STATISTICAL ANALYSIS PLAN

Investigating Gram-negative Infections Treated with Eravacycline (IGNITE) 4: A Phase 3, Randomized, Double-Blind, Double-Dummy, Multicenter, Prospective Study to Assess the Efficacy and Safety of Eravacycline Compared with Meropenem in Complicated Intra-abdominal Infections

Protocol: TP-434-025

Protocol Number:	TP-434-025
Protocol Version and Date:	Version 2.0: 20 March 2017 Version 1.0: 31 May 2016
Name of Test Drug:	Eravacycline (TP-434)
Phase:	Phase 3
Methodology:	Randomized, Double-Blind, Double-Dummy, Multicenter, Non-inferiority, Prospective Study
Sponsor:	Tetraphase Pharmaceuticals, Inc. 480 Arsenal Way, Suite 110 Watertown MA 02472 Tel: 617-715-3600 Fax: 617-926-3557
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Analysis Plan Date:	12 July 2017
Analysis Plan Version:	Version 1.0

APPROVAL SIGNATURE PAGE

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Sponsor:	Tetraphase Pharmaceuticals, Inc. 480 Arsenal Way, Suite 110 Watertown MA 02472
Author:	Veristat, LLC 118 Turnpike Road Southborough, MA 01772

Author Signatory:

Christopher Kenwood
Senior Biostatistician

Signature:_____

Date:_____

Sponsor Approval:

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

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Date: 13 July 2017

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
CE	Clinically evaluable
CI	Confidence interval
cIAI	Complicated intra-abdominal infection
CN	Clinically notable
CRA	Clinical research associate
CrCl	Creatinine clearance
CSR	Clinical study report
eCRF	Electronic case report form
ECG	Electrocardiogram
EMA	European Medical Agency
EOT	End-of-treatment
ERC	Evaluability Review Committee
FDA	Food and Drug Administration
FU	Follow-up
GI	Gastrointestinal
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ITT	Intent-to-treat
IWRS	Interactive web-based response system
MCH	Mean cell hemoglobin
MCHC	Mean cell hemoglobin concentration
MCV	Mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
ME	Microbiologically evaluable
MIC	Minimum inhibitory concentration
Micro-ITT	Microbiological intent-to-treat

MITT	Modified intent-to-treat
MRC	Microbiology Review Committee
NI	Non-inferiority
PK	Pharmacokinetic
RBC	Red blood cell
SAC	Surgical Adjudication Committee
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SI	System International
SOC	System organ class
TEAE	Treatment-emergent adverse event
TOC	Test-of-cure
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

Complicated intra-abdominal infections (cIAIs) extend beyond the hollow viscus of origin into the peritoneal or retroperitoneal spaces and are associated with either abscess formation or peritonitis and systemic signs and symptoms of illness. cIAIs are a common problem in clinical practice and consume substantial hospital resources and costs. Although a wide range of individual antimicrobial agents and combinations of agents are available for use in cIAI, no regimen to date has been consistently demonstrated to be superior or inferior. Antibiotics used for the empiric treatment of cIAIs should have activity against enteric Gram-negative aerobic and facultative bacilli and enteric Gram-positive streptococci, staphylococci, and enterococci. In addition, coverage for obligate anaerobic bacilli is recommended for distal small bowel, appendiceal, and colon-derived infections and for more proximal gastrointestinal (GI) perforations in the presence of obstruction or paralytic ileus. With the exception of carbapenem antibiotics, there are few broad-spectrum antibiotics to cover all the potential pathogens to which the peritoneum is exposed following a perforation of the intestinal tract [1].

Infections due to multidrug-resistant organisms are even more difficult to treat and eradicate because they do not respond to many common antibiotics, and in some cases do not respond to even the most powerful ones, such as carbapenems. The carbapenems are becoming less effective because carbapenemases and porin changes that mediate resistance have become more common, even in enteric bacteria. Enterobacteriaceae, *Pseudomonas*, and *Acinetobacter* species are more likely than others to develop multidrug resistance. Thus, there is a need for broad-spectrum antibiotics with appropriate pharmacokinetics (PK) to empirically cover the wide range of potential pathogens seen in cIAIs. Eravacycline (TP-434) is a candidate for the treatment of serious and life-threatening infections, including those caused by pathogens otherwise resistant to current treatment options. Eravacycline is very effective in animal models of infection [2].

Eravacycline is a novel, synthetic, broad-spectrum fluorocycline antibiotic of the tetracycline class and is highly active in vitro against emerging pathogens like *Acinetobacter baumannii* as well as clinically important species of Enterobacteriaceae (including those isolates that produce extended-spectrum beta-lactamases and/or are carbapenem-resistant) and anaerobes. Eravacycline may not exhibit high activity against *Pseudomonas aeruginosa* when it is the sole pathogen. The full description of the in vitro antibacterial activity of eravacycline can be found in the Investigator's Brochure (IB).

The high degree and reliability of in vitro antibacterial activity against multidrug-resistant Gram-negative and Gram-positive aerobic, facultative, and obligate pathogens; efficacy observed with eravacycline in established animal models of infection; and the efficacy and tolerability established in a phase 2 and a phase 3 study of subjects with cIAIs warrant clinical development of eravacycline as a single therapy treatment option for cIAIs and other serious bacterial infections.

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of data from Study TP-434-025. Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary

tabulations described in this SAP will provide the basis for presentation and interpretation of the data in the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol. Changes, if any, made to the SAP after it has been signed but prior to database lock will be documented in an amendment. Any important changes made to the analysis will be described in the CSR. This SAP is based on protocol version 2.0 dated 20 March 2017.

This protocol is designed to address the guidance requirements of the Food and Drug Administration (FDA; Complicated Intra-abdominal Infections: Developing Drugs for Treatment Guidance for Industry, CDER 2015) and European Medical Agency (EMA; Addendum to the guideline of the evaluation of medicinal products for the treatment of bacterial infections EMA/CHMP/351889/2013) on the development of treatment for cIAIs. While both Regulatory agencies support the use of clinical response at the TOC visit as the primary efficacy outcome, the primary analysis population for the FDA is the micro-ITT and for the EMA, there are co-primary analysis populations, the all treated (MITT) and the CE at TOC (CE-TOC). A separate SAP will be developed to address the different primary analysis populations for the EMA as well as other differences in the statistical analysis.

1.1.2. Study Objectives

The primary objective of this study is to compare the clinical response at the test-of-cure (TOC) visit in the microbiological intent-to treat (micro-ITT) population for subjects in the 2 treatment arms.

The secondary objectives of the study are to:

- Compare the clinical response for subjects in the 2 treatment arms at the end-of-treatment (EOT), TOC, and follow-up (FU) visits in the following populations:
    - Intent-to-treat (ITT) population.
    - All-treated (MITT) population.
    - Clinically evaluable (CE) population.
    - Micro-ITT population (for EOT, FU).
    - Microbiologically evaluable (ME) population.
- Compare the microbiologic response for subjects in the treatment arms at the EOT and TOC visits in the following populations:
    - Micro-ITT population.
    - ME population.
- Assess the safety and tolerability of eravacycline administration in the safety population.
- Explore PK parameters of eravacycline.

1.2. Study Design

1.2.1. Synopsis of Study Design

This is a non-inferiority (NI), phase 3, randomized, double-blind, double-dummy, multicenter, prospective study to assess the efficacy, safety, and PK of eravacycline compared with meropenem. Dosing in the study arms is described in Table 1-1.

Table 1-1: Study Drug Infusion Scheme of a 24-Hour Dosing Cycle

Study Drug Treatment Arm	1st Dose (of Dosing Cycle)	2nd Dose (of Dosing Cycle)	3rd Dose (of Dosing Cycle)	4th Dose (of Dosing Cycle)	5th Dose (of Dosing Cycle)
	60 min infusion	30 min infusion	30 min infusion	60 min infusion	30 min infusion
Eravacycline, 1.0 mg/kg q12h	Eravacycline	Placebo	Placebo	Eravacycline	Placebo
Meropenem, 1g q8h	Placebo	Meropenem	Meropenem	Placebo	Meropenem

All subjects will remain hospitalized for the complete course of drug therapy. Individual subject participation in this study is expected to last approximately 6-8 weeks.

1.2.2. Randomization Methodology

Once an informed consent is obtained and study eligibility is established, a blinded study site member will obtain a subject number and a blinded study drug assignment for each subject from a computer-generated randomization scheme using an interactive web-based response system (IWRS). Randomization to eravacycline (1.0 mg/kg q12h) or meropenem (1 g q8h) treatment arms will occur in a 1:1 ratio. For this study, enrollment is considered to occur at the time a subject is randomized. A subject is considered randomized when the IWRS issues a "confirmation of successful randomization" notification. Randomization will be stratified based on primary site of infection (ie, complicated appendicitis versus all other cIAI diagnoses). No more than approximately 50% of subjects enrolled should have complicated appendicitis.

The study will include approximately 75 sites. No site should enroll more than 35 subjects. Each investigative site should enroll no more than 1 complicated appendicitis subject for every 2 subjects enrolled into the study at their site. A site-specific change to the ratio of "complicated appendicitis: other cIAI diagnoses" or to the total number of subjects that may be enrolled at any 1 site may be granted by the Sponsor.

1.2.3. Stopping Rules and Unblinding

There are no formal stopping rules for this study.

The Sponsor designee (eg, study statistical team, IWRS vendor, etc) will have a designated randomization administrator who will maintain the randomization codes in accordance with standard operating procedures to ensure the blind is properly maintained, and that only personnel who require knowledge of treatment assignments will be unblinded (eg, staff involved in maintaining the clinical supplies or suspected unexpected serious adverse reaction reporting). Except for the responsible site pharmacist or designee and separate, unblinded clinical research

associates (CRAs) to monitor drug supply and adherence to study drug blinding and randomization procedures, all study staff and subjects will be blinded to treatment assignment.

The study drug treatment assignment will be unblinded only in emergency situations when knowledge of the treatment received is absolutely necessary for management of the subject or when it is in the best interest of the subject. The Investigator has unrestricted and immediate access to unblind the treatment code. The instructions for unblinding a subject can be found in the IWRS study manual.

In the event unblinding is necessary, the Investigator is encouraged but not required to contact the appropriate Medical Monitor to discuss the situation and the subject's medical status.

When a subject's treatment assignment is unblinded, a comprehensive source note must be completed by the unblinding Investigator that includes the date and time and the reason(s) the subject's treatment code was unblinded. In the event the Investigator chooses to discuss the unblinding with the Medical Monitor, the source note must also include a record of the discussion.

It is mandatory that all personnel who are involved in the unblinding and who have access to the unblinded treatment assignment information maintain the confidentiality of the information by not divulging the randomization code.

After the database is locked and the SAP is final, the study blind codes will be broken.

1.2.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in Table 1-2.

Table 1-2: Schedule of Assessments

Study Procedure	Screening[1] Within 48-h of Initial Dose	ENROLLMENT	Dose Cycle 1[1]	Dose Cycle 2	Dose Cycle 3	Dose Cycles 4-14	EOT[2]	TOC 25-31 Days after Initial Dose	FU 35-50 Days after Initial Dose
Informed Consent	X								
Medical History / Height and Weight	X								
APACHE II score[3]	X								
Physical Exam	X						X	X	X
Temperature[4]	X		X	X	X	X	X	X	X
Resting Vital Signs[5]	X		X	X	X	X	X	X	X
Abdominal Exam[6]	X		X	X	X	X	X	X	X
Prior/Concomitant Medications[7]	X		X	X	X	X	X	X	X
Hematology/Chemistry[8]	X		X	X	X	X	X[2]	X	X
Coagulation/Urinalysis[9]	X		X				X[2]	X[17]	X[17]
Calculated Creatinine Clearance[10]	X		X	X	X	X			
Serum Pregnancy Test[11]	X						X	X	X
Blood cultures[12]	X					X			
Intra-abdominal cultures[13]	X			X	X	X	X[2]	X	X
Radiologic Examination[14]	X					X			
12-Lead ECG	X						X		
Adverse Events			X	X	X	X	X	X	X
Clinical Response							X	X	X
Study Drug Administration[15]			X	X	X	X			
PK Assessments[16]			X						

1. If Dose Cycle 1 and Screening occur on the same day the resting vital signs, abdominal exam, and safety labs do not need to be repeated.
2. EOT assessments are to be performed at: (i) premature withdrawal, (ii) treatment failure, or (iii) within 24-h of last dose. If EOT occurs on the same day as a Dosing Cycle, then safety labs and any cultures do not need to be repeated provided samples are taken after the last dose of study drug.
3. Serum bicarbonate may be used in place of arterial blood gases. Please referee to Appendix 1: APACHE II Score for instructions on how to calculate APACHE II Score.
4. Record oral, rectal, tympanic, or by temporal artery prior to the initial dose of study drug and then q8h ± 1-h while hospitalized until EOT.
5. RR, HR, B/P are performed prior to the initial dose of study drug; daily while hospitalized; and EOT, TOC, and FU.
6. Performed at least once daily until resolution of all signs and symptoms of cIAI.
7. ≤24-h of continuous systemic antibacterial therapy for cIAI during the 72-h preceding enrollment is permitted. Documented cIAI treatment failures with a known baseline pathogen and ≥ 72-h of systemic antibiotic therapy may be enrolled. No concomitant systemic antibacterials are permitted after the initial dose of study drug through the FU visit. All other medically necessary concomitant medications are permitted.
8. Performed at Screening; Dose Cycles 1-4; every three 24-h dosing cycles thereafter while on study drug; and at EOT, TOC, and FU.
9. Urine microscopy for RBC, WBC, crystals, and casts performed at Screening, Dose Cycle 1, and EOT.
10. Creatinine clearance (Cockcroft-Gault equation) based upon local labs to be performed at: (i) Screening, (ii) Dose Cycles 1-4, and (iii) every three 24-h dosing cycles thereafter while on study drug. A creatinine clearance of ≤ 50 mL/min is exclusionary at Screening. If at any time after Screening the locally calculated creatinine clearance is ≤ 50 mL/min then the subject's meropenem and/or meropenem-matched placebo must be dose-adjusted in accordance with the meropenem package insert. Thereafter, each time the creatinine clearance is calculated locally the meropenem and/or meropenem-matched placebo must be dose-adjusted in accordance with the meropenem package insert. For more information please refer to Protocol Section 10.3.2.
11. If a serum pregnancy test is not available at the investigator site then a urine pregnancy test may be utilized locally.
12. Obtain a set of aerobic and a set of anaerobic samples from 2 separate venipuncture locations at Screening. Upon knowledge of a positive culture for a pathogen, blood cultures should be repeated until sterile (ie, both sets of cultures from 2 separate venipuncture sites are negative for pathogens) through the FU visit. Await results before drawing additional sets of blood cultures. 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).
13. Cultures to be collected from the site of infection at the time of the initial surgical procedure, subsequent surgical re intervention(s) and if there are signs and symptoms of infection (if applicable). If it is not possible to obtain a tissue biopsy or aspirate then a swab may be obtained. Samples collected from superficial swabs and abdominal drains are not allowed. See Microbiologic Specimen Collection for additional information. For subjects that enter the study as a documented cIAI treatment failure (ie, with a known baseline pathogen), reasonable attempts should be made to provide the baseline isolates to the central laboratory.
14. Required for pre-operative enrollment. Only to be obtained at appropriate intervals thereafter if deemed necessary by the Investigator.
15. The expected minimum treatment duration is four 24-h dosing cycles unless Clinical Failure or Clinical Cure occurs earlier. Maximum treatment duration is fourteen 24-h dosing cycles. The 12-h interval between doses can be shortened (but not prolonged) by up to 4-h from the initial dose during Dosing Cycles 1-3 to adapt to a normal hospital schedule. After the 3rd 24-h dosing cycle, the permitted administration window is q12h ± 1-h. Contact Medical Monitor for dosing beyond 7 dosing cycles.
16. Please refer to Appendix 3: Blood PK Sample Collection, Handling, Preparation and Shipping in the protocol for schedule of PK assessments.
17. Coagulation only. Urinalysis does not need to be performed at the TOC and FU visits.

2. DATA MANAGEMENT

Data management procedures, including database design, development of the data dictionary, and coding of medical history, adverse events (AEs) and medications, will be performed at a Contract Research Organization (CRO). Data will be entered into an electronic case report form (eCRF) at the study sites. A series of logic and consistency checks will be conducted to ensure accuracy and completeness of the clinical database. One or more analysis databases, including detailed documentation, will be developed to support the analyses described in this SAP. Safety lab results, microbiology data, and PK data will be electronically transmitted from central labs. After database lock, randomization data will be provided electronically from the IWRS vendor. Refer to the Data Management Plan for further Data Management details.

3. SUBJECT POPULATION

3.1. Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

- Intent-to-Treat (ITT) Population: The ITT analysis set will consist of all randomized subjects regardless of whether or not the subject received study drug. A subject is considered randomized when the Investigator or Investigator's designee receives the IWRS-generated randomization number.
- Safety Population: The Safety analysis set will consist of all randomized subjects who receive any amount of study drug. All safety analyses will be conducted in this population and will be presented in the summary tables by the treatment the subject actually received. A subject randomized to the meropenem arm who mistakenly receives eravacycline will be included in the eravacycline arm. A subject randomized to the eravacycline arm who mistakenly receives meropenem will be included in the meropenem arm if meropenem is given for the entire course of therapy and will be included in the eravacycline arm if both meropenem and eravacycline are received.
- All Treated (MITT) Population: The MITT population will consist of all randomized subjects who receive any amount of study drug. Analyses in this population will be presented in summary tables by the treatment arm to which the subject was randomized.
- Microbiological Intent-to-Treat (micro-ITT) Population: The micro-ITT population will consist of all subjects in the ITT population who have at least 1 baseline bacterial pathogen against which eravacycline has in vitro antibacterial activity. As clinical breakpoints for eravacycline have not yet been determined, for the purpose of this analysis population, all baseline bacterial pathogens will be considered susceptible to eravacycline. Analyses in this population will be presented in summary tables by the treatment arm to which the subject was randomized.

  Baseline intra-abdominal specimens must be obtained at the time of the initial surgical intervention (or during re-intervention in the case of prior treatment failures). For those patients meeting inclusion criteria for pre-operative enrollment, the surgical intervention can occur up to 24 hours post randomization. Microbiological specimens collected during routine operative care prior to subject consent may be used for study purposes. Baseline blood specimens for culture will be drawn at screening before the initiation of study drug. If more than 1 intra-abdominal or blood specimen is obtained, isolates from all specimens will be reviewed for pathogen determination.

  Cultures from suitable intra-abdominal specimens and blood cultures will be reviewed by the Sponsor in a blinded manner prior to database lock and unblinding for final pathogen determination. A suitable intra-abdominal specimen is one that was collected from the site of infection by aspiration and/or tissue sample. Samples collected by swabs are considered suitable only if it is not possible to collect aspirated fluid or tissue samples. Samples collected from abdominal drains are not allowed and are not considered suitable samples.

  Isolates cultured from suitable intra-abdominal specimens and blood cultures are initially identified at the local or regional microbiology laboratories. The identity of isolates as determined at the local or regional laboratories will be verified by the central laboratory. If

the local laboratory grows an isolate but the central laboratory is not able to grow the isolate, the local lab grows a pathogen but the central laboratory grows only a contaminant, if isolates were lost during transportation or storage, or there are major discrepancies between the local and central laboratory in the identification of species, the central laboratory will request that the local or regional laboratory resend the isolate. If the Genus identification is the same between the local and central microbiology laboratories but the species identification is discrepant, the central laboratory identification will be used. If central laboratory data are not available for an isolate, the local Genus and species will be used. Any remaining major discrepancies in species identification between the central and local laboratory will be reviewed by the Sponsor Microbiology Review Committee (MRC) in a blinded manner for final identification of the isolate. Further details are provided in the Microbiological Outcomes Review Plan.

There are 3 categories of pathogen identification as follows:

1. Always a pathogen:
    - All Enterobacteriaceae (eg, *Enterobacter* spp., *Klebsiella* spp., *Proteus* spp.), *Bacteroides* spp., *Clostridium* spp., *Prevotella* spp., *Peptostreptococcus* spp., *Fusobacterium* spp, *Eubacterium* spp., *Eggerthella* spp., *Streptococcus* spp., *Enterococcus* spp., and *Staphylococcus aureus* are always considered pathogens (Complicated Intra-abdominal Infection Guidelines, CID 2010:50 (15 January), p. 147).
    - *Acinetobacter*, *Pseudomonas*, and *Stenotrophomonas* species.
2. Not considered a pathogen:
    - Fungi and Coagulase Negative *Staphylococci.*
3. Pathogens for MRC review: isolates will be reviewed in a blinded manner by the MRC on a case-by-case basis if neither rule 1 nor 2, above, apply.

If multiple specimens are collected at the same time point, the same pathogen could be isolated from more than 1 source. In this case, for summaries of baseline pathogens by genus and species and for per-pathogen microbiological response, a subject will be counted only once for each pathogen and each pathogen type. For summaries of minimum inhibitory concentrations (MICs), a pathogen will be considered a unique pathogen if the biogram is different by more than 1 dilution for at least 1 antibiotic tested. Otherwise, the pathogens will be considered equivalent and a representative isolate will be selected from among them based on the lowest central laboratory accession number.

- Clinically Evaluable (CE) Populations: Three CE analysis sets will be defined; the CE-EOT (used for analysis of the secondary efficacy outcomes for the FDA and EMA), the CE-TOC (used for analysis of the primary efficacy outcome for the EMA and secondary efficacy outcomes for the FDA and EMA), and the CE-FU (used for analysis of secondary efficacy outcomes for the FDA and EMA). Subjects will be included in or excluded from the CE analysis sets based on the criteria listed below.

    1. In the MITT Population: To be in included in the CE-EOT, CE-TOC, and CE-FU populations, subjects must be in the MITT population.

2. Minimal Disease Criteria: Minimal disease criteria is defined as meeting all of the following inclusion criteria:

    - Inclusion criterion 1: Male or female subject hospitalized for cIAI with 1 of the following diagnoses
        - Intra-abdominal abscess: 1 or more abscesses surrounding diseased or perforated viscera (including hepatic and splenic abscesses).
        - Gastric or intestinal perforation associated with diffuse peritonitis.
        - Peritonitis: diffuse infection of the peritoneum (but not spontaneous bacterial peritonitis associated with cirrhosis and chronic ascites).
        - Appendicitis with perforation, peritonitis, or abscess.
        - Cholecystitis with perforation or abscess.
        - Diverticulitis with perforation, peritonitis, or abscess.

        Note: Infections limited to the hollow viscus, such as simple cholecystitis and simple appendicitis, are not eligible. Ischemic bowel disease without perforation is not eligible. Acute suppurative cholangitis and acute necrotizing pancreatitis are not eligible.
    - Inclusion criterion 3: Evidence of a systemic inflammatory response with at least 1 of the following:
        - Fever (oral, rectal, tympanic, or by temporal artery temperature >100.4°F/38°C) or hypothermia (temperature ≤95.9°F/35.5°C).
        - Elevated white blood cells (WBC) (> upper limit of normal [ULN] laboratory range); or proportion of band forms of the WBC differential beyond the ULN laboratory range.
        - Increased pulse (heart rate >90 beats per minute).
        - Increased respiratory rate (>20 breaths per minute).
    - Inclusion criterion 4: Abdominal pain or flank pain (with or without rebound tenderness), or pain caused by cIAI that is referred to another anatomic area such as the back or hip, or localized or diffuse abdominal wall rigidity, or mass, or ileus.

    And either:

    - Inclusion criterion 7A: Meets all inclusion criteria for pre-operative enrollment:
        - Has a sonogram or radiographic imaging result congruent with the diagnosis of cIAI, AND
        - Acute surgical or percutaneous intervention (open laparotomy, laparoscopic surgery, or percutaneous drainage of an abscess) is foreseen within 24-hr.

- Inclusion criterion 7B: Meets all inclusion criteria for intra-operative/post-operative enrollment:
    - Visual confirmation of cIAI (presence of pus within the abdominal cavity), AND
    - Surgical intervention includes open laparotomy, laparoscopic surgery, or percutaneous draining of an abscess, AND
    - Intervention is adequate (ie, a procedure is which all communications between the GI tract and the peritoneal cavity are closed, no necrotic intestine is left, and all infected collections are drained at the procedure), AND
    - Subjects who are enrolled in the trial post-operatively must receive no more than 1 dose of effective antibacterial drug therapy post-operatively before randomization.

3. Prior Antibiotic Therapy: Subjects will be excluded from the CE populations if they meet protocol Exclusion criterion 8. In particular,
    - Receipt of effective antibacterial drug therapy for cIAI for a continuous duration of >24-h during the 72-h preceding randomization. [However, subjects with documented cIAI (ie, known baseline pathogen) who have received at least 72-h of antibiotic therapy and are considered treatment failures may be enrolled. Treatment failure is defined as a persistent fever and/or clinical symptoms; or the development of a new intra-abdominal abscess after ≥72-h of antibiotic therapy], OR
    - Receipt of meropenem or any other carbapenem, or tigecycline for the current infection, OR
    - Need for concomitant systemic antimicrobial agents effective in cIAI other than study drug.
4. Concomitant Antibiotic Therapy: Subjects who receive any systemic concomitant antibiotic therapy from the first dose of study drug through the EOT visit [CE-EOT population], the TOC visit [CE-TOC population], and the FU visit [CE-FU population] that is potentially effective in cIAI will be excluded from the CE-EOT, CE-TOC, and CE-FU populations, respectively, with the following exceptions:
    - The subject is a clinical failure at EOT (CE-EOT population), TOC (CE-TOC population), or FU (CE-FU population) and received non-study antibiotics for insufficient therapeutic effect of the study drug.
    - The subject received 1 dose of a non-study antibiotic administered as prophylaxis for procedures unrelated to the ongoing infection.
    - The subject received an oral antibiotic with no systemic absorption.

    Subjects who receive a systemic concomitant antibiotic that is not effective in cIAI will be included in the CE-EOT, CE-TOC, and CE-FU populations.

5. Adequate Source Control: To be included in the CE-EOT, CE-TOC, and CE-FU populations, subjects must have adequate source control. Adequate source control will be determined by the Surgical Adjudication Committee (SAC) for those subjects with an outcome of clinical failure or with an outcome of clinical cure at TOC or FU, but underwent a second surgical procedure. All other subjects (clinical cures) will be presumed to have adequate source control.
6. Study Drug Therapy: Subjects must meet all of the following to be included in the CE analysis sets:
   - Received the correct study drug based on the randomization assignment for the entire treatment period.
   - Study personnel involved in the assessment of efficacy or monitoring efficacy data remained blinded to treatment assignment, unless a treatment limiting AE occurred which required unblinding.
   - The subject received at least 3 days of study drug.
   - The subject was at least 80% compliant with study drug.
7. Clinical Outcome Assessment: Subjects must meet the following to be included in the CE analysis sets:
   - For the CE-EOT analysis set:
     - Completed the Investigator's assessment of clinical response (ie, was not deemed an indeterminate outcome) at the EOT visit.
     - The EOT visit occurred within 1 day of the last dose of study drug.
   - For the CE-TOC analysis set:
     - Completed the Investigator's assessment of clinical response (ie, was not deemed an indeterminate outcome) at the TOC visit, unless the patient was defined as a clinical failure at the EOT visit.
     - The TOC visit occurred on Study Day 24-32, unless the subject was considered to be a clinical failure based on the Investigator's assessment at the EOT visit.
   - For the CE-FU analysis set:
     - Completed the Investigator's assessment of clinical response (ie, was not deemed an indeterminate outcome) at the FU visit, unless the patient was defined as a clinical failure at the EOT or TOC visit.
     - The FU visit occurred on Study Day 37-51, unless the subject was considered to be a clinical failure based on the Investigator's assessment at the EOT or TOC visit.
8. Baseline or Inter-Current Medical Events:

   Subjects will be excluded from the CE analysis sets if the Investigator has documented in the e-CRF that they meet any 1 of the following protocol-defined exclusion criteria at baseline (ie, prior to randomization):

Exclusion criterion 10: Known or suspected inflammatory bowel disease or associated visceral disease.

Exclusion criterion 12: Systemic malignancy that required chemotherapy, immunotherapy, radiation therapy, or antineoplastic therapy within the previous 3 months or that is anticipated to begin prior to the TOC visit.

Exclusion criterion 13: Known at study entry to have cIAI caused by a pathogen(s) resistant to 1 of the study drugs.

- Microbiologically Evaluable (ME) Populations: The ME-EOT population will consist of all subjects in both the micro-ITT and the CE-EOT populations. The ME-TOC population will consist of all subjects in both the micro-ITT and the CE-TOC populations. The ME-FU population will consist of all subjects in both the micro-ITT and CE-FU populations.

3.2. Evaluability Review

3.2.1. Membership and Responsibilities

The MRC will be responsible for reviewing microbiological data, including pathogen determination, as outlined in the Microbiological Outcomes Review Plan. The Evaluability Review Committee (ERC) will review clinical and microbiological data to assess inclusion in or exclusion from the CE populations as outlined in the Clinical Evaluability Review Plan. MRC and ERC members will be blinded to treatment assignment and will review the data concurrent with the conduct of the study. Final pathogen determinations and inclusion in analysis populations will be determined prior to database lock except for those criteria which require unblinded data (for example, determination of whether or not the subject received the study drug s/he was randomized to).

3.2.2. Process for Determining Inclusion in Analysis Populations

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

Inclusion into the micro-ITT population will be determined programmatically by incorporating the outcome of the review of the isolates by the MRC. The MRC will determine whether each isolate (baseline and post-baseline) is considered a pathogen based on a review of information regarding baseline samples such as method of collection of the specimen, location of specimen collection, local and central genus and species identification. Inclusion into the ME populations will be determined programmatically.

3.3. Surgical Adjudication Committee

The SAC will be responsible for reviewing all subjects classified as a clinical failure and all subjects classified as a clinical cure at the TOC or FU visits who undergo a second procedure to determine the adequacy of the source control and for the clinical cures, to assess whether subjects met the criteria of a clinical cure. The blinded Medical Monitor will review all second surgical procedures and make an assessment as to whether the procedure might be related to the original cIAI. All subjects with a second procedure considered to be related to the original cIAI will be referred to the SAC for adjudication. Membership, primary roles and responsibilities, working procedures, basic decision rules and communication procedures are defined in the SAC charter.

3.4. Protocol Deviations

Deviations will be reviewed by the Sponsor and categorized into general categories such as: informed consent, inclusion/exclusion criteria, randomization procedure, subject visit completion or timing, study procedure or assessment, study medication, excluded concomitant medication, and (serious) AE reporting. The number of subjects with at least 1 protocol deviation, the number of subjects with a minor protocol deviation, the number of subjects with a major deviation, and the number of subjects with at least 1 deviation in each category will be presented by treatment group for the ITT population. A major deviation is defined as 1 that potentially affects the efficacy and/or safety analyses and will be determined by a review by the Sponsor in accordance with the Protocol Deviations Review Plan.

All protocol deviations will be presented in a data listing.

4. GENERAL STATISTICAL METHODS

4.1. Sample Size Justification

This study is designed to demonstrate NI of 1.0 mg/kg q12h eravacycline to meropenem in the primary outcome measure of clinical response at the TOC visit in the micro-ITT population. A NI margin of 12.5% will be used, which is based on historical data regarding the treatment effect of antibiotics and the results of the previously completed eravacycline phase 3 cIAI study. A 12.5% NI margin for the outcome measure of clinical response is robust and can sufficiently confirm a clinically meaningful treatment effect of eravacycline in the treatment of cIAI. A 12.5% NI margin has been discussed with and accepted by the FDA and is consistent with the EMA Addendum to the guideline on the evaluation of medicinal products indicated for the treatment of bacterial infections (EMA/CHMP/351889/2013).

The sample size calculation is based on ensuring sufficient power for the primary efficacy outcome for the FDA as well as the primary efficacy outcomes for the EMA (which are secondary efficacy outcomes for the FDA). Estimations of cure rates and numbers of subjects in the micro-ITT population come from the recent phase 3 study with eravacycline in cIAI in which ertapenem was used as the comparator. Clinical cure rates in the micro-ITT population at the TOC visit were 86.8% and 87.6% in the eravacycline and ertapenem groups, respectively, with 82.4% of randomized subjects included in the micro-ITT population. Thus, it is reasonable to assume that the true rate of clinical cure at the TOC visit will be at least 84% in the eravacycline group and 85% in the meropenem group and that the evaluability rate will be at least 80%.

Using a 12.5% NI margin, 1-sided alpha of 0.025, 80% power, response rates of 84% in the eravacycline group and 85% in the meropenem group, and the methodology of Farrington and Manning, a total of 161 subjects per arm in the micro-ITT population is required. A sample size of approximately 400 randomized subjects should provide sufficient numbers for this study, assuming 80% of enrolled subjects will meet the requirements for inclusion in the micro-ITT population.

For the EMA, the rates of clinical cure in the phase 3 study were approximately 87% in the MITT population and 93% in the CE-TOC population. Assuming clinical cure rates of 84% in the eravacycline group and 85% in the meropenem group in the MITT population and 89% in the eravacycline group and 90% in the meropenem group in the CE-TOC population, an NI margin of 12.5%, a 1-sided alpha of 0.025, evaluability rates of 95% for the MITT population and 85% for the CE-TOC population, and the methodology of Farrington and Manning, there is 86% power in the MITT population and more than 91% power in the CE population to show NI in a trial recruiting 400 patients.

4.2. General Methods

All tabular summaries will present results by treatment. Listings will present data by treatment, country, subject number, and visit (as applicable).

For purposes of all analysis and reporting, days will be numbered relative to the first day of dosing. Day 1 will be defined as the date on which a subject receives the first dose of study drug, as recorded on the eCRF. The day prior to the first dose of study drug is Day –1; there is no Day 0. All procedures and events occurring prior to administration of study drug have an appropriate Day calculation associated with them.

Duration variables will be calculated using the general formula (end date - start date) +1.

Appropriate descriptive statistics will be computed and displayed for both continuous and categorical variables. For continuous variables, descriptive statistics will include n (the number of subjects with non-missing data), mean, standard deviation (SD), median, minimum, and maximum values. For categorical parameters, the number and percentage of subjects within each category will be presented. The denominator for percentage will be based on the number of subjects with non-missing data appropriate for summary purposes. Unless otherwise noted, all percentages will be presented to 1 decimal place.

Sort order for data listings will be subject number, visit, and time point where appropriate.

All output will be incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table (eg, a character string is reported for a parameter of the numerical type), a coded value must be appropriately determined and used in the statistical analyses. In general, a value or lower and upper limit of normal range such as "<10" or "≤5" will be treated as "10" or "5" respectively, and a value such as ">100" will be treated as "100." However, the actual values as reported in the database will be presented in data listings.

Individual patient listings supporting the analyses specified in the SAP will be provided to facilitate the investigation of tabulated values and to allow for the clinical review of all efficacy and safety parameters. Available data at each time point will be presented. Missing data will not be imputed except as noted in Section 4.6.

4.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software Version 9.3, unless otherwise noted. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Version March 2016 Format B.

4.4. Baseline Definitions

The last assessments/measurements prior to the first dose of study drug will be used as the baseline reference for all analyses unless stated otherwise.

4.5. Withdrawals, Dropouts, Loss to Follow-up

Subjects who are randomized and withdraw prematurely from the study will not be replaced.

4.6. Missing, Unused, and Spurious Data

Missing data will be handled as outlined below:

- All missing and partial dates for date of pre-operative cIAI diagnosis and events occurring after randomization or for medications received after randomization will be queried for a value. If no value can be obtained, substitutions will be made as follows:
    - For date of cIAI diagnosis, if the day is missing, day will be defined as "01." If the month and day are missing, no imputation will be made. For start dates, missing months and days will be defined by "01," as long as this occurs on or

after the first dose of study drug. If the algorithm produces a date prior to the first dose of study drug, the date of the first dose of study drug will be used for the partial date. For stop dates, missing months will be defined as "12" and days will be defined by the last day of the respective month. If the algorithm produces a date after the study discontinuation/completion date, the date of study discontinuation/completion will be used for the partial date. These substitutions will be used in calculations; however, the actual value recorded on the eCRF will be used for all listings.

  - Missing times for AEs will be queried for a value. If no value can be obtained and for all other times for events and assessments occurring after randomization, the time will not be imputed but will remain missing.

- The severity and causality assessment for AEs should not be missing and will be queried for a value. Should there be missing data, AEs with missing severity will be considered severe and Aes with missing relationship to study drug will be considered related to study drug.

For clinical and microbiological response, missing data will be handled as follows:

- For the primary and secondary outcome measures of clinical response:
  - Subjects will be defined as an indeterminate if the Investigator cannot determine whether the subject is a clinical cure or failure. Subjects will be summarized as indeterminate, but by definition, subjects with an indeterminate response are included in the denominator for analyses in the ITT, MITT, and micro-ITT analysis sets, and thus, are considered failures. Subjects with an indeterminate response are excluded from the CE-EOT, CE-TOC, CE-FU, ME-EOT, ME-TOC, and ME-FU populations.
- For microbiologic response:
  - If no post-baseline source specimen is obtained and the patient has an Investigator's assessment of clinical response, the per-pathogen microbiological response is based on the Investigator's assessment of clinical response. A per-pathogen microbiological response will be considered missing or indeterminate only if the clinical response is also missing or indeterminate.
- Missing values for other individual data points will remain as missing. Missing values will not be imputed and only observed values will be used in data analyses and presentations.
- Where individual data points are missing, categorical data will be summarized based on reduced denominators (ie, only subjects with available data will be included in the denominators).

4.7. Interim Analyses

A blinded assessment of the proportion of subjects qualifying for the micro-ITT population will be conducted after approximately 250 subjects have been randomized. If the micro-ITT proportion is lower than used in the sample size determination, the sample size may be increased to ensure the study is sufficiently powered. The sample size will not be reduced if the micro-ITT proportion is higher than expected. The process for performing this evaluation is described in a separate document, the "Analysis Plan for the Assessment of the Prevalence of Baseline Intra-abdominal Pathogens in the Initial 250 Subjects Enrolled (micro-ITT population)."

4.8. Visit Windows

Visits will be planned to occur during the visit windows defined in Table 1-2. If visits occur outside of the defined windows, data will still be collected. All data will be included in by-patient listings. For efficacy and safety analyses, analysis visits will be derived as outlined in Table 4-1.

Table 4-1: Derived Analysis Visits for Efficacy and Safety Analyses

Visit	ITT and micro-ITT Efficacy Analysis Window[1]	CE and ME Efficacy Analysis Window	Safety Analysis Window[2]
EOT	N/A	Within 1 day of last dose of study drug	Within 48 hours of last dose of study drug
TOC	N/A	24-32 days after initial dose of study drug unless the subject was a clinical failure at the EOT visit	25-31 days after initial dose of study drug
FU	N/A	37-51 days after initial dose of study drug unless the subject was a clinical failure at the EOT or TOC visits	38-50 days after initial dose of study drug

1. For ITT analyses, visit windows are nominal.
2. If out of window, the visit will be considered an unscheduled visit.

5. STUDY ANALYSES

5.1. Subject Disposition

The number and percentage of subjects included in each of the analysis populations (ie, ITT, Safety, MITT, micro-ITT, CE-EOT, CE-TOC, CE-FU, ME-EOT, ME-TOC, and ME-FU) will be summarized by treatment group, geographic region and country. Regions are as follows: European Union (Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, and Romania), Non-European Union Europe (Georgia, Russia, and Ukraine), and North America (United States). A table will summarize the reasons for exclusion from each population and a listing will be provided that indicates each subject's inclusion/exclusion from the analysis population and the reason for exclusion from each analysis population. The number and percentage of subjects enrolled at each site within each country will also be provided by treatment arm and overall.

The number and percentage of subjects completing the study, prematurely discontinuing from study drug, and prematurely withdrawing from the study will be presented for each treatment group for the ITT, MITT, micro-ITT, CE-EOT and CE-TOC populations. Reasons for premature discontinuation of study drug and/or premature withdrawal from the study as recorded on the eCRF will be summarized (number and percentage) by treatment group. Percentages of subjects discontinued from study drug and withdrawals from the study will be compared between treatment groups using Fisher's exact test. A listing of all subjects who prematurely discontinued from study drug or prematurely withdrew from the study will be presented, and the primary reason for discontinuation of study drug or withdrawal from the study will be provided.

5.2. Demographics and Baseline Characteristics

Demographic data and baseline characteristics will be presented by treatment group for the ITT, MITT, micro-ITT, CE-EOT, and CE-TOC populations. A table will present the subject demographics (eg, gender, age, ethnicity and race) and baseline characteristics (height, weight, BMI, and APACHE II Score) collected before the start of study drug. Age, as collected on the eCRF, will be summarized as both a continuous and categorical variable (<65, 65-75 and >75 years). APACHE II score will be summarized as both a continuous and categorical (0-10, 11-15, 16-20, 21-25, >25 as well as 0-25 and >25) variable.

5.3. Medical History and Disease History

Medical history will be coded using the MedDRA classification, version 20.0. Medical history will be summarized by system organ class (SOC) and preferred term by treatment group for the micro-ITT population. Subjects reporting the same SOC or preferred term more than once will be counted only once for that SOC and preferred term.

The primary disease diagnosis at baseline (complicated appendicitis vs. all other cIAI), whether the subject was enrolled based upon a pre-operative or intra/post-operative diagnosis, and whether the subject was a previous treatment failure will be summarized by treatment group for the MITT and micro-ITT populations. For those subjects considered a previous treatment failure, the reason for treatment failure (persistent fever, persistent clinical symptoms, and new intraabdominal abscess after >72 hours of antibiotic therapy) and descriptive statistics of the time since initial diagnosis (days) will be presented. For those subjects enrolled based on a preoperative diagnosis, the method used to confirm the diagnosis and the procedure

interpretation will be presented by treatment group. For subjects enrolled based on a intra/post-operative diagnosis, the intra-operative findings for the diagnosis of cIAI will be summarized.

Surgical intervention data will also be summarized by treatment group for the MITT, micro-ITT and CE-TOC populations. This includes procedure type, timing of the intervention relative to the first dose of study drug, number of abscesses identified, whether the infection was localized or generalized, whether or not there was primary wound closure, and the number of drains.

Findings from the baseline abdominal assessment, whether the subject is able to tolerate oral or enteral intake, if a nasogastric tube is present and if ileus is present or absent will be summarized by treatment group for the MITT and micro-ITT populations. Evaluation of the surgical wound (skin erythema, induration, tenderness, warmth to touch, fluctuance, swelling, superficial wound pain, and other) will be summarized as mild, moderate or severe at baseline by treatment group for the MITT and micro-ITT populations. The nature of the discharge (non-purulent, purulent, serous, mucoid, and bloody) will also be provided by treatment group for the MITT and micro-ITT populations.

5.4. Baseline Microbiology

The microbiological assessment of the baseline blood and intra-abdominal specimens will be summarized by treatment group for the MITT, micro-ITT, ME-EOT and ME-TOC populations. A frequency distribution of the number of subjects with each type of specimen obtained, whether or not there was growth, and how cultures were obtained will be provided by treatment group.

The pathogenic organisms identified from the baseline blood culture or culture of the intra-abdominal specimen will be presented. The number and percentage of subjects with gram-negative organisms (aerobes), overall and within Enterobacteriaceae and non-Enterobacteriaceae, gram-positive organisms (aerobes) and all anaerobes will be presented by genus and species for the micro-ITT and ME populations overall and by primary disease diagnosis. The same pathogen identified from both the blood and the intra -abdominal culture will be counted only once in the summary. The pathogenic organisms identified at baseline from a blood sample will also be presented separately for the micro-ITT population. The number and percentage of subjects with monomicrobial (gram-negative aerobe, gram-positive aerobe, anaerobe) and poly-microbial infections (gram-negative aerobes only, gram-positive aerobes only, anaerobes only, gram-negative aerobe and anaerobe, gram-positive aerobe and anaerobe, gram-negative and gram-positive aerobe, and gram-negative aerobe, gram-positive aerobe and anaerobe) will be provided for specimens from the blood or intra -abdominal culture.

Several tables providing the frequency distribution of the MIC as reported by the central laboratory will be provided for the micro-ITT and ME populations:

- The MIC distribution to eravacycline of the baseline pathogens.
- The MIC distribution to meropenem of the baseline pathogens.
- The MIC distribution to the study drug received of the baseline pathogens. For those subjects who received the wrong study drug, the summary will be based on actual treatment received.

- MIC summary statistics (ie, range, MIC_{50} and MIC_{90}) for baseline pathogens to the study drug received. Only those pathogens with at least 10 isolates in either treatment group will be summarized.

5.5. Prior and Concomitant Medications

Prior medications will be summarized by WHODRUG (Version March 2016 Format B) Anatomical Therapeutic Chemical Classification (ATC) level 4 (fourth level indicates the chemical/therapeutic/pharmacologic subgroup) and 3 (third level indicates the therapeutic/pharmacologic subgroup). Medications are considered prior if taken prior to the first dose of study drug or if their start date is unknown. Subjects will be counted only once for an ATC class. Concomitant medications taken during the study treatment period will be similarly summarized. Medications are considered concomitant if taken on or after the first dose of study drug, or if their stop date is unknown or marked as continuing.

The proportion of subjects who receive the following prior and concomitant medications will be summarized by treatment group:

- Systemic antibacterial medications taken prior to the first dose of study drug (micro-ITT and CE populations).
- Systemic antibacterial medications (excluding study drug) taken between first dose of study drug and the EOT visit (MITT, CE-EOT population) and the TOC visit (MITT, micro-ITT and CE-TOC populations).
- Non-antibacterial medications prior to the first dose of study drug (MITT and micro-ITT populations).
- Non-antibacterial medications taken from the first dose of study drug through the FU visit (Safety population).

5.6. Study Drug Exposure and Compliance

Exposure to study drug will be characterized by the duration of treatment, the number of infusion days, the number of active doses, total dose received, and the average daily dose over all infusion days. Descriptive statistics for each measure of exposure to study drug will be summarized by treatment group for MITT, Safety and micro-ITT populations.

Duration of treatment is defined as the number of days from when the subject first received study treatment until the day that they last received study treatment and is calculated as (date of last dose – date of first dose +1).

An infusion day is the 24-hour period during which the full daily dose of study drug is to be administered. An infusion day can be coincidental with a calendar day or can start in the afternoon of 1 day and complete in the morning of the next day. For subjects randomized to the eravacycline arm, if only 1 of the 2 doses was administered on the last infusion day then this will constitute one-half an infusion day. For subjects randomized to the meropenem arm, for subjects with creatinine clearance (CrCl) >50, 3 doses are expected in an infusion day; if only 1 of the 3 doses was administered on the last infusion day, then this will constitute a third of an infusion day; if 2 of the 3 doses were administered on the last infusion day, then this will constitute two-thirds of an infusion day. For subjects with CrCl $\geq$10 and $\leq$50, 2 doses are expected in an infusion day; if only 1 of the 2 doses was administered on the last infusion day,

then this will constitute a half of an infusion day. For subjects with CrCl <10, 1 dose is expected in an infusion day.

An active dose of study drug is defined as study treatment other than placebo. The number of active doses of study drug given will be counted as the total number of infusions of active study drug started, irrespective of the planned or actual duration of the infusion. Each subject is expected to have 2 or 3 active infusions during each infusion day depending on the treatment assignment.

Study drug is administered in mg/kg for the eravacycline arm and in g for the meropenem arm. Actual daily dose in mg is dependent on the treatment received, weight (in the case of eravacycline), the volume of drug administered (recorded on the eCRF), and the volume of drug prepared (recorded on the eCRF), as follows:

For eravacycline:

> actual daily dose (mg) = 1.0 * weight (kg) * (total volume of drug administered for dose 1 + dose 4) / total volume of drug prepared for dose 1 + dose 4

For meropenem:

> actual daily dose (mg) = 1000 * (total volume of drug administered for dose 2 + dose 3 + dose 5) / total volume of drug prepared for dose 2 + dose 3 + dose 5

The average daily dose of eravacycline, expressed as mg and as mg/kg, is based on the dose of active drug per infusion day, as follows:

> average daily dose (mg) = Σactual daily dose (mg) eravacycline over all doses / number of infusion days
>
> average daily dose (mg/kg) = average daily dose (mg) / screening weight (kg)

It is expected that the average daily dose of eravacycline will be approximately 2.0 mg/kg.

The average daily dose of meropenem, expressed in mg, is based on the dose of active drug per infusion day, as follows:

> average daily dose (mg) = Σactual daily dose (mg) meropenem over all doses / number of infusion days

The duration of infusions will be listed and deviations from the dosing regimen will be presented.

Treatment compliance will be based on expected doses of study drug (active and placebo) received and will be calculated as the number of doses received/expected number of doses received. The expected number of active doses received is based on the number of days the subject received study drug and the subject's CrCl category. A dose is defined as receipt of any amount of study drug received regardless of whether the full volume was infused.

Descriptive statistics of percent compliance as well as the number and percentage of subjects at least 80% compliant will be provided by treatment group for the MITT, Safety and micro-ITT populations.

5.7. Efficacy Evaluation

For all efficacy analyses, subjects will be analyzed in the group to which they were randomized. By definition, subjects who receive the wrong study drug are not included in the CE and ME populations. For the primary analysis, subjects who are randomized to the wrong primary site of infection stratum will be analyzed in the stratum to which they were randomized.

5.7.1. Primary Efficacy Analysis

The primary efficacy outcome measure is clinical response at the TOC visit (incorporating the SAC assessment) in the micro-ITT population. Clinical response is classified by the Investigator as cure, failure, or indeterminate/missing based on the following definitions:

- Clinical Cure: Clinical cure is defined as complete resolution or significant improvement of signs and symptoms of the index infection such that no additional antibacterial therapy, surgical, or radiological intervention (eg, an ultrasound guided drainage) is required. Routine imaging procedures (eg, an investigational ultrasound) are not considered radiological interventions.
- Clinical Failure: Subjects are classified as a clinical failure based on:
    - Death related to cIAI.
    - Persistence of clinical symptoms of cIAI.
    - Unplanned surgical procedures or percutaneous drainage procedures for complications or recurrence of cIAI.
    - Post-surgical wound infections requiring systemic antibiotics.
    - Initiation of rescue antibacterial drug therapy for cIAI.
- Indeterminate/Missing: If the subject's outcome is neither clinical cure nor clinical failure, the Investigator did not complete an assessment, if the study visit was not conducted, or the subject died for a cause unrelated to cIAI, then the outcome should be listed as indeterminate/missing.

Subjects who are assessed as a failure at the EOT visit will have the failure carried forward to the TOC visit. Clinical response at TOC (based on Investigator's assessment) is determined as in Table 5-1 from the assessments at the EOT and TOC visits.

Table 5-1: Derived Clinical Response at TOC Visit

Investigator's Assessment of Clinical Response		Derived TOC Clinical Response
EOT Visit	**TOC Visit**	
Cure	Cure	Cure
Cure	Failure	Failure
Cure	Indeterminate/Missing	Indeterminate/Missing
Failure	Cure	Failure
Failure	Failure	Failure
Failure	Indeterminate/Missing	Failure
Indeterminate/Missing	Cure	Cure
Indeterminate/Missing	Failure	Failure
Indeterminate/Missing	Indeterminate/Missing	Indeterminate/Missing

For those subjects reviewed by the SAC, the committee assessment of clinical response will be used as the primary efficacy outcome. For those subjects reviewed by the committee because they were deemed a clinical failure, if there is inadequate source control, the clinical outcome at all visits will be reclassified as indeterminate. For those subjects reviewed by the committee because they were a clinical cure at the TOC or FU visit and had a second surgical procedure, if there is inadequate source control, the clinical outcome at all visits will be reclassified as indeterminate. If there is adequate source control but the second surgical procedure represents clinical failure, clinical response at TOC and FU visits subsequent to the second surgical procedure will be reclassified as clinical failure.

The number and percentage of subjects in each treatment group defined as a clinical cure, clinical failure, and indeterminate/missing will be tabulated. A 2-sided 95% confidence interval (CI) for the observed difference in clinical cure rates (eravacycline treatment group minus meropenem treatment group) will be calculated using the method without stratification of Miettinen and Nurminen.[3] If the lower limit of the 95% CI for the difference in clinical cure rates in the micro-ITT population exceeds -12.5%, then NI of eravacycline to meropenem will be declared.

The noninferiority test will be a 1-sided hypothesis test performed at the 2.5% level of significance and will be based on the lower limit of the 2-sided 95% CI. The primary analysis is unadjusted.

The null and alternative hypotheses are as follows:

$$H_0: p_1 - p_2 \leq -\Delta \text{ and } H_1: p_1 - p_2 > -\Delta$$

Where p_1 is the primary efficacy outcome rate in the eravacycline treatment group, p_2 is the primary efficacy outcome rate in the meropenem treatment group, and Δ is the NI margin of 12.5%. For notation purposes, assume 1 represents the eravacycline group (Group 1) and 2 represents the meropenem group (Group 2).

Based on Miettinen and Nurminen, the 2-sided 95% CI is given by the roots for $RD = p_1 - p_2$ of the following equation:

$$\chi_\alpha^2 = \frac{(\hat{p}_1 - \hat{p}_2 - RD)^2}{V}$$

Where χ_α^2 is the cut point of size α from the chi-square distribution ($\chi_\alpha^2 = 3.84$ for 2-sided 95% CI), RD is the difference between the 2 true rates ($RD = p_1 - p_2$), $\hat{p}_1$ is the observed proportion in the eravacycline group (Group 1), $\hat{p}_2$ is the observed proportion in the meropenem group (Group 2), and

$$V = \left[\frac{\tilde{p}_1(1-\tilde{p}_1)}{n_1} + \frac{\tilde{p}_2(1-\tilde{p}_2)}{n_2}\right]\frac{n_1 + n_2}{n_1 + n_2 - 1}$$

Where n_1 is the number of subjects in the eravacycline group (Group 1), n_2 is the number of subjects in the meropenem group (Group 2), and $\tilde{p}_1$ and $\tilde{p}_2$ are the maximum likelihood estimators for the cure rates in the eravacycline and meropenem groups, respectively, and computed under the constraint that $\tilde{p}_1 - \tilde{p}_2 = RD$.

As stated above, the 2-sided 95% CI for the difference in rates is given by the roots for $RD = p_1 - p_2$ from the equation above, but this equation does not allow for explicit solution for RD. Therefore, a numerical algorithm will be used to obtain the 2 roots (CI) for RD. This CI approach corresponds to the NI test (a p-value approach) proposed by Farrington and Manning.

5.7.1.1. Additional Analyses of the Primary Efficacy Outcome

If eravacycline is determined to be NI to meropenem, superiority of eravacycline to meropenem will be assessed. If the lower bound of the 2-sided 95% CI is greater than 0, superiority of eravacycline for clinical cure at the TOC visit will be concluded.

The reasons for clinical failure will be summarized by treatment group for the micro-ITT population. The primary efficacy outcome will also be assessed across the randomization stratification factor of primary site of infection. For each infection site stratum, a 2-sided 95% CI for the observed difference in the clinical cure rate at the TOC visit will be calculated for the micro-ITT population. In addition, the primary analysis results will also be assessed separately across geographical region and country by treatment group to assess for consistency of results across regions. For each geographical region and country, a 2-sided 95% CI for the observed difference in the clinical cure rate at the TOC visit will be calculated for the micro-ITT population.

Sensitivity analyses of the primary outcome will also be conducted. The first analysis will be an adjusted analysis (adjusted for the stratification factor of primary site of infection). A 2-sided stratified 95% CI will be computed for the difference in clinical cure rate at the TOC visit between the eravacycline and meropenem treatment groups using the method of Miettinen and Nurminen. Cochran-Mantel-Haenszel weights will be used for the stratum weights in the calculation of the CI as follows:

$$W_i = \frac{n_{1i}n_{2i}}{n_{1i}+n_{2i}}$$

Where n_{1i} is the number of subjects in the eravacycline treatment group (Group 1) in the i-th stratum, and n_{2i} is the number of subjects in the meropenem treatment group (Group 2) in the i-th stratum.

The second sensitivity analysis will analyze those subjects who are considered indeterminates in the primary analysis as clinical cures.

A third sensitivity analysis will analyze the primary efficacy outcome across the randomization stratification factor of primary site of infection based upon the actual diagnosis recorded in the eCRF. For each infection site stratum, a 2-sided 95% CI for the observed difference in the clinical cure rate at the TOC visit will be calculated for the micro-ITT population. This sensitivity analysis will only be performed if more than 10 subjects are randomized to a stratum different from the stratum indicated in the eCRF.

A fourth sensitivity analysis will analyze the primary efficacy outcome based upon the actual treatment each subject received. Subjects who received both eravacycline and meropenem will be excluded from this analysis. This sensitivity analysis will only be performed if more than 10 subjects receive the treatment to which they were not randomized.

Additional sensitivity analyses will be stratified analyses for the following combinations: primary site of infection and geographic region, primary site of infection and prior antibiotic use, and geographic region and prior antibiotic use. Prior antibiotic use is defined as use of any systemic antibiotic in the 72 hours prior to enrollment. Two-sided 95% CIs will be computed for the difference in clinical cure rate at the TOC visit between the eravacycline and meropenem treatment groups within each stratum using the method of Miettinen and Nurminen. Two-sided 95% CIs will be computed for the difference in clinical cure rate at the TOC visit between the eravacycline and meropenem treatment groups across the strata using the stratified method of Miettinen and Nurminen (using Cochran-Mantel-Haenszel weights).

5.7.2. Secondary Efficacy Analyses

The number and percentage of subjects in each treatment group with an efficacy outcome (the SAC assessment of clinical response will be used, if available) of clinical cure, clinical failure and indeterminate/missing (by definition the CE and ME populations do not include subjects with an indeterminate/missing response) will be presented for the following time points and analysis populations:

- EOT Visit – ITT, MITT, CE-EOT, micro-ITT and ME-EOT populations.
- TOC Visit – ITT, MITT, CE-TOC, ME-TOC populations.
- FU Visit – ITT, MITT, CE-FU, micro-ITT, ME-FU. Failure at the EOT or TOC visit will be carried forward to the FU visit.

Two-sided 95% unadjusted CIs will be constructed for the observed difference in the clinical cure rates between the treatment groups for descriptive purposes; no conclusion of NI will be made. Analyses at the TOC visit will also be presented by primary diagnosis at baseline.

5.7.3. Additional Efficacy Analyses

5.7.3.1. Clinical Outcome Measures

The Investigator's assessment of clinical response at the TOC visit (not incorporating the assessment of the SAC) in the micro-ITT population will be presented to support the findings of

the primary and secondary efficacy analyses. The number and percentage of subjects classified by the Investigator as clinical cure, clinical failure, or indeterminate will be tabulated for both treatment groups. A 2-sided 95% CI will be constructed for the observed difference in the clinical cure rate between the eravacycline and meropenem groups. A listing will be provided of those subjects where the SAC response was different from the Investigator's assessment.

The primary efficacy outcome of clinical cure at the TOC visit by treatment group and baseline pathogen will be provided for the micro-ITT and ME-TOC populations.

A summary (number and percentage of subjects) of the shift from baseline to each visit (Days 1-4, EOT, TOC and FU visits) in the surgical wound assessment will be presented by treatment group for the MITT, micro-ITT, and CE-TOC populations.

5.7.3.2. Microbiological Outcomes

Microbiological outcome assessments will be made at the EOT and TOC visits.

Per-pathogen microbiologic response categories are eradication, presumptive eradication, persistence, persistence with decreased susceptibility, presumed persistence, and indeterminate/missing and are defined as follows:

- Eradication – Absence of causative organism from an appropriately obtained specimen at the site of infection at each time point.
- Presumed eradicated – Absence of material to culture in a subject who has responded clinically to treatment (clinical cure, based on SAC assessment, if available).
- Persistence – Continued presence of the original pathogen in cultures from the original site of infection or blood culture obtained during or upon completion of therapy.
- Persistence with decreased susceptibility – Continued presence of the original pathogen in cultures from the original site of infection obtained during or upon completion of therapy, and the MIC for the study drug received of the pathogen is > 2-fold (as least 2 dilutions) higher than that of the original isolate.
- Presumed persistence – Absence of material to culture in a subject who is given additional antibiotics to treat the study entry cIAI (clinical failure, based on SAC assessment, if available).
- Indeterminate/Missing – Culture not obtained and clinical response is indeterminate/ missing.

These categories will be further classified as follows:

- Favorable
    - Eradication.
    - Presumed eradicated.
- Unfavorable
    - Persistence.
    - Persistence with decreased susceptibility.
    - Presumed persistence.

- Indeterminate/Missing.

Overall per-pathogen microbiological response will incorporate intra-abdominal and blood cultures, and will be based on the last post-baseline culture obtained prior to the relevant visit.

Per-subject microbiological response will be determined by the per pathogen microbiological outcomes. Per-subject microbiological response will be summarized as favorable, unfavorable or indeterminate at the EOT and TOC visits in the Micro-ITT and ME (ME-EOT at the EOT visit and ME-TOC at the TOC visit) populations. To have an overall per-subject favorable microbiologic response, the outcome for each baseline pathogen must be favorable (eradicated or presumed eradicated). If the outcome for any pathogen is unfavorable (persistence, persistence with decreased susceptibility or presumed persistence), the subject will be considered to have an unfavorable per-subject microbiologic response. If the outcome for any pathogen is indeterminate, the per-subject microbiologic response will be indeterminate, unless the outcome for another pathogen is unfavorable, in which case the per-subject response will be unfavorable. Two-sided 95% unadjusted CIs will be constructed for the observed difference in the rates of favorable response between the treatment groups for descriptive purposes; no conclusion of NI will be made.

Microbiologic response by baseline pathogen will be determined as the proportion of subjects with a favorable per-pathogen microbiological response (eradication or presumed eradication) at the EOT and TOC visits for each pathogen isolated at baseline. The number and percentage of subjects in each treatment group with a microbiologically favorable outcome will be tabulated for the micro-ITT, ME-EOT, and ME-TOC populations.

For subjects with baseline pathogens obtained from blood culture (ie, for bacteremic subjects), favorable per-pathogen microbiologic response by baseline pathogen will also be summarized separately for the micro-ITT population. Microbiologic response for bacteremic subjects will be based on the last post-baseline blood culture obtained prior to the relevant visit. If no post-baseline blood culture was obtained, response will be presumed based on the clinical response at the relevant visit.

In addition, a table will list all subjects in each treatment group with at least 1 baseline pathogen obtained from blood culture, including the per subject clinical response, per subject microbiological response, and the per-pathogen microbiological response at EOT and TOC for each pathogen.

Favorable per-pathogen microbiological response will also be summarized by baseline pathogen and MIC to study drug received for those pathogens with a sample size of at least 10 in 1 of the treatment groups in the micro-ITT population.

Microbiological categories for pathogens identified after baseline assessment are superinfection and new infection, which are defined as follows:

- Superinfection: Emergence of a new pathogen during therapy, from intraabdominal or blood cultures, with emergence or worsening of signs and symptoms of infection (ie, is determined by the Investigator to be a clinical failure).
- New infection: Emergence of a new pathogen after completion of therapy, from intraabdominal or blood cultures, with emergence or worsening of signs and symptoms of infection (ie, is determined by the Investigator to be a clinical failure).

The number and percentage of subjects with a superinfection or new infection after baseline will be presented by treatment group. A listing will be provided that presents the subjects with a superinfection and new infection including the type of specimen and pathogen.

Decreasing susceptibility of a pathogen is defined as a > 2-fold (at least 2 dilutions) increase from baseline to any subsequent study time point in the MIC of the study drug received. The number and percentage of subjects in the micro-ITT population with a pathogen showing decreasing susceptibility will be tabulated for each treatment group. In addition, a table will list all subjects in each treatment group with a pathogen showing decreasing susceptibility, including the type of specimen, pathogen, and MIC values for the drug received.

5.8. Safety Analyses

5.8.1. Adverse Events

Verbatim descriptions of AEs will be coded using Version 20.0 of MedDRA. Summary tables will be provided for all treatment-emergent AEs (TEAEs). A TEAE is defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug. An AE is considered treatment emergent if the AE starts on or after the first dose of study drug. In addition, all AEs (including non-TEAEs), serious TEAEs, and TEAEs leading to study drug discontinuation will be provided in listings by treatment group, site, subject, verbatim term, MedDRA SOC and preferred term, start and end date, seriousness flag, severity, relationship to study drug, action taken with study treatment, frequency and outcome. All AEs will be coded using the MedDRA coding system and displayed in tables and data listings using SOC and preferred term.

An overall summary of AEs will include number and percentage of subjects in each treatment group who experienced at least 1 AE of the following categories: any AE, any TEAE, any drug-related TEAE (defined as possibly, probably or definitely related to study drug), any severe TEAE, any serious TEAE (SAE), any drug-related SAE, any SAE leading to death, any TEAE leading to premature discontinuation of study drug, and any SAE leading to premature study drug discontinuation.

The number and percentage of subjects reporting a TEAE in each treatment group will be tabulated by SOC and preferred term; by SOC, preferred term, and severity (mild, moderate, and severe); and by SOC, preferred term, and relationship (unrelated [defined as unrelated or unlikely related to study drug] or related to study drug). The number and percentage of subjects reporting a SAE and reporting a TEAE leading to premature discontinuation of study drug in each treatment group will also be summarized by SOC and preferred term. Summary tables will be presented alphabetically by SOC and preferred term within SOC. The incidence of TEAEs that occur in at least 2% of subjects in either treatment group will be summarized by preferred term and treatment group, sorted by decreasing frequency in the eravacycline group. For all analyses of TEAEs, if the same AE (based on preferred term) is reported for the same subject more than once, the AE is counted only once for that preferred term and at the highest severity and strongest relationship to study drug. Events with missing severity will be considered severe and events with missing relationship to study drug will be considered related to study drug.

5.8.2. Laboratory Data

Summaries of central laboratory data will include hematology (erythrocyte count [RBC], hematocrit, hemoglobin, mean cell hemoglobin [MCH], mean cell hemoglobin concentration

[MCHC], mean cell volume [MCV], leukocyte count [WBC], absolute and differential basophils, absolute and differential eosinophils, absolute and differential lymphocytes, absolute and differential monocytes, absolute and differential neutrophils, and absolute and differential platelets), chemistry (tests included in the table below), coagulation (fibrinogen, partial thromboplastin time, and prothrombin time), and urinalysis (bilirubin, casts, crystals, glucose, ketones, pH, protein, RBC, urobilinogen, and WBC) laboratory parameters. Laboratory parameters will be presented in alphabetic order with the following exceptions: differentials of WBC counts will be presented following the WBC results, and chemistry parameters will first be grouped by organ class (renal, liver, electrolytes and other) and presented alphabetically within each of these classes, as shown in Table 5-2. Clinical laboratory values will be expressed in reported units or System International (SI) units.

Table 5-2: Presentation of Chemistry Parameters

Renal	Blood urea nitrogen Creatinine
Liver	Alkaline phosphatase ALT AST Bilirubin indirect Bilirubin total GGT LDH
Electrolytes	Bicarbonate Calcium Chloride Magnesium Potassium Sodium
Other	Albumin Amylase Cholesterol (total) Creatine kinase Glucose, non-fasting Lipase Phosphorus Total protein Uric acid

Baseline is defined as the value closest to but prior to the start of study drug administration. Analyses will utilize assessments occurring during the scheduled visit windows (see Table 1-2). Thus, if a subject has a visit outside the scheduled visit window, for example, a TOC visit on Day 35, the laboratory assessment will not be summarized with the TOC visit but will be considered an unscheduled assessment. If more than 1 measurement is taken during the visit window, the value taken on the scheduled visit will be utilized or if no scheduled visit was done, the first (earliest) measurement will be used. If more than 1 measurement is taken on the same day, the last measurement on the day will be used. For worst overall post-baseline analyses, all laboratory assessments including those obtained from unscheduled visits and the FU visit will be included.

Several analyses of the laboratory data will be presented. Descriptive statistics (based on SI units) for chemistry, hematology and coagulation values and the change from baseline will be summarized by treatment group at Days 1 through Day 4, EOT, TOC and FU visits, and for the overall worst value post-baseline (which includes unscheduled visits). Change from baseline will be calculated for each patient at the specified time point as the value at the specified time point minus the baseline value.

Toxicity grade will be determined based on the modified DMID criteria in Table 5-3. The DMID Adult Toxicity Table (November 21, 2007) was modified to exclude the clinical component of the toxicity grading. In addition, Grade 0 was added to the table so that shifts from normal could be analyzed. For toxicity grades based on a multiple of the ULN, the normal range from the central laboratory will be applied. For toxicity grades based on fixed values, the grades will be assigned regardless of the normal actual range values from the central laboratory. For example, a hemoglobin value of 10.0 gm/dL will be assigned a grade of 1 toxicity, even if the lower limit of normal from the laboratory was 9.8 gm/dL. Shift tables will be presented to show the number of subjects with a laboratory value with a grade of 0, 1, 2, 3 or 4 at baseline versus the worst post-baseline value.

Table 5-3: Modified Division of Microbiology and Infectious Diseases Adult Toxicity Criteria (November, 2007)

Hematology					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin (gm/dL)	>10.5	9.5-10.5	8.0-9.4	6.5-7.9	<6.5
Absolute Neutrophil Count (count/mm^3)	>1,500	1,000-1,500	750-999	500-749	<500
Platelets (counts/mm^3)	≥100,000	75,000-99,999	50,000-74,999	20,000-49,999	<20,000
WBC (count/mm^3)	1,000-10,999	11,000-12,999	13,000-14,999	15,000-30,000	>30,000
% Polymorphonuclear Leucocytes + Band Cells	≤80%	>80%-90%	>90-95%	>95%	--

Chemistry					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia (mEq/L)	>135	130-135	123-129	116-122	<116
Hypernatremia (mEq/L)	<146	146-150	151-157	158-165	>165
Hypokalemia (mEq/L)	>3.4	3.0-3.4	2.5-2.9	2.0-2.4	<2.0
Hyperkalemia (mEq/L)	<5.6	5.6-6.0	6.1-6.5	6.6-7.0	>7.0
Hypoglycemia (mg/dL)	≥65	55-64	40-54	30-39	<30
Hyperglycemia (mg/dL) (nonfasting and regardless of prior history of diabetes)*	<116	116-160	161-250	251-500	>500
Hypocalcemia (mg/dL) (corrected for albumin)	>8.4	7.8-8.4	7.0-7.7	6.1-6.9	<6.1
Hypercalcemia (mg/dL)	≤10.5	10.6-11.5	11.6-12.5	12.6-13.5	>13.5
Hypomagnesemia (mEq/L)	>1.4	1.2-1.4	0.9-1.1	0.6-0.8	<0.6
Hypophosphatemia (mg/dL)	≥2.5	2.0-2.4	1.5-1.9	1.0-1.4	<1.0
Hyperbilirubinemia (total bilirubin)	<1.1×ULN	1.1-1.5×ULN	1.6-2.5×ULN	2.6-5.0×ULN	>5.0×ULN
BUN	<1.25×ULN	1.25-2.5×ULN	2.6-5.0×ULN	5.1-10.0×ULN	>10.0×ULN
Hyperuricemia (uric acid) (mg/dL)	<7.5	7.5-10.0	10.1-12.0	12.1-15.0	>15.0
Creatinine	<1.1×ULN	1.1-1.5×ULN	1.6-3.0×ULN	3.1-6.0×ULN	>6.0×ULN

* The DMID toxicity table reports hyperglycemia detected in nonfasting specimens obtained from patients with no prior diabetes.

Enzymes					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	<1.25×ULN	1.25-2.5×ULN	2.6-5×ULN	5.1-10×ULN	>10×ULN
ALT (SGPT)	<1.25×ULN	1.25-2.5×ULN	2.6-5×ULN	5.1-10×ULN	>10×ULN
GGT	<1.25×ULN	1.25-2.5×ULN	2.6-5×ULN	5.1-10×ULN	>10×ULN
Alkaline Phosphatase	<1.25×ULN	1.25-2.5×ULN	2.6-5×ULN	5.1-10×ULN	>10×ULN
Amylase	<1.1×ULN	1.1-1.5×ULN	1.6-2.0×ULN	2.1-5.0×ULN	>5.1×ULN
Lipase	<1.1×ULN	1.1-1.5×ULN	1.6-2.0×ULN	2.1-5.0×ULN	>5.1×ULN

Coagulation					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Fibrinogen (mg/dL)	>200 - <400	100-200 (low) or 400-600 (high)	50 - <100 (low) or >600 (high)	<50 (low)	Fibrinogen associated with gross bleeding or with disseminated coagulation
Activated Partial Thromboplastin (APPT)	<1.01×ULN	1.01-1.66×ULN	1.67-2.33×ULN	2.34-3×ULN	>3×ULN
Prothrombin Time (PT)/International Normalized Ratio (INR)	<1.01×ULN	1.01-1.25×ULN	1.26-1.5×ULN	1.51-3.0×ULN	>3×ULN

Abbreviations: ULN = upper limit of normal

Number and percentage of subjects with at least a 2-grade increase from baseline or a post-baseline grade 4 abnormality (based on DMID criteria) will be summarized by treatment arm. Percentages for each lab test will be based on the number of subjects with a post-baseline evaluation of that laboratory test. A listing will be provided which gives all laboratory results for a given laboratory test for subjects who have at least one 2-grade increase from baseline or a post-baseline grade 4 abnormality.

The number and percentage (based on the number of subjects with a normal level at baseline) of subjects in each treatment group with an elevated transaminase level (>3 × ULN, >5 ×ULN, and >10 ×ULN), an elevated bilirubin level (>1.5 ×ULN and >2 ×ULN) will be presented by study visit. A listing of subjects who meet the laboratory criteria for Hy's law will also be provided. The laboratory criteria for Hy's law is defined as ALT or AST >3 ×ULN, ALP ≤2.0 ×ULN, and total bilirubin >2 ×ULN.

Detailed patient listings of all laboratory data collected during the study will be provided. Laboratory values outside normal limits will be identified in the patient data listings with flags for low (L) and high (H) as will laboratory values that meet the clinically notable (CN) thresholds (at least a 2-grade increase from baseline or a post-baseline grade 4 abnormality).

5.8.3. Vital Signs and Physical Examination

Blood pressure (systolic and diastolic), respiration rate, and heart rate will be summarized using descriptive statistics by treatment group at each time point at which they were measured. Descriptive statistics of the change from baseline to each post-baseline time point will also be provided. Change from baseline will be calculated for each subject at the specified time point as the value at the specified time point minus the baseline value. Visit windows will be determined in the same manner as described for the laboratory data. Detailed patient listings of all temperature assessments will be provided but data will not be summarized in a table.

A summary of abnormal values, identified by the threshold levels provided in Table 5-4 will be analyzed using the methodology described for CN laboratory values with the exception that only subjects with both baseline and post-baseline values will be evaluable for the analysis of a diastolic blood pressure increase >20 mmHg.

Table 5-4: Clinically Notable Abnormal Vital Sign Threshold Values

ABNORMAL VALUES		
Vital Sign	**Threshold**	**Reference**
Diastolic blood pressure	>20 mmHg increase from baseline	CTCAE Grade 2
Systolic blood pressure	≥140 mmHg	CTCAE Grade 2
Heart rate	<60 beats/min	Noble et al 1990
Heart rate	>120 beats/min	-

CTCAE = Common Terminology Criteria for Adverse Events, Version 4.0

Clinically significant physical examination findings will be reported, analyzed and presented as AEs.

5.8.4. Electrocardiogram

Descriptive statistics for electrocardiogram (ECG) parameters (eg, ventricular rate, PR interval, QRS duration, QT interval, and QTcB interval) at baseline and the EOT visit, and the change from baseline will be presented by treatment group. For QTcB, a distribution of the increase from baseline (0 or less [no increase], 1-29 msec, 30-60 msec, and >60 msec) will also be presented. QTcB will be categorized as ≤450, >450 -≤480, >480 - ≤500, and >500 msec) and a distribution by treatment group at the EOT visit will be presented. A shift table will present the percentage of normal, abnormal-not clinically significant and abnormal-clinically significant ECGs at baseline and the EOT visit by treatment group. All ECG data will be provided in a by-subject listing.

6. CHANGES TO PLANNED ANALYSES

7. REFERENCES

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