For the primary efficacy evaluation, the proportions of patients achieving cure, failure or indeterminate will be determined in the microbiologic-modified intent to treat population (m-MITT). The m-MITT population will be comprised of all randomized patients who received at least one dose of study drug and had a baseline pathogen causing cIAI isolated from a culture specimen taken at baseline, prior to initiation of study drug therapy.

Study Population:

A total of 670 patients are planned; the sample size will be adjusted at the blinded interim analysis if the baseline assumptions for clinical cure rate are not met.

Patients will be randomized using an Interactive Web Randomization System (IWRS) system into the study, 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.

Inclusion Criteria:

1. Patient or the patient's legally acceptable representative able to provide a signed written informed consent prior to any study-specific procedures.
2. Adult patients ≥18 years of age.
3. EITHER:
    a. Intra-operative/post-operative enrollment with visual confirmation (presence of pus within the abdominal cavity) of an intra-abdominal infection associated with peritonitis including at least 1 of the following diagnosed during the surgical intervention:
        i. Cholecystitis with gangrenous rupture or perforation or progression of the infection beyond the gallbladder wall
        ii. Diverticular disease with perforation or abscess
        iii. Appendiceal perforation or peri-appendiceal abscess
        iv. Traumatic perforation of the intestines, only if operated on >12 hours after perforation occurs
        v. Secondary peritonitis (but not spontaneous bacterial peritonitis associated with cirrhosis and chronic ascites)
        vi. Intra-abdominal abscess (including of liver or spleen provided that there was extension beyond the organ with evidence of intraperitoneal involvement).

    OR:

    b. Pre-operative enrollment where one of the following surgical procedures are planned within 24 hours of the first dose of study drug:
        i. Open laparotomy, percutaneous drainage of an intra-abdominal abscess, or laparoscopic surgery.
4. Evidence of systemic inflammatory indicators, with at least one of the following:
    a. Fever (defined as body temperature >38°C) or hypothermia with a core body temperature <35°C
    b. Elevated white blood cell count (>12,000 cells/mm^3), or leukopenia (defined as white blood cell count <4,000 cells/mm^3)
    c. Drop in blood pressure (systolic BP must be <90 mm Hg without pressor support)
    d. Increased heart rate (>90 bpm) and respiratory rate (>20 breaths/min)
    e. Hypoxia (oxygen saturation ≤90 percent on room air)
5. Physical findings consistent with intra-abdominal infection, such as:

a. Abdominal pain and/or tenderness, with or without rebound
b. Localized or diffuse abdominal wall rigidity
c. Abdominal mass
d. Nausea and/or vomiting
e. Altered mental status

6. Specimen/s from the surgical intervention were sent (or planned to be sent in case of pre-operative enrollment) for culture.

Microbiologic specimens collected during routine operative care prior to subject providing informed consent may be used for study purposes.

Exclusion Criteria

1. Patient diagnosed with traumatic bowel perforation undergoing surgery within 12 hours; perforation of gastroduodenal ulcers undergoing surgery within 24 hours. Other intra-abdominal processes in which the primary etiology was not likely to be infectious.
2. Patient has abdominal wall abscess or bowel obstruction without perforation or ischemic bowel without perforation.
3. Patient has simple cholecystitis or gangrenous cholecystitis without rupture, or simple appendicitis, or acute suppurative cholangitis, or infected necrotizing pancreatitis or pancreatic abscess.
4. Patient whose surgery included staged abdominal repair, or "open abdomen" technique, or marsupialization.
5. Patient known at study entry to have a complicated intra-abdominal infection caused by pathogens non-susceptible to the study antimicrobial agents.
6. Patient needed effective concomitant systemic antibacterials (oral, IV, or intramuscular) or antifungals in addition to those designated in the 2 study groups, except vancomycin, linezolid, or daptomycin if started for known or suspected methicillin-resistant *Staphylococcus aureus* (MRSA) or *Enterococcus* spp..
7. Patient has perinephric infections or an indwelling peritoneal dialysis catheter.
8. Patient has suspected intra-abdominal infections due to fungus, parasites (e.g., amoebic liver abscess), virus, or tuberculosis.
9. Patient has a known history of serious allergy, hypersensitivity or any serious reaction to carbapenem antibiotics, other β-lactam antibiotics, quinolones, metronidazole, or probenecid.
10. Patient is known to have any of the following laboratory values as defined below:
    a. Hematocrit <25% or hemoglobin <8 g/dL
    b. Absolute neutrophil count <1000/mm^3
    c. Platelet count <75,000/mm^3
    d. Bilirubin >3 x the upper limit of normal (ULN), unless isolated hyperbilirubinemia was directly related to the acute infection or known Gilbert's disease
    e. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x ULN values at Screening. Patients with elevations of AST and/or ALT up to 5 x ULN

will be eligible if these elevations are acute and directly related to the infectious process being treated. This must be documented.

f. Alkaline phosphatase (ALP) >3 x ULN. Patients with values >3.0 x ULN and <5.0 x ULN are eligible if this value is acute and directly related to the infectious process being treated. This must be documented.

11. Patient has a body mass index >45 kg/m^2.
12. Patient has APACHE II score >30 (serum bicarbonate may be used in place of arterial blood gases; see Appendix 5)
13. Patient considered unlikely to survive the 4 week study period or has a rapidly progressive or terminal illness, including septic shock that was associated with a high risk of mortality.
14. Patient unlikely to respond to 10–14 days of treatment with antibiotics.
15. Patient received systemic antibacterial agents within the 72-hour period prior to study entry, unless either of the following pertained:
    a. Patient has a new infection (not considered a treatment failure) and both of the following were met:
        i. Patient received no more than 24 hours of total prior antibiotic therapy
        ii. Patient received ≤1 dose of a treatment regimen post-operatively and antibiotics were not received more than 6 hours post-procedure.
    b. Patient considered to have failed the previous treatment regimen i.e., pre-operative treatment of any duration with non-study systemic antimicrobial therapy for peritonitis or abscess permitted provided that all of the following are met:
        i. The treatment regimen had been administered for at least 72 hours and was judged to have been inadequate
        ii. The patient had an operative intervention that was just completed or was intended no more than 24 hours after study entry
        iii. Findings of infection were documented at surgery
        iv. Specimens for bacterial cultures and susceptibility testing were taken at operative intervention
        v. No further non-study antibacterials were administered after randomization.
16. Patient has a concurrent infection that may interfere with the evaluation of response to the study antibiotic.
17. Patient receiving hemodialysis, hemofiltration or peritoneal dialysis.
18. Patient has a history of acute hepatitis in the recent past (3 months prior to study entry), chronic hepatitis, cirrhosis, acute hepatic failure, or acute decompensation of chronic hepatic failure.
19. Patient has past or current history of epilepsy or seizure disorders excluding febrile seizures of childhood.
20. Patient immunocompromised as evidenced by any of the following:
    a. Human immunodeficiency virus infection, with either a recent (in the past 6 months) acquired immune deficiency syndrome-defining condition or a CD4 + T lymphocyte count <200/mm^3

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

21. Patient participating in any other clinical study that involved the administration of an investigational medication at the time of presentation, during the course of the study, or who had received treatment with an investigational medication in the 30 days prior to study enrollment, or had previously been enrolled in this study or had been treated with sulopenem.
22. Patient is in a situation or has a condition that, in the investigator's opinion, may interfere with optimal participation in the study.
23. Patient unlikely to comply with protocol e.g., uncooperative attitude, inability to return for follow-up visits, and unlikely to complete the study.
24. Patient has known inflammatory bowel disease (ulcerative colitis or Crohn's disease) or *Clostridium difficile*-associated diarrhea
25. Patients with a history of blood dyscrasias
26. Patients with a history of uric acid kidney stones
27. Patients with acute gouty attack
28. Patients on chronic methotrexate therapy
29. Females of child-bearing potential who are unable to take adequate contraceptive precautions (refer to Section 4.4.1), have a positive pregnancy test result within 24 hours of study entry, are otherwise known to be pregnant, or are currently breastfeeding an infant.
30. Male subjects who do not agree to use an effective barrier method of contraception during the study and for 14 days post treatment (refer to Section 4.4.2).

Test Product, Dose, and Mode of Administration:

Investigational study medications include sulopenem 1000 mg IV over 3 hours, sulopenem etzadroxil 500 mg PO twice daily co-administered with probenecid 500 mg PO twice daily, ertapenem 1000 mg once daily IV over 30 minutes, ciprofloxacin 500 mg PO twice daily along with metronidazole 500 mg PO four times daily. If patients on the ertapenem arm are found to have causative pathogens that are non-susceptible to ciprofloxacin, but susceptible to amoxicillin-clavulanate, they may receive amoxicillin-clavulanate 875 mg PO twice daily instead.

Other Systemic Antibiotics:

Vancomycin IV, linezolid IV or PO, or daptomycin IV can be given for known or suspected methicillin-resistant *Staphylococcus aureus* (MRSA) or *Enterococcus* spp.

Formulation and Packaging:

Sulopenem treatment group: Sulopenem 1000 mg IV will be supplied as a single-use vial with lyophilized powder for injection. The IV solution will be prepared for dosing by an unblinded pharmacist. The oral medications will be packaged in a suitable packaging container and provided to the sites.

Comparator treatment group: Ertapenem 1000 mg IV will be supplied as a single-use vial. The IV solution will be prepared for dosing by an unblinded pharmacist. The oral medications will be packaged in a suitable packaging container and provided to the sites.

Preparation and Dispensing

Sulopenem or ertapenem IV: Each dose of IV study medication will be prepared by an unblinded pharmacist or other qualified personnel at the site according to the dosing instruction provided by the sponsor. The pharmacy manual will be provided under separate cover for preparation of doses using the sulopenem vials and comparator.

Sulopenem etzadroxil/probenecid or comparator oral solid dose (OSD): All OSD study drugs will be provided to the study site by Iterum Therapeutics. Preparation and administration of study medication will be done and documented in accordance with the treatment schedule as outlined in the study protocol. Written study medication preparation and administration instructions will be provided to each study site in a study pharmacy manual.

This pharmacy manual will contain detailed instructions for the preparation and administration of study medication.

Administration

Sulopenem arm:

Patients with normal renal function: Patients randomized to the sulopenem treatment group will receive 1000 mg sulopenem IV infused over 3 hours, once daily for 5 days, and a saline IV infusion over 30 minutes to simulate the comparator.

After at least 5 days of intravenous therapy, those patients with a baseline pathogen susceptible to ciprofloxacin and who meet criteria for oral step-down will take one sulopenem etzadroxil/probenecid tablet twice daily, one over-encapsulated placebo ciprofloxacin tablet twice daily and one over encapsulated placebo metronidazole capsule four times daily to complete 7-10 total days of treatment (may be extended to 14 days for certain patients if approved by the medical monitor and meets criteria).

For patients found to have a baseline organism non-susceptible to ciprofloxacin, but susceptible to amoxicillin-clavulanate after at least 5 days of IV therapy those patients who meet criteria for oral step-down will take one sulopenem etzadroxil/probenecid tablet twice daily, one over-encapsulated placebo amoxicillin-clavulanate capsule twice daily, and one over encapsulated placebo metronidazole capsule four times daily to complete 7-10 total days of treatment (may be extended to 14 days for certain patients if approved by the medical monitor and meets criteria). Patients with baseline pathogens non-susceptible to both ciprofloxacin and amoxicillin-clavulanate will need to continue on IV saline infusions over 30 minutes to match IV ertapenem for the entire duration of therapy, and take one sulopenem etzadroxil/probenecid tablet twice daily, in order to keep blinding intact.

Patients with severe renal impairment (CrCl <30mL/min): Patients with severe renal impairment randomized to the sulopenem treatment group will receive 250 mg sulopenem IV infused over 3 hours once daily for 5 days and a saline IV infusion over 30 minutes to simulate the comparator.

After at least 5 days of intravenous therapy those patients with a baseline pathogen susceptible to ciprofloxacin and who meet criteria for oral step-down will take one sulopenem etzadroxil/probenecid tablet twice daily, one over-encapsulated placebo ciprofloxacin capsule approximately every 18 hours and one over encapsulated placebo metronidazole capsule four

times daily to complete 7-10 total days of treatment. Patients with a baseline pathogen non-susceptible to ciprofloxacin will need to continue on IV saline infusions over 30 minutes once daily to match the comparator infusion and will take one sulopenem etzadroxil/probenecid tablet twice daily to complete 7-10 total days of treatment (may be extended to 14 days for certain patients if approved by the medical monitor and meets criteria).

Comparator arm:

Patients with normal renal function: Patients randomized to the comparator treatment group will receive 1000 mg of ertapenem IV infused over 30 minutes, once daily for 5 days, and a saline IV infusion over 3 hours to simulate the comparator.

After at least 5 days of intravenous therapy those patients with a baseline pathogen susceptible to ciprofloxacin who meet criteria for oral step-down will take one placebo sulopenem etzadroxil/probenecid tablet twice daily, one over-encapsulated ciprofloxacin capsule twice daily, and one over-encapsulated metronidazole capsule four times daily to complete 7-10 total days of treatment (duration may be extended to 14 days for certain patients if approved by the medical monitor and meets criteria).

For patients found to have a baseline organism non-susceptible to ciprofloxacin, but susceptible to amoxicillin-clavulanate, after at least 5 days of IV therapy, those patients who meet criteria for oral step-down will take one placebo sulopenem etzadroxil/probenecid tablet twice daily, one over-encapsulated amoxicillin-clavulanate capsule twice daily and one over-encapsulated placebo metronidazole capsule four times daily to complete 7-10 total days of treatment (duration may be extended to 14 days for certain patients if approved by the medical monitor and meets criteria). Patients with baseline pathogens non-susceptible to both ciprofloxacin and amoxicillin-clavulanate will need to continue on IV ertapenem infusions over 30 minutes for the entire duration of therapy, and take one placebo sulopenem etzadroxil/probenecid tablet twice daily, in order to keep blinding intact. The total duration of treatment may be extended to 14 days for certain patients if approved by the medical monitor and meet criteria.

Patients with severe renal impairment (CrCl <30mL/min): Patients with severe renal impairment randomized to the comparator treatment group will receive 500 mg ertapenem IV infused over 30 minutes once daily for 5 days and a saline IV infusion over 3 hours to simulate the comparator.

After at least 5 days of intravenous therapy those patients with a baseline pathogen susceptible to ciprofloxacin and who meet criteria for oral step-down will take one placebo sulopenem etzadroxil/probenecid tablet twice daily, one over-encapsulated ciprofloxacin capsule approximately every 18 hours and one over encapsulated placebo metronidazole capsule four times daily to complete 7-10 total days of treatment. Patients with a baseline pathogen non-susceptible to ciprofloxacin will need to continue on IV ertapenem infusions over 30 minutes once daily and will take one placebo sulopenem etzadroxil/probenecid tablet twice daily to complete 7-10 total days of treatment. The total duration of treatment may be extended to 14 days for certain patients if approved by the medical monitor and meet criteria.

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

Both Treatment Groups:

In both treatment groups, patients found to have pathogens isolated from blood cultures that are resistant to carbapenems including ertapenem should be discontinued from study drug therapy, but should remain in the study and treated appropriately. Patients found to have pathogens isolated from intra-abdominal cultures that are resistant to carbapenems including ertapenem, may be allowed to continue on study drug therapy based on clinical response and investigator judgement.

Dosing with food: Food significantly increases bioavailability of sulopenem and consequently results in decreased rates of diarrhea. Therefore, dosing of oral sulopenem etzadroxil/probenecid with food whenever possible is recommended. Since adequate target attainment appears to be achieved in the fasted state, an inability to administer the dose with food should not preclude dosing. The overall absorption of ciprofloxacin is not substantially affected by food.

Efficacy Assessments:

The assessment of clinical response includes a review of the following signs and symptoms of cIAI: fever, leukocytosis, systolic blood pressure, heart rate, respiratory rate, oxygen saturation, abdominal pain or tenderness, abdominal mass, altered mental status, and nausea or vomiting.

Microbiologic response assessments will be made based on cultures performed on collected surgical specimens.

Other Assessments

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

Safety Assessments

Safety will be assessed by means of vital signs, collection of adverse events and clinical laboratory tests. A targeted physical examination will be performed at the Screening visit, Day 5, Day 10 (+/- 1 day) or Day 11-14 (+/- 1 day), and Day 28 (+/- 1 day) visits or at premature discontinuation; a targeted physical examination may also be performed as needed according to symptoms. Vital signs will be collected at the Screening Visit, and at Day 5, Day 10 (+/- 1 day) or Day 11-14 (+/- 1 day), and Day 28 (+/- 1 days) or premature discontinuation. Adverse events will be collected at every visit, beginning from the signing of Informed Consent. Clinical laboratory tests will be obtained at the Screening Visit, and at Day 5, Day 10 (+/- 1 day), or Day 11-14 (+/- 1 day), and Day 28 (+/- 1 day) visit, and in follow-up of any clinically significant laboratory finding or at premature discontinuation.

Statistical Methods:

Sample Size Considerations:

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 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 m-MITT evaluable. The sample size of the m-MITT population is 268 patients per arm based on a Z-test with unpooled variance. This 536 m-MITT sample size assumes a non-inferiority margin of 10%, a power of 90%, a one-sided alpha level of 0.025 and an 85% clinical cure rate in both treatment groups. The final ITT sample size may be increased based on the observed clinical cure rate at the blinded interim analysis, as well as the evaluability rate, to maintain a power of 90%.

General Statistical Considerations:

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

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

Efficacy Analyses:

The study is designed to determine whether sulopenem/sulopenem etzadroxil co-administered with probenecid is NI to ertapenem/ciprofloxacin plus metronidazole or amoxicillin-clavulanate for the outcome measure of clinical response on Day 28.

The number and percentage of patients assessed as a clinical cure, failure and indeterminate will be determined in each treatment group in the m-MITT population. The observed difference in the percentage of patients with a clinical cure at Day 28 (+/- 1 day) (sulopenem/sulopenem etzadroxil plus probenecid group minus the ertapenem/ciprofloxacin plus metronidazole or amoxicillin-clavulanate group) will be determined and 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 clinical cure rates in the m-MITT population is greater than -10% the NI of sulopenem to the comparator group will be concluded.

Safety analyses will be conducted in the Safety population (all patients who received any amount of study drug). Safety will be assessed through summaries of AEs, laboratory evaluations, and vital signs. All safety analyses will be based on the Safety population and will be summarized by treatment group.

Date of Original Approved Protocol: May 29, 2018

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

Prepared in: Microsoft Word 2016

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate Aminotransferase
AUC_{0-24}	Area under the curve from zero to 24 hours
βhCG	Beta Human Chorionic Gonadotropin
BID	Bis-in-die
BUN	Blood Urea Nitrogen
C_{max}	Maximum concentration
CA	Community-acquired
CBC	Complete Blood Count
CE	Clinically Evaluable
CI	Confidence Interval
CFU	Colony forming units
CLSI	Clinical and Laboratory Standards Institute
Cmax	Maximum concentration
CrCl	Creatinine Clearance
CRE	Carbapenem resistant Enterobacteriaceae
CRF	Case Report Form
CTA	Clinical Trial Application
cUTI	Complicated urinary tract infections
DMC	Data monitoring committee
EARS-NET	European Antimicrobial Resistance Surveillance Network
ECG	Electrocardiogram
E.coli	*Escherichia coli*
EIU	Exposure in Utero
EOT	End of Treatment Visit
ESBL	Extended Spectrum Beta-lactamase

FDA	Food and Drug Administration
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transpeptidase
GMP	Good Manufacturing Practice
hERG	Human Ether-a-go-go-Related Gene
HIV	Human Immunodeficiency Virus
hs-CRP	High-sensitivity C-reactive Protein
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IRB/IEC	Institutional Review Board /Independent Ethics Committee
ITT	Intent-to-Treat
IUD	Intrauterine Device
IV	Intravenous
IWRS	Interactive Web Randomization System
LDH	Lactate Dehydrogenase
LTFU	Lost to Follow-Up
ME	Microbiologically Evaluable
MEDRA	Medical Dictionary of Regulatory Activities
MIC	Minimal Inhibitory Concentration
MITT	Modified ITT
m-MITT	Microbiologic-MITT (micro-MITT)
MRSA	Methicillin-resistant *Staphylococcus aureus*
NI	Non-inferior
NOAEL	No Observed Adverse Effect Level
OSD	Oral solid dose
PBP	Penicillin-Binding Proteins
PCS	Potentially clinically significant
PK	Pharmacokinetic

PK/PD	Pharmacokinetic / Pharmacodynamic
PO	Per-oral
PV	Pharmacovigilance
RBC	Red blood cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA	Target attainment
TEAE	Treatment Emergent Adverse Event
TOC	Test of Cure
T_{max}	Time to maximum concentration
uUTI	Uncomplicated urinary tract infection
WBC	White Blood Cell
2-EBA	2-Ethylbutryic Acid

1 INTRODUCTION

1.1 Indication

Sulopenem is being studied for the treatment of the following indications:

- Complicated and uncomplicated urinary tract infections
- Complicated intra-abdominal infections

1.2 Background and Rationale

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

The prevalence of infections caused by extended-spectrum β-lactamases (ESBL) producing Enterobacteriaceae has been increasing worldwide and includes both hospital acquired and community onset infections. An analysis of data reported from 2011 to 2014 to the National Healthcare Safety Network performed by the Centers for Disease Control in March 2016 revealed that the proportion of *E.coli* resistant to extended-spectrum cephalosporins causing hospital-acquired infection was 13.4% nationally, with rates as high as 24% reported in some Northeastern, Southern and Western states. The same analysis also demonstrated that over a third of *E.coli* isolates in 2014 were resistant to quinolones. Oral antibiotic treatment options are extremely limited for patients with these infections, resulting in lengthy hospital stays to facilitate administration of intravenous antibiotics. Data reported by the European Antimicrobial Resistance Surveillance Network (EARS-NET) in Europe demonstrate that the prevalence of quinolone resistant *E.coli* and *E.coli* resistant to third-generation cephalosporins is > 25% and *E.coli* resistant to third generation cephalosporins, aminoglycosides and quinolones has increased to >10% in some southern and eastern European countries. Consequently, options for oral antibiotic step-down therapy for patients with resistant gram-negative infections are limited.

Sulopenem (CP-70,429) is a broad-spectrum penem β-lactam antibiotic which is being developed for the treatment of infections caused by multi-drug resistant bacteria. Sulopenem possesses potent activity against species of the Enterobacteriaceae that encode ESBLs or AmpC-type β-lactamases that confer resistance to third generation cephalosporins. The targeted gram-negative spectrum of sulopenem is balanced by its potent *in vitro* activity against anaerobic pathogens, which is similar to that of imipenem.

An *in-vitro* susceptibility study of sulopenem was conducted in April 2016 utilizing contemporary clinical bacterial isolates from patients in the United States and Europe. Minimal inhibitory concentrations (MICs) of sulopenem and 18 comparators were determined against

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

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

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

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

Sulopenem is available as an intravenous formulation (CP-70,429 is active moiety). Intravenous sulopenem was previously evaluated in Phase 1 and Phase 2 clinical studies in Japan in approximately 1474 subjects, at doses up to 1 g BID administered intravenously over 3-14 days in the early 1990's. Safety data collected from these trials regarding both adverse events as well as laboratory examinations provides support for the safety and tolerability of sulopenem in patients and its further development.

Sulopenem and its oral pro-drug, sulopenem etzadroxil, have been studied in single and multiple dose Phase 1 studies, and the oral prodrug has been studied with and without co-administration of probenecid. One small Phase 2 study in patients with community acquired pneumonia was

conducted, in which 35 adult patients were randomized to one of three treatment groups to receive either: a single loading dose of intravenous (IV) sulopenem with switch to oral sulopenem etzadroxil, 4 dose minimum of IV sulopenem with switch to oral sulopenem etzadroxil, or ceftriaxone (IV) for a minimum of 2 doses, with step down to amoxicillin/ clavulanate. The cure rates in the clinically evaluable subjects in this study at TOC were 90%, 88% and 63% in the single IV dose sulopenem, multiple IV dose sulopenem and ceftriaxone groups (IV), respectively. While these efficacy results were not statistically significant due to the small numbers enrolled, they provide encouraging support for further clinical testing in this indication. Phase 2 studies in patients with urinary tract infection or intra-abdominal infection have not been conducted in the United States.

Sulopenem etzadroxil has minimal *in vitro* antibacterial activity. Upon oral absorption, sulopenem etzadroxil yields the active moiety sulopenem in addition to the non-active moieties formaldehyde and 2-ethylbutyric acid (2-EBA).

The currently proposed study will compare the safety, tolerability and efficacy of sulopenem followed by sulopenem etzadroxil co-administered with oral probenecid with ertapenem followed by oral ciprofloxacin and metronidazole or amoxicillin-clavulanate for the treatment of complicated intra-abdominal infection.

1.2.1 Safety data

1.2.1.1 Sulopenem etzadroxil (oral prodrug)

Pre-clinical data

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

Previous human experience

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

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

Mean time to observed maximum concentration (T_{max}) was on average 1 hour for all doses. Neither sulopenem etzadroxil nor formic acid has been detected in either plasma or whole blood following dosing with sulopenem etzadroxil. In addition, the levels of 2 EBA were much lower (~1/20) than sulopenem concentrations. During the administration of multiple doses of sulopenem etzadroxil for 10 days due to the short half-life of sulopenem there is no accumulation on Day 10 of dosing. Sulopenem etzadroxil doses of 2000 mg produced a mean sulopenem C_{max} of 4.7 μg/mL and a mean AUC_{last} of 13.1 h•μg/mL. Sulopenem systemic exposure parameters (C_{max} and AUC_{last}) following sulopenem etzadroxil single doses ranging from 400 to 2000 mg, increased in a dose-related manner.

There is a significant effect of food (high fat meal) on the PK of sulopenem, given as

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

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

Overall sulopenem etzadroxil was well tolerated in the Phase 1 program. The most common adverse events occurring in the program were diarrhea and abnormal urine odor.

1.2.1.2 Sulopenem (CP-70,429) (Intravenous)

Preclinical intravenous data

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

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

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

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

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

Previous human experience (intravenous)

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

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

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

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

Complete information on sulopenem etzadroxil and sulopenem are available in the Investigator's Brochure.

1.2.2 Rationale for Study

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

For *Escherichia coli*, ampicillin resistance has risen to ≥50% in high-risk populations, and resistance to third generation cephalosporins is now increasingly common in certain areas. Only through the recognition of factors associated with increasing resistance and the mechanisms responsible can strategies be designed for minimizing ß-lactam resistance. As antibiotic resistance leads to increased costs of treatment, increased morbidity as well as increased mortality, there is an unmet urgent medical need for antimicrobial agents that can be utilized in serious hospital and community infections, especially agents that can be delivered orally.

The penems are considered to exhibit advantages to the ß-lactam class as they possess good

antibacterial activity against gram-negative pathogens commonly responsible for a wide range of community and hospital infections, and are stable to many ß-lactamases.

Sulopenem has in vitro activity against many common hospital pathogens, including extended spectrum ß-lactamase (ESBL) producing gram-negative pathogens (except *Pseudomonas spp., Acinetobacter spp., Stenotrophomonas spp.*), and anaerobes such as *Bacteroides fragilis*.

Rationale for probenecid

Probenecid has been shown in a dog model to increase the systemic exposure of a penem CP-65,207 (sulopenem [CP-70,429] is the S-isomer of CP-65,207) by about 2-fold, suggesting a role of active renal tubular secretion in drug elimination. Findings from a previous clinical pharmacokinetic study indicate that renal clearance accounts for a significant proportion (approximately 50%) of total clearance of sulopenem in healthy volunteers suggesting that probenecid could increase exposure and thus time over MIC for sulopenem. Probenecid is known to increase plasma levels of weak organic acids such as penicillins, cephalosporins, and other beta-lactam antibiotics, including penems, by competitively inhibiting their renal tubular secretion. Probenecid has been used safely with other beta-lactam antibiotics, to either reduce dose or dosing frequency of beta-lactams when used to treat infectious diseases in human beings. Please refer to probenecid product label for more pharmacology information on probenecid.

The pharmacokinetics, safety and tolerability of sulopenem etzadroxil in combination with probenecid 1000 mg was evaluated in 6 subjects in Study A8811006. Escalating oral doses of sulopenem etzadroxil administered with 1000 mg probenecid produced approximately proportional increases in systemic exposure of sulopenem over the dose range of 800 mg to 1200 mg. The combination of sulopenem etzadrozil 500 mg and probenecid 500 mg was evaluated in study IT001-101. Results from this study were consistent with those observed in previous studies.

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

Rationale for dosing with food

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

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

1.2.3 Dose Rationale

Sulopenem and Sulopenem etzadroxil

Doses of sulopenem and sulopenem etzadroxil were chosen by PK/PD modeling using a combination of (1) modeling (Naïve Pool analysis) of the sulopenem effect on net change in colony forming units (CFU) over 24 hours of clinically relevant organisms in an

immunocompetent mouse thigh infection model, (2) defining targets of percent time above the MIC (T>MIC) for sulopenem from this mouse model, and (3) population PK modeling using nonlinear mixed effects models, generated from clinical data in multiple IV sulopenem and oral sulopenem etzadroxil Phase 1 studies in healthy volunteers.

Monte Carlo simulations were performed using the human population PK parameters for sulopenem etzadroxil and mean pharmacodynamic parameters from a murine thigh infection model to determine % target achievement (TA) for the selected doses. A %TA of ≥90% was deemed desirable for selecting particular doses. The 1000 mg IV dose delivered over 3 hours and the 500 mg dose of sulopenem etzadroxil co-administered with 500 mg of probenecid administered twice daily meets the criteria of %T>MIC for achieving 1-log kill in >90% of bacteria with MIC's expected in this indication.

Probenecid

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

Ertapenem

The recommended dose of IV ertapenem in this study is 1000 mg administered over 30 minutes and is consistent with the ertapenem USPI and SmPC for treatment of complicated intra-abdominal infections.

Amoxicillin-clavulanate

The recommended dose of oral amoxicillin-clavulanate in this study is 875 mg bid, consistent with the amoxicillin-clavulanate US FDA Package Insert and SmPC for severe infections.

Ciprofloxacin

The recommended dose of oral ciprofloxacin in this study is 500 mg bid following an initial course of ertapenem IV to complete 10 days of therapy, consistent with the ciprofloxacin USPI and SmPC for treatment of cIAI.

Metronidazole

The recommended dose of oral metronidazole in this study is 500 mg qid, consistent with the metronidazole USPI and SmPC for treatment of IAI.

For the full prescribing information for probenecid and all comparator study drugs, please refer to respective local country product labels (USPI or SmPC).

2 STUDY OBJECTIVES

2.1 Objectives

The primary objective of this study is to compare the efficacy of sulopenem 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.

The secondary objectives of this study are:

To compare the efficacy outcomes at other relevant time points as well as the safety profile of treatment with sulopenem followed by sulopenem etzadroxil plus probenecid versus ertapenem followed by ciprofloxacin and metronidazole or amoxicillin-clavulanate for treatment of complicated intra-abdominal infection in adults.

To assess the population PK profile of sulopenem when administered either intravenously or as the prodrug of sulopenem etzadroxil co-administered with probenecid.

3 STUDY DESIGN

Sulopenem is an investigational penem antibiotic being developed for treatment of uUTI , complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI). Sulopenem etzadroxil is an oral pro-drug of sulopenem. Upon oral absorption, sulopenem etzadroxil is expected to be rapidly hydrolyzed to yield sulopenem, the active moiety, as well as the non-active moieties, formaldehyde and 2-ethylbutyric acid (2-EBA).

Sulopenem possesses potent activity against species of the Enterobacteriaceae that encode ESBLs or AmpC-type β-lactamases that confer resistance to third generation cephalosporins. Sulopenem etzadroxil is expected to be the first oral penem on the market in the United States or Europe and will offer the option of treatment in the outpatient setting as well as IV to oral switch therapy for early discharge of patients hospitalized with serious complicated infections. Probenecid, co-administered with the oral prodrug, will reduce renal clearance and increase systemic exposure of the active moiety, sulopenem.

This Phase 3, multicenter, double-blind, randomized, controlled study compares IV sulopenem followed by sulopenem etzadroxil with probenecid and ertapenem IV followed by an oral regimen of ciprofloxacin and metronidazole or amoxicillin-clavulanate for treatment of cIAI. The site pharmacist will be unblinded in order to prepare the intravenous study medications and select the appropriate oral follow on therapy for patients randomized to the ertapenem regimen. Approximately 670 adults with cIAI will be randomized in a 1:1 fashion to receive either IV sulopenem for at least 5 days followed by sulopenem etzadroxil 500mg co-administered with oral probenecid 500 mg twice daily to complete 7-10 days of treatment or ertapenem IV for at least 5 days followed by ciprofloxacin and metronidazole or amoxicillin-clavulanate, based on quinolone susceptibility of baseline pathogen to complete 7-10 days of therapy. 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.

The primary outcome measure for efficacy evaluation on Day 28 will be the resolution of the symptoms of cIAI present at trial entry.

See Appendix 1, Schedule of Activities Table.

3.1 Investigational Study Medications

Investigational study medications include sulopenem 1000 mg IV over 3 hours, sulopenem etzadroxil (PF-03709270) 500 mg PO twice daily co-administered with probenecid 500 mg PO twice daily, ertapenem 1000 mg once daily IV over 30 minutes, and ciprofloxacin 500 mg PO twice daily along with metronidazole 500 mg PO four times daily. If patients on the ertapenem

arm are found to have causative pathogens that are non-susceptible to ciprofloxacin, they will receive amoxicillin-clavulanate 875 mg PO twice daily.

3.2 Adjunctive Systemic Antibiotics

Other Systemic Antibiotics:

Vancomycin IV, linezolid IV or PO, or daptomycin IV can be given for known or suspected methicillin-resistant *Staphylococcus aureus* (MRSA) or *Enterococcus* spp.

4 STUDY POPULATION SELECTION

Male or female patients who present with cIAI and who meet all of the inclusion and none of the exclusion criteria will be eligible for participation in this study.

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

4.1 Inclusion Criteria

1. Patient or the patient's legally acceptable representative able to provide a signed written informed consent prior to any study-specific procedures.
2. Adult patients ≥18 years of age
3. EITHER:
    a. Intra-operative/post-operative enrollment with visual confirmation (presence of pus within the abdominal cavity) of an intra-abdominal infection associated with peritonitis including at least 1 of the following diagnosed during the surgical intervention:
        i. Cholecystitis with gangrenous rupture or perforation or progression of the infection beyond the gallbladder wall
        ii. Diverticular disease with perforation or abscess
        iii. Appendiceal perforation or peri-appendiceal abscess
        iv. Traumatic perforation of the intestines, only if operated on >12 hours after perforation occurs
        v. Secondary peritonitis (but not spontaneous bacterial peritonitis associated with cirrhosis and chronic ascites)
        vi. Intra-abdominal abscess (including of liver or spleen provided that there was extension beyond the organ with evidence of intraperitoneal involvement).

    OR:

    b. Pre-operative enrollment where one of the following surgical procedures are planned within 24 hours of the first dose of study drug:

i. Open laparotomy, percutaneous drainage of an intra-abdominal abscess, or laparoscopic surgery.

4. Evidence of systemic inflammatory indicators, with at least one of the following:
    a. Fever (defined as body temperature >38°C) or hypothermia with a core body temperature <35°C
    b. Elevated white blood cell count (>12,000 cells/mm^3) or leukopenia (defined as white blood cell count <4,000 cells/mm^3)
    c. Drop in blood pressure (systolic BP must be <90 mmHg without pressor support)
    d. Increased heart rate (>90 bpm) and respiratory rate (>20 breaths/min)
5. Hypoxia (oxygen saturation ≤90 percent on room air)
   Physical findings or symptoms consistent with intra-abdominal infection, with at least one of the following:
    a. Abdominal pain and/or tenderness, with or without rebound
    b. Localized or diffuse abdominal wall rigidity
    c. Abdominal mass
    d. Nausea and/or vomiting
    e. Altered Mental Status
6. Specimen/s from the surgical intervention were sent or planned to be sent for culture.

Microbiologic specimens collected during routine operative care prior to subject providing informed consent may be used for study purposes.

4.2 Exclusion Criteria

1. Patient diagnosed with traumatic bowel perforation undergoing surgery within 12 hours; perforation of gastroduodenal ulcers undergoing surgery within 24 hours. Other intra-abdominal processes in which the primary etiology was not likely to be infectious.
2. Patient has abdominal wall abscess or bowel obstruction without perforation or ischemic bowel without perforation.
3. Patient has simple cholecystitis or gangrenous cholecystitis without rupture, or simple appendicitis, or acute suppurative cholangitis; or infected necrotizing pancreatitis or pancreatic abscess.
4. Patient whose surgery included staged abdominal repair, or “open abdomen” technique, or marsupialization.
5. Patient known at study entry to have a complicated intra-abdominal infection caused by pathogens non-susceptible to the study antimicrobial agents.
6. Patient needed effective concomitant systemic antibacterials (oral, IV, or intramuscular) or antifungals in addition to those designated in the 2 study groups, except vancomycin, linezolid, or daptomycin if started for known or suspected methicillin-resistant *Staphylococcus aureus* (MRSA) or *Enterococcus* spp.
7. Patient has perinephric infections or an indwelling peritoneal dialysis catheter.

8. Patient has suspected intra-abdominal infections due to fungus, parasites (e.g., amoebic liver abscess), virus, or tuberculosis.
9. Patient has a known history of serious allergy, hypersensitivity or any serious reaction to carbapenem antibiotics, other β-lactam antibiotics, quinolones, metronidazole, or probenecid.
10. Patient known to have any of the following laboratory values as defined below:
    a. Hematocrit <25% or hemoglobin <8 g/dL
    b. Absolute neutrophil count <1000/mm^3
    c. Platelet count <75,000/mm^3
    d. Bilirubin >3 x the upper limit of normal (ULN), unless isolated hyperbilirubinemia was directly related to the acute infection or known Gilbert's disease
    e. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x ULN values at Screening. Patients with elevations of AST and/or ALT up to 5 x ULN will be eligible if these elevations are acute and directly related to the infectious process being treated. This must be documented
    f. Alkaline phosphatase (ALP) >3 x ULN. Patients with values >3.0 x ULN and <5.0 x ULN are eligible if this value is acute and directly related to the infectious process being treated. This must be documented.
11. Patient has a body mass index >45 kg/m^2.
12. Patient has APACHE II score >30 (serum bicarbonate may be used in place of arterial blood gases; see Appendix 5).
13. Patient considered unlikely to survive the 4-week study period or has a rapidly progressive or terminal illness, including septic shock that was associated with a high risk of mortality.
14. Patient unlikely to respond to 10–14 days of treatment with antibiotics.
15. Patient received systemic antibacterial agents within the 72-hour period prior to study entry, unless either of the following pertained:
    a. Patient has a new infection (not considered a treatment failure) and both of the following were met:
        i. Patient received no more than 24 hours of total prior antibiotic therapy
        ii. Patient received ≤1 dose of a treatment regimen post-operatively and antibiotics were not received more than 6 hours post-procedure.
    b. Patient considered to have failed the previous treatment regimen i.e., pre-operative treatment of any duration with non-study systemic antimicrobial therapy for peritonitis or abscess permitted provided that all of the following are met:
        i. The treatment regimen had been administered for at least 72 hours and was judged to have been inadequate
        ii. The patient had an operative intervention that was just completed or was intended no more than 24 hours after study entry
        iii. Findings of infection were documented at surgery
        iv. Specimens for bacterial cultures and susceptibility testing were taken at operative intervention
        v. No further non-study antibacterials were administered after randomization.

16. Patient has a concurrent infection that may interfere with the evaluation of response to the study antibiotic.
17. Patient receiving hemodialysis, hemofiltration, or peritoneal dialysis.
18. Patient has a history of acute hepatitis in the recent past (3 months prior to study entry), chronic hepatitis, cirrhosis, acute hepatic failure, or acute decompensation of chronic hepatic failure.
19. Patient has past or current history of epilepsy or seizure disorders excluding febrile seizures of childhood.
20. Patient immunocompromised as evidenced by any of the following:
    a. Human immunodeficiency virus infection, with either a recent (in the past 6 months) acquired immune deficiency syndrome-defining condition or a CD4 + T lymphocyte count <200/mm^3
    b. Systemic or hematological malignancy requiring chemotherapeutic or radiologic/immunologic interventions within 6 weeks prior to randomization, or anticipated to begin prior to completion of study
    c. Immunosuppressive therapy, including maintenance corticosteroid therapy (>40 mg/day equivalent prednisolone for 5 days or more).
21. Patient participating in any other clinical study that involved the administration of an investigational medication at the time of presentation, during the course of the study, or who had received treatment with an investigational medication in the 30 days prior to study enrollment, or had previously been enrolled in this study or had been treated with sulopenem.
22. Patient is in a situation or has a condition that, in the investigator's opinion, may interfere with optimal participation in the study.
23. Patient unlikely to comply with protocol e.g., uncooperative attitude, inability to return for follow-up visits, and unlikely to complete the study.
24. Patient has known inflammatory bowel disease (ulcerative colitis or Crohn's disease) or *Clostridium difficile*-associated diarrhea.
25. Patients with a history of blood dyscrasias
26. Patients with a history of uric acid kidney stones
27. Patients with acute gouty attack
28. Patients on chronic methotrexate therapy
29. Females of child-bearing potential who are unable to take adequate contraceptive precautions (refer to Section 4.4.1), have a positive pregnancy test result within 24 hours of study entry, are otherwise known to be pregnant, or are currently breastfeeding an infant.
30. Male subjects who do not agree to use an effective barrier method of contraception during the study and for 14 days post treatment (refer to Section 4.4.2).

4.3 Randomization Criteria

Patients will be randomized in a 1:1 ratio to sulopenem followed by sulopenem etzadroxil with probenecid versus ertapenem followed by ciprofloxacin plus metronidazole or amoxicillin-

clavulanate using an IWRS system provided they have satisfied all patient selection criteria. Randomization will be stratified by the type of infection (cIAI caused by appendicitis with perforation or peri-appendiceal abscess versus all other cIAI diagnoses). The proportion of patients who have cIAI caused by appendicitis with perforation or peri-appendiceal abscess will not exceed approximately 50%.

4.4 Life Style Guidelines

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

4.4.1 Women of Child-Bearing Potential

If the patient is a woman of childbearing potential, she and any male partner are required to simultaneously use 2 effective contraceptive methods, from the following list of 5:

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

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

4.4.2 Males

It is required that all male subjects use one of the following methods of contraception from the first dose of study medication and until 28 days after last dosing:

1. Abstinence
2. Use of condom for males that have not been vasectomized for at least 6 months.
3. Male subjects who have not had a vasectomy must use a condom. In addition, such a male subject should be instructed that, unless his female partner has had a tubal ligation, hysterectomy, or bilateral oophorectomy or is post-menopausal, his female partner should use another form of contraception from the time of the first dose of study medication until 28 days after dosing. Such other forms of contraception include an IUD, spermicidal foam/gel/film/cream/suppository, diaphragm with spermicide, oral contraceptive, injectable progesterone, or subdermal implant.

5 STUDY TREATMENTS

5.1 Allocation to Treatment

This is a randomized double blind study in which approximately 670 patients will be randomized to receive either sulopenem followed by sulopenem etzadroxil plus probenecid or ertapenem

followed by ciprofloxacin plus metronidazole or oral amoxicillin-clavulanate in the treatment of cIAI. Randomization will be based on an IWRS-generated schedule in a 1:1 allocation ratio.

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

5.1.1 Criteria for Switch from IV to Oral Therapy

After 5 days of IV treatment (at least 5 administrations of IV therapy) patients are eligible to switch to oral treatment if they have met the following criteria:

1. Patient can tolerate oral medications
2. Fever and white blood cell count are improving; these signs of infection do not have to return to normal
3. Clinical signs or symptoms such as ileus, abdominal pain or tenderness, abdominal wall rigidity or guarding, nausea or vomiting, if present at baseline, are improving.

5.2 Drug Supplies

5.2.1 Formulation and Packaging

Sulopenem treatment group: Sulopenem 1000 mg IV will be supplied as a single-use vial with lyophilized powder for injection. The IV solution will be prepared for dosing by an unblinded pharmacist. The oral medications will be packaged in a suitable packaging container and provided to the sites.

Comparator treatment group: Ertapenem 1000 mg IV will be supplied as a single-use vial. The IV solution will be prepared for dosing by an unblinded pharmacist. The oral medications will be packaged in a suitable packaging container and provided to the sites.

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

5.2.2 Preparation and Dispensing

Sulopenem or ertapenem IV: Each dose of IV study medication will be prepared by an unblinded pharmacist or other qualified personnel at the site according to the dosing instruction provided by the sponsor. Dosage Administration Instructions (DAI) will be provided under separate cover for preparation of doses using the sulopenem vials and comparator.

Sulopenem etzadroxil/probenecid or comparator oral solid dose (OSD): All OSD study drugs will be provided to the study site by Iterum Therapeutics. Preparation and administration of

study medication will be done and documented in accordance with the treatment schedule as outlined in the study protocol.

5.2.3 Administration

Sulopenem arm:

Patients with normal renal function: Patients randomized to the sulopenem treatment group will receive 1000 mg sulopenem IV infused over 3 hours, once daily for 5 days, and a saline IV infusion over 30 minutes to simulate the comparator.

After at least 5 days of intravenous therapy, those patients with a baseline pathogen susceptible to ciprofloxacin and who meet criteria for oral step-down will take one sulopenem etzadroxil/probenecid tablet twice daily, one over-encapsulated placebo ciprofloxacin tablet twice daily and one over encapsulated placebo metronidazole capsule four times daily to complete 7-10 total days of treatment (may be extended to 14 days for certain patients if approved by the medical monitor and meets criteria).

For patients found to have a baseline organism non-susceptible to ciprofloxacin but susceptible to amoxicillin-clavulanate, after at least 5 days of IV therapy those patients who meet criteria for oral step-down will take one sulopenem etzadroxil/probenecid tablet twice daily, one over-encapsulated placebo amoxicillin-clavulanate capsule twice daily, and one over encapsulated placebo metronidazole capsule four times daily to complete 7-10 total days of treatment (may be extended to 14 days for certain patients if approved by the medical monitor and meets criteria). Patients with baseline pathogens non-susceptible to both ciprofloxacin and amoxicillin-clavulanate will need to continue on IV saline infusions over 30 minutes to match IV ertapenem for the entire duration of therapy, and take one sulopenem etzadroxil/probenecid tablet twice daily, in order to keep blinding intact.

Patients with severe renal impairment (CrCl <30mL/min)*:* Patients with severe renal impairment randomized to the sulopenem treatment group will receive 250 mg sulopenem IV infused over 3 hours once daily for 5 days and a saline IV infusion over 30 minutes to simulate the comparator.

After at least 5 days of intravenous therapy those patients with a baseline pathogen susceptible to ciprofloxacin and who meet criteria for oral step-down will take one sulopenem etzadroxil/probenecid tablet twice daily, one over-encapsulated placebo ciprofloxacin capsule approximately every 18 hours and one over encapsulated placebo metronidazole capsule four times daily to complete 7-10 total days of treatment (may be extended to 14 days for certain patients if approved by the medical monitor and meets criteria). Patients with a baseline pathogen non-susceptible to ciprofloxacin will need to continue on IV saline infusions over 30 minutes once daily to match the comparator infusion and will take one sulopenem etzadroxil/probenecid tablet twice daily to complete 7-10 total days of treatment (may be extended to 14 days for certain patients if approved by the medical monitor and meets criteria).

Comparator arm:

Patients with normal renal function: Patients randomized to the comparator treatment group will receive 1000 mg of ertapenem IV infused over 30 minutes, once daily for 5 days, and a saline IV infusion over 3 hours to simulate the comparator.

After at least 5 days of intravenous therapy those patients with a baseline pathogen susceptible to ciprofloxacin who meet criteria for oral step-down will take one placebo sulopenem

etzadroxil/probenecid tablet twice daily, one over-encapsulated ciprofloxacin capsule twice daily, and one over-encapsulated metronidazole capsule four times daily to complete 7-10 total days of treatment (may be extended to 14 days for certain patients if approved by the medical monitor and meets criteria).

For patients found to have a baseline organism non-susceptible to ciprofloxacin but susceptible to amoxicillin-clavulanate, after at least 5 days of IV therapy, those patients who meet criteria for oral step-down will take one placebo sulopenem etzadroxil/probenecid tablet twice daily, one over-encapsulated amoxicillin-clavulanate capsule twice daily, and one over encapsulated placebo metronidazole capsule four times daily to complete 7-10 total days of treatment (may be extended to 14 days for certain patients if approved by the medical monitor and meets criteria). Patients with baseline pathogens non-susceptible to both ciprofloxacin and amoxicillin-clavulanate will need to continue on IV ertapenem infusions over 30 minutes for the entire duration of therapy, and take one placebo sulopenem etzadroxil/probenecid tablet twice daily, in order to keep blinding intact. The total duration of treatment may be extended to 14 days for certain patients if approved by the medical monitor and meet criteria.

Patients with severe renal impairment (CrCl <30mL/min): Patients with severe renal impairment randomized to the comparator treatment group will receive 500 mg ertapenem IV infused over 30 minutes once daily for 5 days and a saline IV infusion over 3 hours to simulate the comparator.

After at least 5 days of intravenous therapy those patients with a baseline pathogen susceptible to ciprofloxacin and who meet criteria for oral step-down will take one placebo sulopenem etzadroxil/probenecid tablet twice daily, one over-encapsulated ciprofloxacin capsule approximately every 18 hours and one over encapsulated placebo metronidazole capsule four times daily to complete 7-10 total days of treatment (may be extended to 14 days for certain patients if approved by the medical monitor and meets criteria). Patients with a baseline pathogen non-susceptible to ciprofloxacin will need to continue on IV ertapenem infusions over 30 minutes once daily and will take one placebo sulopenem etzadroxil/probenecid tablet twice daily to complete 7-10 total days of treatment. The total duration of treatment may be extended to 14 days for certain patients if approved by the medical monitor and meet criteria.

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

The site pharmacist will be unblinded in order to prepare the intravenous study medications and select the appropriate oral follow on therapy for patients randomized to the ertapenem regimen.

Both Treatment Groups:

In both treatment groups, patients found to have pathogens isolated from blood cultures that are resistant to carbapenems including ertapenem should be discontinued from study drug therapy, but should remain in the study and treated appropriately. Patients found to have pathogens isolated from intra-abdominal cultures that are resistant to carbapenems including ertapenem, may be allowed to continue on study drug therapy based on clinical response and investigator judgement.

Dosing with food: Food significantly increases bioavailability of sulopenem and consequently results in decreased rates of diarrhea. Therefore, dosing of oral sulopenem etzadroxil/probenecid with food whenever possible is recommended. Since adequate target attainment appears to be

achieved in the fasted state, an inability to administer the dose with food should not preclude dosing. The overall absorption of ciprofloxacin is not substantially affected by food.

5.2.4 Compliance

All patients should be informed that compliance with taking all medication as instructed is imperative. Intravenous treatment will be administered under the supervision of investigative site personnel at a hospital or, for centers approved by the Sponsor to do so, in an outpatient infusion center, and infusion date, start and stop time will be documented on the CRF.

Patients discharged on oral medication will be asked to bring all study medication bottles (used and unused) to the next scheduled study visit for drug accountability. Patients will be asked to record oral dosing on a dosing record and bring it to the site at each visit. The total amount of oral dosing completed (determined by tablet count from returned bottles/blister packs) will be recorded on the CRF. A urine sample will be collected and frozen for all patients at the EOT visit if a need to confirm compliance with study drug therapy arises for any patient.

5.3 Drug Storage and Drug Accountability

The investigator, or an approved representative, e.g., pharmacist/designee, will ensure that all investigational products are stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. To ensure adequate records, all study drugs will be accounted for by using site standard accountability form or forms provided by Iterum Therapeutics. In either case, the forms must identify the investigational product, including batch or code numbers, and account for its disposition on a patient-by-patient basis, including specific dates and quantities.

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

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

5.4.1 Concomitant Medications

Any medication taken by the patient, other than study drug, is considered a concomitant medication. All concomitant medications from Screening (Day -1) through the Day 28 (TOC) must be recorded in the patient's source record and on the CRFs.

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

The use of other (non-antibacterial) medications should be limited to those essential for the care of the patient. All medications required by the patient to manage underlying illnesses, other than

infection under study, and any drugs that may be required for emergency treatments must be recorded on the CRF.

5.4.2 Concomitant Antibacterial Medications

Concomitant systemic antibacterials are prohibited during the study, up to the EOT visit, with the following exceptions:

- Vancomycin IV, linezolid IV or PO, or daptomycin IV can be given for known or suspected methicillin-resistant *Staphylococcus aureus* (MRSA) or *Enterococcus* spp. The Sponsor will not provide any of these medications.

5.4.3 Non-drug Adjunctive Therapy

The potential need for surgical intervention in patients with cIAI during the study must be prospectively defined at Baseline. Patients expected to require more than 2 surgical interventions for the cIAI under study are not to be enrolled.

The following adjunctive therapies are permitted for the treatment of cIAI:

- Percutaneous drainage procedures, open laparotomy or laparoscopic surgery
- Topical solutions including antiseptic agents such as povidine-iodine;
- Local bedside wound care as per hospital protocol.

6 STUDY PROCEDURES

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

The investigator (or an appropriate delegate at the investigator site) will obtain written informed consent from each patient prior to the initiation of any study related activities. Sites participating in the population PK substudy should obtain written consent from willing patients. PK sampling procedures are detailed in Appendix 4.

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

- Demographics and medical history.
- Targeted physical examination (including general appearance, examination of heart, lungs, abdomen, and extremities)
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate) and height and weight
- Assess cIAI specific signs and symptoms
- Blood for laboratory testing (including hematology and chemistry studies as well as urine or serum (βhCG) pregnancy test (women of child-bearing potential, including peri-menopausal women until FSH value is known); serum follicle stimulating hormone [FSH] for postmenopausal females <50 years of age or those ≥50 years of age who have been post-menopausal for <2 years.
- Banked serum and urine for retrospective safety and efficacy assessments
- Collect urine for urinalysis

- Infection site specimen collection (including Gram-stain, culture and susceptibility [Appendix 2]) and blood cultures
- Adverse events occurring after signing of ICF
- Review previous (defined as within the prior 30 days) and concomitant drug and non-drug treatments

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

6.2 Treatment Period

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

- Blood pressure/pulse rate: obtain as close as possible to scheduled time, but prior to blood specimen collection.
- Pharmacokinetic blood specimens: obtain at scheduled time.

6.2.1 Day 1

The following activities will be completed:

- Review concomitant drug and non-drug treatments
- Administer the study medication as described in the Study Treatment Section (Administration Section)
- Collect blood samples for PK analyses for patients in the PK substudy (Appendix 4)
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?

6.2.2 Day 5

- Targeted physical examination, if required, based on patient’s symptoms
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate)
- Assess cIAI specific signs and symptoms
- Blood for laboratory testing (including hematology and chemistry studies)
- Collect blood samples for PK analyses for patients in the PK substudy (Appendix 4)
- Review concomitant drug and non-drug treatments
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?

6.2.3 Day 10 (End of Treatment)

- Targeted physical examination, if required, based on patient’s symptoms
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate)
- Assess cIAI specific signs and symptoms

- Blood for laboratory testing (including hematology and chemistry studies)
- Review concomitant drug and non-drug treatments
- Check and document compliance with study medication if stepped down to oral therapy
- Banked urine specimen to document compliance if needed
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?
- Investigator Assessment of Clinical Response (Section 7.2.2)

6.2.4 Day 11-14 (End of Treatment) – only to be conducted for patients who receive longer than 10 days of treatment, instead of Day 10 visit

- Targeted physical examination, if required, based on patient's symptoms
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate)
- Assess cIAI specific signs and symptoms
- Blood for laboratory testing (including hematology and chemistry studies)
- Review concomitant drug and non-drug treatments
- Check and document compliance with study medication if stepped down to oral therapy
- Banked urine specimen to document compliance if needed
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?
- Investigator Assessment of Clinical Response (Section 7.2.2)

6.3 Follow-Up Period

6.3.1 Day 21 (+/- 1 day) – Phone Call

- Assess cIAI specific signs and symptoms
- Review concomitant drug and non-drug treatments
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?
- Investigator Assessment of Clinical Response (Section 7.2.2)

6.3.2 Day 28 (+/- 1 day) – (Test of Cure)

- Targeted physical examination, if required, based on patient's symptoms
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate)
- Assess cIAI specific signs and symptoms
- Blood for laboratory testing if needed to follow up on abnormal test results from the Day 10 visit (including hematology and chemistry studies)
- Urine pregnancy test
- Review concomitant drug and non-drug treatments

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?
- Investigator Assessment of Clinical Response (Section 7.2.2)

6.4 Premature Discontinuation from Study

- Targeted physical examination, if required, based on patient's symptoms
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate)
- Assess cIAI specific signs and symptoms
- Blood for laboratory testing (including hematology and chemistry studies)
- Review concomitant drug and non-drug treatments
- Check and document compliance with study medication, if applicable
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?
- Investigator Assessment of Clinical Response (Section 7.2.2)

6.5 Patient Withdrawal from Treatment or Study

Patients may withdraw from the study or study drug at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. If the patient withdraws or is withdrawn from study drug treatment, the investigator should inquire about the reason for withdrawal, request the patient to return for all protocol-specified assessments, if possible, and follow-up with the patient regarding any unresolved AEs through Day 28.

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

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

7 ASSESSMENTS

7.1 Safety

7.1.1 Physical Examination

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

7.1.2 Vital Signs (Blood Pressure, Respiration Rate, Temperature and Pulse Rate)

Vital signs are performed at Baseline, Day 5, Day 10 (or Day 11-14) and Day 28 (+/- 1 days).

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

7.1.3 Clinical Laboratory Assays

The following laboratory parameters will be measured:

- Hematology: Complete blood count (CBC), including white blood cell (WBC) and differential counts; at Baseline, Day 5, Day 10 (or Day 11-14), and premature discontinuation. If abnormal at the Day 10 or Day 11-14 visit, need to repeat on Day 28.
- Serum Clinical Chemistry: AST, ALT, GGT, alkaline phosphatase, albumin, total and direct bilirubin, BUN or urea, creatinine, Na+, K+, Cl-, total CO2 (Bicarbonate), glucose, C-reactive protein (CRP) and LDH at Baseline, Day 5, Day 10 (or Day 11-14) and premature discontinuation. If abnormal at the Day 10 or Day 11-14 visit, need to repeat on Day 28.
- Urinalysis at Baseline.
- Pregnancy Test (women of child-bearing potential): Urine or serum βhCG only at Baseline/Day 1; urine βhCG at Day 28 or premature discontinuation; Pregnancy test at Baseline should also be performed on peri-menopausal women until FSH value is available.
- Serum FSH (to confirm postmenopausal status [amenorrheic for at least 1 year] for women <50 years of age or those ≥50 years of age who have been post-menopausal for <2 years): FSH at Baseline only, as needed.
- Blood cultures: 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) and repeated until negative. If baseline cultures are negative, follow up cultures should be obtained only if clinically indicated (eg, worsening of signs and symptoms, relapse, or new infection). Specific instructions for sample collection, processing, and shipment can be found in the laboratory manual(s) for this study.
- In addition, serum and urine samples will be banked at baseline for retrospective safety and efficacy analyses if needed. Urine specimens may be collected at EOT and banked if a need to document compliance with study drug therapy is identified.

7.1.4 Clinically Significant Laboratory Tests

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

7.2 Efficacy

7.2.1 Clinical Response

A patient's outcome will be programmatically defined as a clinical cure if the following criteria are met:

- Patient is alive
- Resolution of baseline signs and symptoms of the index infection
    - No new symptoms
- No new antibiotics or interventions for treatment failure are required

Clinical failure is defined as:

- Death due to cIAI
- 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
- Initiation of non-trial antibacterial drug therapy for treatment of cIAI based on documented worsening symptoms or signs of cIAI

If data are unavailable to determine if the patient is a cure or a failure the patient outcome will be considered indeterminate. Deaths not due to cIAI will also be considered indeterminate. Patients with an indeterminate response are included in the denominator for determination of the clinical cure rate in the m-MITT population.

7.2.2 Investigator Assessment of Clinical Response

Investigators will use the definitions below to document clinical response at the EOT, TOC and premature discontinuation visits:

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 or TOC for the EOT or TOC assessments, respectively
	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
	Patient previously met criteria for failure based on receipt of rescue antibiotics or death, as above

Clinical response	Definition
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 or TOC visit Death prior to EOT or TOC for the EOT and TOC assessments, respectively, where cIAI was clearly noncontributory

7.2.3 Other Efficacy Outcomes

Microbiologic response will be determined at EOT and TOC in the ME and m-MITT populations. For each pathogen, microbiologic response will be defined as follows:

- Eradication: An acceptable specimen at a post-baseline visit indicates absence of the baseline pathogen
- Presumed eradication: There was no acceptable post-baseline specimen for culture and the patient was assessed as a clinical curebased on the programmatic determination of clinical response.
- Persistence: An acceptable post-baseline specimen indicates presence of the baseline pathogen
- Presumed persistence: There was no acceptable post-baseline specimen for culture and the patient was assessed as a clinical failure based on the programmatic determination of clinical response.
- Persistence with increasing MIC: An acceptable post-baseline culture taken after at least 2 full days of treatment indicates presence of the baseline pathogen and displayed ≥4-fold higher MIC to study drug therapy after treatment with study therapy. For patients with bacteremia at Baseline, follow-up blood cultures after 72 hours of treatment show growth of baseline pathogen and displayed ≥4-fold higher MIC to study drug therapy.
- Indeterminate: Study data were not available for evaluation of efficacy, for any reason including:
    - 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) at either the Day 5, EOT or the TOC visit
    - Death prior to Day 5, EOT or TOC respectively, where the underlying infection was clearly non-contributory
    - Circumstances that precluded classification as an eradication, persistence, or persistence with increasing MIC

A microbiologic success is defined as eradication or presumed eradication whereas a failure is defined as persistence or presumed persistence.

The per-patient microbiological response is based on the outcomes for each baseline pathogen. For a subject to be a microbiological success, the outcome for each baseline pathogen must be a

success (eradication or presumed eradication). If the outcome is failure for any pathogen (as defined by persistence or presumed persistence) then the patient will be regarded as a per-patient microbiologic failure.

8 ADVERSE EVENT REPORTING

8.1 Adverse Events

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

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

8.2 Reporting Period

Adverse events will be collected from the time that the patient provides informed consent through the Day 28 (TOC) visit.

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

All AEs should be recorded on the CRF if they occur from the time the patient provides informed consent through the Day 28 (TOC) visit.

8.3 Definition of an AE

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

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

Events represented by the study endpoints include all of the following:

- Symptoms of cIAI have not resolved from Baseline to such an extent that new antibiotics are not needed for the infection under study
- Development of new cIAI symptoms not present at Baseline

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

- Abnormal test findings (see Section 8.4);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease.

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

- Drug overdose;
- Drug withdrawal;
- Drug abuse;
- Drug misuse;
- Drug interactions;
- Drug dependency;
- Extravasation of study drug;
- Exposure during Pregnancy.

8.4 Abnormal Test Findings

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

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

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

8.5 SAEs

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

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

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

8.6 Hospitalization

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

Hospitalization does not include the following:

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

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

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

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

begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded as treatment of the AE.

8.7 Severity Assessment

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

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

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

8.8 Causality Assessment

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

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

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

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

- PROBABLY, Event or laboratory test abnormality, with reasonable time relationship to drug intake; Unlikely to be attributed to disease or other drugs; Response to withdrawal clinically reasonable; Rechallenge not required

8.9 Exposure during Pregnancy

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

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

If any study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, no further study drugs should be given and the investigator must submit this information to Iterum Therapeutics on a Pregnancy Form. In addition, the investigator must submit information regarding environmental exposure to sulopenem in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to sulopenem by spillage) using the Pregnancy Form. This reporting must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

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

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

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

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

- "Spontaneous abortion" includes miscarriage and missed abortion.

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

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator must obtain permission from the patient's partner in order to conduct any follow-up or collect any information.

8.10 Discontinuation from Study Drug Due to AEs (See also Patient Withdrawal, Section 6.4)

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

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

8.11 Eliciting AE Information

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

8.12 Reporting Requirements

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

8.12.1 SAE Reporting Requirements

If an SAE or exposure during pregnancy occurs, Iterum Therapeutics (Iterum's PV Service provider) is to be notified within 24 hours of awareness of the event by the investigator on an SAE form or Pregnancy form. If the SAE is fatal or life-threatening, notification to Iterum must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of Pregnancy cases.

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

For all SAEs and pregnancies, the investigator is obligated to pursue and provide information to Iterum in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Iterum Therapeutics to obtain specific additional follow-up

information in an expedited fashion. This information may be more detailed than that captured on the SAE form. In general, this information may include hospital discharge summary, laboratory test and X-ray results. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Iterum Therapeutics. The information should be reported on an SAE/Pregnancy form and sent to the PSI Pharmacovigilance unit.

8.12.2 Non-SAE Reporting Requirements

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

8.12.3 Sponsor Reporting Requirements to Regulatory Authorities

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

9 DATA ANALYSIS/STATISTICAL METHODS

9.1 Sample Size Determination

The study is designed to determine whether 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 m-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 m-MITT evaluable. The sample size of the m-MITT population is 268 patients per arm based on a Z-test with unpooled variance. This 536 m-MITT sample size 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 9.7.

9.2 Definition of Analysis Populations

1. **Intent-to-Treat (ITT)**: all randomized patients regardless of whether or not the subjects received study drug
2. **Modified ITT (MITT)**: randomized patients who received at least a single-dose of study medication
3. **Safety**: randomized patients who received any amount of a single-dose of study medication
4. **Micro-MITT (m-MITT)**: All MITT patients who have at least one gram-negative pathogen identified at study entry (regardless of isolate susceptibilities). Patients with a bacterial species typically not expected to respond to either study drug (e.g. *Acinetobacter* spp., *Stenotrophomonas* spp., *Pseudomonas* spp.) will be excluded.
5. **Clinically evaluable: Clinically evaluable (CE) at the EOT and TOC visits population:**

   a) Received a minimum number of days of study drug (to be defined in the Statistical Analysis Plan [SAP])

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

   c) Had an outcome assessment of clinical cure or failure (and not indeterminate) at the EOT or TOC visits (ie, within the protocol allowed visit window), respectively.

   d) Had not received prior antibiotic within 48 hours of the initiation of study therapy for this infection unless the patient had received only 1 dose of a short-acting antibiotic regimen within 24 hours

   e) Did not receive any non-study antibiotic therapy with potential activity against any of the baseline pathogens collected at screening between the time of the baseline culture and the EOT or TOC culture, respectively. This excludes the protocol defined study therapy and patients who were considered clinical failures and required additional antibiotic therapy. Patients with a coinfection with a gram-positive pathogen resistant to study drugs are allowed to receive agents with narrow spectrum gram-positive coverage (ie, such as linezolid, daptomycin or vancomycin)

6. **Microbiologically evaluable (ME):** all patients included in both the m-MITT and CE populations at the EOT visit (ME-EOT) and at the TOC visit (ME-TOC).

9.3 General Statistical Considerations

Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided. All comparisons will be for the sulopenem treatment group and the comparator treatment group. Exploratory analyses may also be performed. Listings of individual

patient's data will be produced. A comprehensive SAP will be finalized prior to the interim analysis.

9.4 Patient Characteristics

Enrollment, protocol deviations, discontinuations from the study drug and withdrawal from the study will be summarized by treatment group. Demographics (age, race, sex), medical and surgical history, baseline assessment of the symptoms of cIAI, baseline pathogen, and study drug administration will also be summarized. Differences between treatment groups will be analyzed using the chi-square or Fisher's exact test for dichotomous variables and the Wilcoxon Rank Sum test for ordinal variables and continuous variables.

9.5 Efficacy Analysis

For all efficacy analyses, patient data will be analyzed in the treatment group to which the patient was randomized. For the primary analysis, patients who were randomized to the wrong type of infection will be analyzed in the stratum to which they were randomized.

9.5.1 Analysis of Primary Outcome Measure

The primary efficacy outcome is clinical response at the Day 28 (TOC) visit in the m-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 and 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.

9.5.1.1 Additional Analyses of the Primary Efficacy Outcome

The primary efficacy outcome will also be assessed within each geographic region and by type of infection by treatment group. For each geographic region, a two-sided 95% CI for the observed difference in the clinical cure rates in the m-MITT population will be calculated. For each type of infection, a two-sided 95% CI for the observed difference in the clinical cure rates in the m-MITT population will be calculated.

Sensitivity analyses of the primary outcome will also be conducted. An adjusted analysis (95% CI will be adjusted for the stratification factor of type of infection using the stratified method of Miettinen and Nurminen) will be provided for the difference in the clinical cure rate between the two treatment groups. Cochran-Mantel-Haenszel weights will be used for the stratum weights in the calculation of the CI.

9.5.2 Analysis of Secondary Efficacy Outcome Measure

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 m-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 the method of Miettinen and Nurminen.

9.5.3 Analysis of Additional Efficacy Outcome Measures

Additional efficacy outcome measures will be presented for the following time points and analysis populations:

1. Clinical response at Day 28 (TOC) in the MITT, CE-TOC and ME-TOC populations.

2. Clinical response at EOT (+/- 1 day) in the MITT, CE-EOT and ME-EOT populations.

3. Clinical response by pathogen for key pathogens at TOC in the ME and m-MITT populations

4. Per-subject microbiologic response at EOT and TOC in the ME and m-MITT populations. Per-pathogen microbiologic response at EOT and TOC in the ME and m-MITT populations

5. Investigators assessment of response (clinical cure, failure and indeterminate) at the EOT and TOC visits will be presented by treatment group for the m-MITT and CE populations.

6. Efficacy analyses in the subgroups of patients who did and did not receive prior effective antibiotic therapy will be presented.

7. Other analyses of the impact on clinical efficacy of baseline demographic variables such as age, APACHE score, etc. may be performed.

For selected additional efficacy outcome measures, two-sided 95% unstratified CIs will be constructed for the observed difference between the treatment groups for descriptive purposes; no conclusion of NI will be made.

9.6 Safety Analyses

Safety will be assessed through summaries of AEs, clinical laboratory tests and vital signs. All safety analyses will be based on the Safety population. Patients who receive the wrong regimen of study drug for their entire course of treatment will be analyzed in the group based on the regimen received.

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

Descriptive statistics summarizing central laboratory data (hematology and chemistry) will be presented for all study visits. The change from baseline to each post-baseline visit and to the overall worst post-baseline value will also be summarized by treatment group. Laboratory values will be classified as of potential clinical concern and the number and percentage of patients with a lab value of potential clinical concern will be summarized by visit and treatment group. Descriptive statistics of the vital signs will be presented by treatment group and study visit, as well as the change from baseline at each study visit.

9.7 Interim Analysis

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 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 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 sulopenem/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.

9.8 Handling of Missing Data

Details of the handling of missing data will be provided in the SAP. For the primary and secondary efficacy analyses, if any data field needed to determine clinical response is missing at the TOC visit, the patient will be considered an indeterminate response. By definition, patients with an indeterminate response are included in the denominator in the m-MITT population and thus, are analyzed in the same manner as clinical failures. Additional sensitivity analyses for handling missing data will be detailed in the SAP. Imputation may be performed to understand the impact of any imbalance in indeterminate outcomes between treatment regimens. By definition, patients with missing data are excluded from the CE populations.

10 QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

11 DATA HANDLING AND RECORD KEEPING

11.1 Case Report Forms / Electronic Data Record

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

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

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

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

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Iterum and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2 Record Retention

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

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

12 ETHICS

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

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

be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Iterum.

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

12.2 Ethical Conduct of the Study

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

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

12.3 Patient Information and Consent

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

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

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

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

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

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

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

13 DEFINITION OF END OF STUDY

13.1 End of Study in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient patients have been recruited and have completed the study as stated in the regulatory application (i.e., Clinical Trial Application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2 End of Study in all Participating Countries

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

14 SPONSOR STUDY TERMINATION CRITERIA

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

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

15 PUBLICATION OF STUDY RESULTS

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

15.1 Communication of Results by Iterum

Iterum fulfills its commitment to publicly disclose the results of studies through registration and posting of the results of this study on clinicaltrials.gov and EudraCT.

15.2 Publications by Investigators

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

The Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Iterum at least 30 days before they are submitted for publication or otherwise disclosed. If any patent

action is required to protect intellectual property rights, the Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

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

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

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

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

16 REFERENCE LIST

John E. Mazuski, Leanne B. Gasink, Jon Armstrong, Helen Broadhurst, Greg G. Stone, Douglas Rank, Lily Llorens, Paul Newell, and Jan Pachl. Efficacy and Safety of Ceftazidime-Avibactam Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-abdominal Infection: Results From a Randomized, Controlled, Double-Blind, Phase 3 Program. Clin Inf Dis 2106; 62: 1380-1389.

Complicated Intra-Abdominal Infections: Developing Drugs for Treatment. Guidance for Industry. U.S. Department of Health and Human Services. Food and Drug Administration Center for Drug Evaluation and Research (CDER). February 2015

Committee for Medicinal Products for Human Use (CHMP). Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. 15 December 2011. CPMP/EWP/558/95 rev 2.

APPENDIX 1 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	
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 CP-70,429[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 2 MICROBIOLOGY

Culture and Susceptibility testing

At baseline, intra-abdominal specimens should be sent for culture of aerobes and anaerobes. Samples collected from abdominal drains are not allowed. Samples should be inoculated into aerobic and anaerobic culture bottles, incubated at 35°C–37°C, and transferred to the microbiology laboratory. All gram-negative pathogens will be tested locally for antimicrobial susceptibility, as appropriate. Specific instructions for sample collection, processing, and shipment can be found in the laboratory manual(s) for this study.

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

Gram-staining of material from the site of infection

One slide for Gram-stain is to be prepared from each specimen obtained from the site of the intra-abdominal infection. The slide is to be stained and read by the local laboratory and then sent to the central laboratory for re-reading and confirmation.

Organisms considered as pathogens

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.
- 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.

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

APPENDIX 3 METHOD FOR DETERMINATION OF CREATININE CLEARANCE

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

For females:

GFR = [(140-age) * (Ideal body wt in kg) * 0.85] / (72 * Cr)

For males:

GFR = [(140-age) * (Ideal body wt in kg)] / (72 * Cr)

Ideal body weight is calculated as:

For females:

If height (H) > 152.5 cm

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

If H < 152.5 cm

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

For males:

If H > 152.5 cm

Ideal body weight = 50 + [(H-152.4) * 0.89]

If H < 152.5 cm

Ideal body weight = 50 – [(152.4 – H)* 0.89]

In order to determine the need to adjust the dose and/or dosing interval of IV study therapy to be administered, the patient's estimated CrCl should be calculated using the most recent serum creatinine value obtained at the local laboratory.

Dose adjustments for each of the study drugs based on estimated CrCl are outlined below.

Study Drug	CrCl ≥30 mL/min	CrCl <30 mL/min
Sulopenem IV	1000 mg QD	250 mg QD
Ertapenem IV	1000 mg QD	500 mg QD
Ciprofloxacin	500 mg BID	500 mg every 18 hours

No dose adjustment is required for metronidazole in patients with renal impairment, however, a 50% dose reduction is required for patients with severe hepatic impairment (Child-Pugh C).

APPENDIX 4 POPULATION PK SUBSTUDY

1 INTRODUCTION

This study will be conducted within the context of an ongoing Phase 3 sulopenem clinical trial in order to generate confirmatory data for the population PK profile of both the IV and oral pro-drug regimens of sulopenem.

1.1 Overall Study Design and Plan

This protocol appendix describes the plan for collection, processing and analysis of population PK samples collected within Study IT001-303.

At selected IT001-303 study sites, randomized patients will also be asked to provide plasma samples for population PK, according to the schedule noted below. Samples will be collected from subjects in both treatment arms. The study will remain blinded, regardless of whether or not any individual patient chooses to participate in the population PK sampling.

See Study Events Table below.

1.2 Rationale for Study Design and Control Group

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

2 STUDY PROCEDURES

2.1 Study Population

Patients at selected investigational sites who meet the inclusion criteria and none of the exclusion criteria for study IT001-303 will be eligible for participation in this study.

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

2.2 Inclusion Criteria

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

- Patient is randomized into study IT001-303
- Patient has given informed consent to participate in the population PK sampling.

2.3 Exclusion Criteria

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

- Patients who are not participating in clinical study IT001-303
- Patients in study IT001-303 who have not received study treatment.

2.4 Pharmacokinetic Assessments

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

- Two hours (+/- 30 minutes) after end of Day 1 infusion
- Four hours (+/- 2 hours) after end of Day 1 infusion
- Two hours (+/- 1 hour) after end of administration of first dose of oral study drug after IV to oral switch
- Four hours (+/- 2 hours) after end of administration of first dose of oral study drug after IV to oral switch
- Six hours (+/- 2 hours) after end of administration of first dose of oral study drug after IV to oral switch

4 mL of blood will be collected at each time point in Gray top Sodium Fluoride (2.5 mg/mL)/Potassium Oxalate (2 mg/mL) tubes (BD part#368587). The labels for all biological sample collection and storage containers will contain, at a minimum, the subject's number, study number, collection date and collection time. Additional details are provided in the Study Laboratory Manual.

3. PLANNED STATISTICAL METHODS

3.1 General Considerations

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

3.2 Sample Size Considerations

For this class of drugs, the pharmacokinetic-pharmacodynamic (PK-PD) index which best describes efficacy is the time of free concentration of sulopenem above MIC (T>MIC). Therefore, the sparse pharmacokinetic (PK) sampling strategy chosen for this study are the times which are most informative of the T>MIC, as determined using optimal sampling theory. The optimal times at which the five samples should be drawn, in hours after the beginning of the first infusion are as follows (the acceptable sampling window is provided in parentheses): 2 (1.5-2.5) and 4 (2-6); and after the first dose of oral medication, are as follows: 2 (1-3), 4 (2-6), and 6 (4-8).

□

The number of subjects (with pharmacokinetic sampling) needed to provide adequate precision for a PK-PD model is described above. The intention is to gather quality PK-PD data in several studies and to pool the concentration and effect data to achieve reasonable precision. Therefore, as many subjects as possible should be studied during this trial. It has been determined that up to 125 sulopenem treated subjects will have pharmacokinetic samples drawn in this study.

4 PLASMA SAMPLE HANDLING AND ANALYSIS

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

4.1 Sample Collection and Processing

- Blood samples for PK analysis of sulopenem levels will be collected via direct venipuncture using 4 mL Gray top Sodium Fluoride (2.5 mg/mL)/Potassium Oxalate (2 mg/mL) tubes (BD part#368587).
- Immediately after the sample is drawn, the tube must be mixed gently by inversion 8 to 10 times and placed on ice.
- The samples will be centrifuged at 2500 g for 10 minutes at 4ºC within 60 minutes of collection to achieve a clear plasma layer over the red cells.
- The plasma will be immediately separated into two 0.5 ml aliquots, transferred into 1.8 mL NUNC Cryovials and stored at approximately -70ºC or -20ºC within 60 minutes of collection. Samples may only be stored at -20ºC for a maximum of 5 days. Samples stored at -20ºC must be shipped on dry ice for -70ºC storage prior to the 7 day expiry.
- The time of the sampling as well as the time when the dose was administered prior to the sampling will be noted in the CRF.

4.2 Transport of Samples

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

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

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

4.3 Bioanalytical Sample Analyses

The sulopenem plasma concentrations will be measured using a validated bioanalytical method and according to the Bioanalytical Laboratory's Standard Operating Procedures and FDA Guidances.

4.4 Bioanalytical Methodology

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

4.5 Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons

4.6 Handling Dropout and Withdrawn Subjects

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

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

4.7 Final Integrated Report

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

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

5 PHARMACOKINETIC AND STATISTICAL DATA ANALYSES

Pharmacokinetic and statistical analyses will be performed for sulopenem plasma data.

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

5.1 Pharmacokinetic Data Analyses

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

6 SCHEDULE OF EVENTS

Evaluation	Baseline		Day 1		Day 6-14: IV to Oral Switch			
	Within 24 hours prior to first dose	Dose Day 1[a]	Sample 1 2 hr ± 0.5 hr [b]	Sample 2 4 hrs ±2 hrs	First dose of oral medication	Sample 3 2 hrs ± 1 hr	Sample 4 4 hrs ± 2 hrs	Sample 5 6 hrs ± 2 hrs
Informed Consent	X							
Study drug dose		X			X			
PK sample collection			X	X		X	X	X

[a] Study "Day" is calendar day beginning with Day 1, the calendar day the first infusion of study medication is started.
[b] All times from end of study drug infusion.

APPENDIX 5 APACHE II SCORE

Acute Physiology Score (APS)		High Abnormal Range				Normal	Low Abnormal Range				Points
		+4	+3	+2	+1	0	+1	+2	+3	+4	
1.	Temperature rectal or tympanic (°C) *Add 0.5°C if oral*	2:41	39-40.9		38.5-38.9	36.0-38.4	34-35.9	32-33.9	30-31.9	:S29.9	
2.	Mean arterial pressure (mmHg)	2:160	130-159	110-129		70-109		50-69		:S49	
3.	Heart rate (ventricular response)	2:180	140-179	110-139		70-109		55-69	40-54	:S39	
4.	Respiratory rate (non-ventilated or ventilated)	2:50	35-49		25-34	12-24	10-11	6-9		<5	
5.	Oxygenation: $AaDO_2$ or PaO_2 (mmHg) i. if FiO_2>0.5, record $AaDO_2$ ii. if FiO2<0.5, record PaO2	2:500	350-499	200-349		<200 >70	61-70		55-60	<55	
6.	Arterial pH If no ABGs record Serum HCO_3 below *Not preferred, use ONLY if no ABGs* Serum HCO_3 (venous-mMol/L)	2:7.7 <52	7.6-7.69 41-51.9		7.5-7.59 32-40.9	7.33-7.49 22-31.9		7.25-7.32 18-21.9	7.15-7.24 15-17.9	<7.15 <15	
7.	Serum Sodium (mMol/L)	2:180	160-179	155-159	150-154	130-149		120-129	111-119	:S110	
8.	Serum Potassium (mMol/L)	2:7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5	
9.	Serum Creatinine (mg/dL) *Double points for acute renal failure*	2:3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6			
10.	Hematocrit (%)	2:60		50-59.9	46-49.9	30-45.9		20-29.9		<20	
11.	White Blood Count (k/mm^3)	2:40		20-39.9	15-19.9	3-14.9		1-2.9		<1	
12.	Glasgow Coma Scale (see below) *(Score = 15 minus actual GCS)*									15 – GCS =	
										Total APS Points *Sum of the 12 individual variable points*	**A**

Glasgow Coma Scale *(Circle Appropriate Responses)*	
Eyes open	**Verbal - nonintubated**
4 - spontaneously	5 - oriented
3 - to speech	4 - confused
2 - to pain	3 - inappropriate words
1 - no response	2 - incomprehensible sounds
	1 - no response
Motor response	**Verbal - intubated**
6 - to verbal command	5 - seems able to talk
5 - localizes to pain	3 - questionable ability to talk
4 - withdraws to pain	1 - generally unresponsive
3 - flexion to pain	
2 - extension to pain	
1 - no response	

Age Points		
Age	Points	
:S44	0	
45-54	2	
55-64	3	
65-74	5	
2:75	6	
Total Age Points		**B**

Chronic Health Evaluation (CHE)		
If "yes" give +5 for non-operative or emergency postoperative subjects and give +2 if elective postoperative subjects		
Liver Cirrhosis with PHT or encephalopathy		
Cardiovascular Class IV angina or at rest or with minimal self-care activities		
Pulmonary Chronic hypoxemia or hypercapnia or polycytaemia of PHT > 40 mmHg		
Kidney Chronic peritoneal or hemodialysis		
Immune System Immune compromised host		
Total CHE Points		**C**

APACHE II Score (A + B +C)	
APS Points	A
Age Points	B
CHE Points	C
Total APACHE II Score	

APPENDIX 6 CRITERIA FOR SAFETY VALUES OF POTENTIAL CLINICAL CONCERN

Hematology	
Hemoglobin	<0.8 times the lower limit of the reference range
Leukocytes	<1.5 or >20 x $10^3/mm^3$
Platelets	<75 or >700 x $10^3/mm^3$
Chemistry	
Total bilirubin	>2 times the upper limit of the reference range
Direct bilirubin	>2 times the upper limit of the reference range
AST	>3 times upper limit of the reference range
ALT	>3 times upper limit of the reference range
GGT	>3 times upper limit of the reference range
Alk Phosphatase	>3 times upper limit of the reference range
Creatinine	>1.5 times upper limit of the reference range
BUN/Urea	>1.3 times upper limit of the reference range
Sodium	<0.95 or >1.05 times the limits of the reference range
Potassium	<0.9 or >1.1 times the limits of the reference range
Calcium	<0.9 or >1.1 times the limits of the reference range
Albumin	<0.8 times the lower limit of the reference range
Total protein	<0.8 times the lower limit of the reference range
Creatine Kinase	>3.0 times upper limit of the reference range
Urinalysis	
Urine WBC	≥10/HPF
Urine RBC	≥50/HPF
Vital Signs	
Pulse Rate	<40 or >130 bpm, when baseline resting heart rate is 60-120 bpm
Blood Pressure	Systolic ≥30 mm Hg change from baseline in same posture Systolic <80 mm Hg Diastolic ≥20 mm Hg change from baseline in same posture Diastolic <50 mm Hg

APPENDIX 7 INVESTIGATOR'S SIGNATURE

Study Title:	A prospective Phase 3, 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*
Final Date:	May 29, 2018

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

Name: _____

Signature: _____ **Date:** _____