STATISTICAL ANALYSIS PLAN

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

Protocol: TP-434-021

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Name of Test Drug:	Eravacycline (TP-434)
Phase:	Phase 3
Methodology:	Randomized, Double-Blind, Double-Dummy, Multicenter, Non-inferiority, Prospective Study
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Analysis Plan Date:	22January2018
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APPROVAL SIGNATURE PAGE

Protocol Title:	Investigating Gram-negative Infections Treated with Eravacycline (IGNITE) 3: A Phase 3, Randomized, Double-Blind, Double-Dummy, Multicenter, Prospective Study to Assess the Efficacy and Safety of IV Eravacycline Compared with Ertapenem in Complicated Uterine Tract Infections
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Signature: Jiani Yin

Date: 24 Jan 2018

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.

Sponsor Signatory:
Larry W. Tsai, MD
Chief Medical Officer

Signature:

Date: 23 JAN 2018

Anita F. Das, PhD
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Signature: Anita F Das

Date: 24 Jan 2018

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
AE	Adverse Event
ALT (SGPT)	Alanine Aminotransferase (Serum Glutamic Pyruvic Transaminase)
AST (SGOT)	Aspartate Aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
ATC	Anatomical Therapeutic Chemical
BUN	Blood Urea Nitrogen
CE	Clinically Evaluable
CFU	Colony-Forming Unit
CHF	Congestive Heart Failure
CI	Confidence Interval
cIAI	Complicated Intra-abdominal Infections
CN	Clinically Notable
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSR	Clinical Study Report
cUTI	Complicated Urinary Tract Infection
DMID	Division of Microbiology and Infectious Diseases
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOI	End of IV
EOT	End of Treatment
ERC	Evaluability Review Committee
FDA	Food and Drug Administration
FU	Follow-Up
IB	Investigator's Brochure
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGNITE	Investigating Gram-Negative Infections Treated with Eravacycline
ITT	Intent-To-Treat
IV	Intravenous
IWRS	Interactive Web-Based Response System

Term	Definition
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
micro-ITT	Microbiological Intent-To-Treat
micro-MITT	Modified Microbiological Intent-To-Treat
MITT	All Treated
MRC	Microbiology Review Committee
PK	Pharmacokinetic
NI	Non-Inferiority
PO	Per Oral
RBC	Red Blood Cell
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

The increasing incidence of multidrug resistance among Gram-positive and Gram-negative pathogens in complicated urinary tract infections (cUTIs) has raised concerns among experts, especially since there is a dearth of new antibiotics in the drug development pipeline and a limited number of marketed antibiotics with activity against these pathogens (1,2). The high degree of in vitro antibacterial activity against multidrug resistant Gram-positive and Gram-negative pathogens and efficacy observed with eravacycline in established animal models of infection (3,4,5), as well as the results from initial clinical studies (6,7), warrant clinical development of intravenous (IV) eravacycline as a treatment option for cUTIs. A potential advantage of eravacycline, based on nonclinical and human pharmacokinetic (PK) data, is the possibility of convenient daily IV dosing.

Eravacycline is a novel, synthetic, broad-spectrum fluorocycline antibiotic of the tetracycline class and is highly active in vitro against emerging pathogens. 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 pathogens, the efficacy observed with eravacycline in established animal models of infection, and the efficacy and tolerability established in phase 2 and phase 3 studies of complicated intra-abdominal infections (cIAIs) warrant clinical development of eravacycline as a single daily dose IV treatment option for cUTIs.

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of data from Study TP-434-021. 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 1.1 dated 9 August 2016.

Analysis of PK parameters is covered in a separate analysis plan.

This protocol is designed to address the guidance requirements of the Food and Drug Administration (FDA; Complicated Urinary Tract 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 cUTIs. The FDA supports the use of a responder outcome (clinical cure and microbiological success) at the End of IV (EOI) and Test of Cure (TOC) visit in the microbiological intent-to-treat (micro-ITT) population. For the EMA, the primary efficacy outcome is microbiologic response in the microbiological modified ITT (micro-MITT) and microbiologically evaluable (ME) populations. 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 is to demonstrate that IV eravacycline is non-inferior to ertapenem in responder outcome (clinical cure and microbiologic success) in the micro-ITT population at the EOI visit (within 1 day of the completion of IV study drug treatment) and TOC visit (defined as 14-17 days after randomization).

The secondary objectives of the study are:

- To compare responder outcomes in the treatment arms at Day 5 in the micro-ITT population
- To compare clinical outcomes in the treatment arms at Day 5, EOI, End of Treatment (EOT), TOC, and Follow-up (FU) visits in the following populations:
    - ITT population
    - Clinically evaluable (CE) population
    - Micro-ITT population
    - Micro-MITT population
    - ME population
- To compare microbiologic outcomes in the treatment arms at Day 5, EOI, EOT, TOC and FU visits in the following populations:
    - Micro-ITT population
    - Micro-MITT population
    - ME population
- To assess safety and tolerability of IV eravacycline administration in the safety population
- To explore PK parameters of IV 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 ertapenem. Dosing in the study arms is described in Table 1.

Table 1 Study Drug Administration

Treatment Arms	For at Least the First 5 Doses	After EOI through Study Drug Completion
	IV Infusion	Oral Administration
Eravacycline (IV) / Levofloxacin (PO)	Eravacycline 1.5 mg/kg IV q24h	Levofloxacin 750mg PO QD
Ertapenem (IV) / Levofloxacin (PO)	Ertapenem 1.0 g IV q24h	Levofloxacin 750mg PO QD

Key: EOI = End of IV Therapy; IV= Intravenous; q24h= every 24 hours; QD=once daily. 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 (1.5 mg/kg q24h) or ertapenem (1.0 g q24h) 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 2 criteria: (1) by primary site of infection (pyelonephritis and normal urinary tract anatomy vs all other diagnoses) and (2) by the receipt of a single dose of effective non-study antibiotics for the acute cUTI within 72 hours of enrollment (yes vs no). An enrollment cap of approximately 50% is planned for subjects with pyelonephritis with normal urinary tract anatomy. Also, an enrollment cap of approximately 20% is planned for subjects who have received a single dose of effective non-study antibiotics for the acute cUTI within 72 hours of enrollment.

Approximately 1200 subjects will be randomized to receive study drug.

Subjects will be recruited at approximately 130 investigative sites worldwide.

1.2.2. 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.

1.2.3. Study Procedures

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

Table 2 Schedule of Assessments

Study Procedure	Screening[1] *within 36 hours prior to Randomization*	RANDOMIZATION	Days 1-10 *During Hospitalization*[2]	Day 5 *(5 Days After Randomization)*	EOI[3] *IV-to-Oral Transition*	EOT[4] *Within 1 Day of Last Dose (IV or PO)*	TOC *(14-17 Days After Randomization & ≥ 5 days after last dose)*	FU *(21-28 Days After Randomization)*
Informed Consent[1]	X							
Medical History/Height & Weight	X							
Signs and Symptoms	X		X	X	X	X	X	X
Physical Exam	X		X[4]	X	X	X	X	X
Temperature	X		X[5]	X	X	X	X	X
Resting Vital Signs[6]	X		X	X	X	X	X	X
Prior/Concomitant Medications[7]	X		X	←		X		→
Hematology/Chemistry[8]	X				X	X	X	X
Coagulation	X				X	X		X
Urinalysis[9]	X			X	X	X	X	X
Calculated Creatinine Clearance	X		X[10]	X	X *as clinically indicated*			
Serum Pregnancy Test[11]	X						X	
Blood Cultures	X		X[12]	←		X[12]		→
Urine Cultures[13]	X			X	X	X	X	X
Adverse Events[14]	X		X	←		X		→
Clinical Outcome Assessment				X	X	X	X	X
Study Drug Administration[15]			X	X	X			
Length of Treatment Determination[16]				X				
Verify PO Study Drug Compliance						X		
Plasma PK Assessments[17]			X	X				

See footnotes below and on following page.

Key: B/P = blood pressure; CFU = colony-forming unit; cUTI = complicated urinary tract infection; eCRF = electronic case report form; EOI = End of IV visit; EOT = End of Treatment visit; FU = Follow-up visit; HR = heart rate; IV = intravenous; PK = pharmacokinetic; PO = oral; RBC = red blood cell; RR = respiration rate; TOC = Test of Cure visit; WBC = white blood cell.

1. If Dose 1 and Screening occur on the same day then the signs and symptoms, physical exam, temperature, resting vital signs, and hematology/chemistry do not need to be repeated. Procedures performed as standard of care within 36 hours prior to randomization may be used to determine eligibility. Informed consent must be obtained prior to performing any study specific procedures that are not standard of care. However, urine and blood specimens collected during routine care prior to subject consent may be used for study purposes. If routine care results are used to determine eligibility, central laboratory blood tests must still be performed.
2. If EOI occurs on the same day as a dosing day during hospitalization then the visit should be completed as an EOI visit.
3. EOT assessments are to be performed at premature withdrawal or treatment failure and within 24-h of last dose. If EOT occurs on the same day as a dosing day during hospitalization then the visit should be completed as an EOT visit.
4. A symptom directed Physical Exam should be conducted daily while in hospital. Complete physical exams should be performed at Screening, Day 5, EOI, EOT, TOC and FU visits.
5. Temperature (oral, rectal, tympanic, or by temporal artery) should be assessed per institution guidelines while in hospital, and the highest daily value recorded in the eCRF.
6. RR, HR, B/P at: (i) Screening, (ii) daily while in hospital, (iii) Day 5, (iv) EOI, (v) EOT, (vi) TOC, and (vii) FU.
7. At screening visit, record all prior and concomitant medications, including all prescription, over-the-counter and herbal medications, taken within 1 week prior to randomization, including both day and time for all antibiotics administered in the 72-h prior to randomization. The following subjects who have received previous/ongoing antibiotics are eligible for enrollment: (a) subjects with suspected acute cUTI who have received a single dose of effective non-study antibiotics for the acute cUTI; (b) subjects who developed signs and symptoms of cUTI while on an antibiotic for another indication.
   No concomitant systemic antibacterials effective in cUTI are permitted after the initial dose of study drug through the FU visit, other than subjects on rescue/non-study antibacterial therapy. See Protocol Section 10.6 for prohibited concomitant medications.
8. Hematology and chemistry will be performed at: Screening, EOI, EOT, TOC, and FU.
9. Urine microscopy for RBC, WBC, crystals, and casts performed at: (i) Screening, (ii) Day 5, (iii) EOI, (iv) EOT, (v) TOC, and (vi) FU.
10. If creatinine clearance is <50 at Screening, creatinine clearance should be recalculated daily through Day 5 and thereafter as clinically indicated. Creatinine clearance should be calculated based upon local laboratory results in order to make timely dose adjustments, if needed; however, samples are also required to be sent to the central lab for assessment. Ertapenem/placebo and levofloxacin dosing should be increased or decreased according to the prescribing information.
11. If a local serum pregnancy test is not available or results cannot be received within 4 hours of sampling at the investigative site then a urine pregnancy test may be utilized locally to obtain timely results for randomization. All female subjects of childbearing potential will have a serum pregnancy test performed by the central laboratory.
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, signs and symptoms of persistence, relapse, or new infection).
13. Collected from a mid-stream urine specimen, a newly-placed urinary catheter, cystoscopy, suprapubic aspiration, or a properly disinfected collection port.
    Urine cultures should be processed using a calibrated loop to identify a quantitative count of bacteria at a lower limit of 103 CFU/mL. The colony count and pathogenic microorganism(s) identification will be recorded and the purified isolate(s) will be sent to the central laboratory where species confirmation and antimicrobial susceptibility testing will be performed.
14. Document any adverse events that occur from the signing of informed consent through study completion. Prior conditions should be documented as medical history
15. Expected treatment duration is 7 days unless clinical failure occurs earlier; maximum treatment duration is ten days (total IV and PO). The 24-h interval between IV doses can be shortened (but not prolonged) by up to 2-h (ie, interval of 22-h to 24-h) from the first dose during doses 1-3 to adapt to a normal hospital schedule. After the third dose, the permitted IV administration window is q24h ± 90 minutes. At a minimum, the first 5 IV doses must be administered in an in-patient hospital setting; subsequent doses may be administered on an out-patient basis. Contact Medical Monitor for dosing beyond 7 doses.
16. Subjects should receive 7-10 days of treatment. Specific criteria for determining length of treatment are described in Protocol Section 11.3.3.
17. Please refer to Protocol Section 24 for schedule of plasma PK sample collection on Day 1, Day 2, and Day 5.

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 pharmacokinetic 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 subject populations defined in this section will be evaluated and used for presentation and analysis of the data.

3.1.1. **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.

3.1.2. **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 ertapenem arm who mistakenly receives eravacycline will be included in the eravacycline arm. A subject randomized to the eravacycline arm who mistakenly receives ertapenem will be included in the ertapenem arm if ertapenem is given for the entire course of IV therapy and will be included in the eravacycline arm if both ertapenem and eravacycline are received.

3.1.3. **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.

3.1.4. **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 on culture of urine or blood that causes urinary tract infection against which eravacycline and ertapenem have expected 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 with the exception of *Pseudomonas* species. Analyses in this population will be presented in summary tables by the treatment arm to which the subject was randomized.

To be considered a baseline pathogen, both of the following must be met:

1. The organism must have been isolated from a suitable urine or blood specimen obtained between 36 hours prior to enrollment and the first dose of study drug). A suitable urine specimen is one collected from a clean-catch mid-stream urine specimen, a newly-placed urinary catheter (including uretheral catheters, supra pubic catheters, and nephrostomy tubes), cystoscopy, supra pubic aspiration, or a properly disinfected collection port.
2. The baseline urine specimen must grow at least 1, but no more than 2 bacterial isolates at ≥10^5 CFU/mL each (or at ≥10^4 CFU/mL if obtained via suprapubic aspiration, new nephrostomy or cystoscopy). If more than 2 bacterial isolates are identified, the urine culture will be considered uninterpretable unless the specimen is obtained via suprapubic aspiration, nephrostomy tube newly placed or cystoscopy, 1 of the isolates comprises ≥80% of the total growth (predominant), or 1 or more isolates are also isolated

simultaneously from a blood culture. In the second case, only the predominant organism will be considered a baseline pathogen. In the latter case, only organisms isolated simultaneously from the urine culture and the blood culture will be considered baseline pathogens.

All baseline urine cultures will be reviewed in a blinded manner by the Sponsor Microbiology Review Committee (MRC) for acceptability and final pathogen determination. The organism's identity as determined at the local laboratory will be verified by the central laboratory. If the Genus identification is the same between the local and central microbiology laboratory but the species identification is discrepant, the central laboratory identification will be used. If the local laboratory grows an acceptable pathogen but the central laboratory is not able to grow the isolate, 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 laboratory resend the isolate. If the central laboratory is still not able to identify the isolate for any reason, the local laboratory determination of Genus and species will be used for pathogen identification. Any remaining major discrepancies in species identification between the central and local laboratory will be reviewed by the Sponsor MRC in a blinded manner for final identification of the isolate.

There are 3 categories of pathogen identification as follows:

1. Always a pathogen:
    - *Escherichia coli*
    - *Klebsiella* spp.
    - *Proteus* spp.
    - *Citrobacter* spp.
    - *Enterobacter* spp.
    - *Serratia* spp.
    - *Providencia* spp.
    - *Morganella* spp.
    - Other Enterobacteriaceae
    - *Enterococcus* spp.
    - Beta-hemolytic streptococci including:
        - *Streptococcus agalactiae*
        - *Streptococcus pyogenes*
        - *Streptococcus bovis*
    - *Staphylococcus aureus*
    - *Staphylococcus saprophyticus*
    - *Acinetobacter* spp.

- *Corynebacterium urealyticum*

2. Not considered a pathogen:
    - *Lactobacillus* spp.
    - *Corynebacterium spp. (*EXCEPT *Corynebactrium urealyticum)*
    - *Propionibacterium* spp.
    - Viridans group streptococci, including:
        - *Streptococcus oralis*
        - *Streptococcus mitis*
        - *Streptococcus salivarius*
        - *Streptococcus parasanguinis*
        - *Streptococcus milleri*
        - *Streptococcus constellatus*
        - *Streptococcus intermedius*
        - *Streptococcus anginosus*
        - *Streptococcus gordonii*
        - *Streptococcus sanguis*
        - *Streptococcus sanguinis*
        - *Streptococcus sobrinus*
        - *Streptococcus vestibularis*
        - *Streptococcus oralis*
        - *Streptococcus salivarius*
        - *Streptococcus mutans*
3. The following organisms will be considered pathogens if grown from urine culture at ≥10^5 CFU/mL if obtained via a newly placed catheter or at ≥10^4 CFU/mL if obtained via suprapubic aspiration, new nephrostomy or cystoscopy. They will not be considered pathogens when grown from urine culture if obtained via midstream clean catch or a disinfected collection port. They will also not be considered pathogens when grown from blood cultures, unless simultaneously grown from urine culture at ≥10^5 CFU/mL if

obtained via a newly placed catheter or at ≥10^4 CFU/mL if obtained via suprapubic aspiration, new nephrostomy or cystoscopy:

- Coagulase negative staphylococci, including:
  - *Staphylococcus epidermidis*
  - *Staphylococcus hominis*
  - *Staphylococcus haemolyticus*
  - *Staphylococcus simulans*
  - *Staphylococcus capitis*
  - *Staphylococcus warneri*
- *Bacillus* spp. (other than *B. anthracis*)

4. The following organisms will be considered non-susceptible to eravacycline or comparator and will NOT be analyzed as pathogens:
   - *Pseudomonas* spp.
   - Yeast and fungi
5. Pathogens for MRC review: isolates will be reviewed in a blinded manner by the MRC on a case-by-case basis if none of rules 1 through 3 above apply.

If more than 1 suitable urine culture specimen is obtained prior to the first dose of study drug therapy, and the same pathogen is isolated, the one with the highest MIC to study drug will be utilized in all analyses and the highest colony count will be used. If pathogens have the same MIC to study drug, the pathogens will be considered equivalent and a representative isolate will be selected from among them based on the lowest central laboratory accession number and the highest colony count will be used.

3.1.5. Modified Microbiological Intent-to-Treat (Micro-MITT) Population

The micro-MITT population will consist of all subjects in the micro-ITT population who receive at least 1 dose of study drug. Analyses in this population will be presented in summary tables by the treatment arm to which the subject was randomized.

3.1.6. Clinically Evaluable (CE) Populations

Five CE populations will be defined: the CE-Day 5, CE-EOI, CE-EOT, CE-TOC and CE-FU. Subjects will be included in or excluded from the CE populations based on the criteria listed below:

1. Minimal Disease Criteria:

   Minimal disease is defined as meeting all of the following inclusion criteria:

   - Inclusion criterion 1: Male and female subjects with either:
     a. Pyelonephritis and normal urinary tract anatomy (approximately 50% of the total population), OR

b. cUTI with at least 1 of the following conditions associated with a risk for developing cUTI:

   i. Indwelling urinary catheter

   ii. Urinary retention (at least approximately 100 mL of residual urine after voiding)

   iii. History of neurogenic bladder

   iv. Partial obstructive uropathy (eg, nephrolithiasis, bladder stones, and ureteral strictures)

   v. Azotemia of renal origin (not Congestive Heart Failure (CHF) or volume related) such that the serum blood urea nitrogen (BUN) is elevated (> 20 mg/dL) AND the serum BUN: creatinine ratio is < 15

   vi. Surgically modified or abnormal urinary tract anatomy (eg, bladder diverticula, redundant urine collection system, etc) EXCEPT surgery within the last month (placing of stents or catheters is not considered to be surgical modification)

- Inclusion criterion 4: At least 2 of the following signs or symptoms:

  a. Chills, rigors, or warmth associated with fever (oral, rectal, tympanic, or by temporal artery temperature > 100.4°F / 38°C) or hypothermia (oral, rectal, tympanic, or by temporal artery temperature < 95°F / 35°C)

  b. Flank pain (pyelonephritis) or pelvic pain (cUTI)

  c. Nausea or vomiting

  d. Dysuria, urinary frequency, or urinary urgency

  e. Costo-vertebral angle tenderness on physical examination

- Inclusion criterion 5: Urine specimen with evidence of pyuria:

  a. Dipstick analysis positive for leukocyte esterase, OR

  b. ≥ 10 white blood cells per cubic millimeter, OR

  c. ≥ 10 white blood cells per high power field

2. Prior Antibiotic Therapy:

   Subjects who receive only a single dose of effective non-study antibiotics in the 72 hours prior to randomization can be enrolled in the study. Subjects who receive more than a single dose of effective non-study antibiotics in the 72 hours prior to randomization will be excluded from the CE populations.

3. Concomitant Antibiotic Therapy:

   Subjects who receive any systemic concomitant antibiotic therapy from the first dose of study drug through the Day 5 Visit (CE-Day 5 population), EOI Visit (CE-EOI population), EOT Visit (CE-EOT population), TOC Visit (CE-TOC population) and FU Visit (CE-FU population) that is potentially effective against the baseline pathogen will be excluded from the CE populations with the following exceptions:

   - The subject is a clinical failure at Day 5 (CE-Day 5 population), EOI (CE-EOI population), 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 an oral antibiotic with no systemic absorption

   Subjects who do not have a pathogen isolated at baseline and receive an antibiotic with expected activity against cUTI pathogens will also be excluded from the CE populations unless considered a failure by the Investigator at Day 5, EOI, EOT, TOC or FU and received non-study antibiotics for insufficient therapeutic effect of the study drug. Subjects who receive a systemic concomitant antibiotic that is not effective against the baseline pathogen, or if no pathogen is isolated and the antibiotic does not have activity against cUTI pathogens, will be included in the CE populations.

4. Study Drug Therapy:

   Subjects must meet all of the following to be included in the CE populations:

   - 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

5. Clinical Outcome Assessment:

   Subjects must meet the following to be included in the CE populations:

   - For the CE-Day 5 population:
     - Completed the Investigator's assessment of clinical response (ie, was not deemed an indeterminate outcome) at the Day 5 Visit
     - The Day 5 Visit occurred 4-6 days following randomization
   - For the CE-EOI population:
     - Completed the Investigator's assessment of clinical response (ie, was not deemed an indeterminate outcome) at the EOI Visit

- The EOI Visit occurred within 1 day of the last dose of IV study drug

- For the CE-EOT population:
  - 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 (IV or PO)
- For the CE-TOC population:
  - 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 13-18 days following randomization and at least 5 days following the last dose of study drug, unless the subject was considered to be a clinical failure based on the Investigator's assessment at the EOT Visit
- For the CE-FU population:
  - 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 Visits.
  - The FU Visit occurred 20-29 days following randomization, unless the subject was considered to be a clinical failure based on the Investigator's assessment at the EOT or TOC Visits.

6. Baseline or Inter-Current Medical Events:

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

   - Exclusion criterion 2: History of an ertapenem-resistant urinary tract infections within 1 year of consent
   - Exclusion criterion 3: Likely to require > 10 days of antibiotic treatment to cure the acute cUTI or likely to receive ongoing antibacterial drug prophylaxis prior to the FU visit (eg, subjects with vesiculo-ureteral reflux)
   - Exclusion criterion 6: Complicated pyelonephritis with complete obstruction or known or suspected renal or perinephric abscess, emphysematous pyelonephritis, OR Any condition likely to require surgery to achieve cure (this does NOT include procedure to place catheters or obtain diagnosis)
   - Exclusion 7: Known or suspected fungal infection
   - Exclusion 8: Uncomplicated lower urinary tract infection

- Exclusion 9: Suspected or confirmed active prostatitis, or currently under treatment for prostatitis
- Exclusion 10: Subjects with high risk for cUTI due to *Pseudomonas* sp. (eg, History of prior cUTIs due to *Pseudomonas*, ≥ 20 mg QD prednisone or equivalent steroid, and other risk factors as perceived by the investigator)

3.1.7. **Microbiologically Evaluable (ME) Populations**

The ME-Day 5, ME-EOI, ME-EOT, ME-TOC and ME-FU populations will consist of all subjects in the micro-ITT and the CE-Day5, CE-EOI, CE-EOT, CE-TOC, CE-FU populations, respectively who also meet the following:

- Had a suitable urine specimen (as defined in Section 3.1.4) collected at the Day 5 (ME-Day 5), EOI (CE-EOI), EOT (ME-EOT), TOC (ME-TOC) and FU (ME-FU) Visits. Subjects who are microbiological failures prior to the TOC or FU Visit, and are otherwise evaluable, will be included in the ME-TOC and ME-FU populations regardless of when the TOC and FU visits occurred.
- The urine culture at the Day 5 (ME-Day 5), EOI (ME-EOI), EOT (ME-EOT), TOC (ME-TOC) and FU (ME-FU) Visits is interpretable with respect to determining microbiological outcome. An interpretable urine culture is one that has a clearly identified pathogen or one where the baseline pathogen(s) can be excluded. A urine culture will be considered uninterpretable if more than 2 bacterial isolates are identified unless the specimen is obtained via suprapubic aspiration, nephrostomy tube newly placed or cystoscopy, 1 of the isolates comprises ≥80% of the total growth (predominant), 1 or more isolates are also isolated simultaneously from a blood culture, or there is <10^4 CFU/mL (including no growth) of the baseline pathogen(s).

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 to which s/he was randomized).

3.2.2. Process for Determining Inclusion in Analysis Populations

Inclusion into the ITT 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, CFU/mL, local and central genus and species identification. Inclusion into the ME and micro-MITT populations will be determined programmatically.

3.3. 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 major deviation in each category will be presented by treatment group for the ITT population. A major deviation is defined as one 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 eravacycline to ertapenem in the co-primary efficacy measures of responder outcome at the EOI and TOC visits in the micro-ITT population. An NI margin of 10% will be used which is based on historical data regarding the treatment effect of antibiotics. A 10% NI margin for the efficacy measure of responder outcome is robust and can sufficiently confirm a clinically meaningful treatment effect of eravacycline in the treatment of cUTI.

The sample size calculation is based on ensuring sufficient power for the co-primary efficacy outcomes for the FDA as well as the co-primary efficacy outcomes for the EMA (which are secondary efficacy outcomes for the FDA). Using a 10% NI margin, one-sided alpha of 0.025, 80% power, response rates at TOC of 71% in the eravacycline group and 72% in the ertapenem group, and the sample size methodology of Farrington and Manning, a total of 395 subjects per arm in the micro-ITT population is required. This sample size provides >90% power for the response rates at EOI assuming the response rates are 93% and 94% in the eravacycline and ertapenem groups, respectively. A sample size of approximately 1200 randomized subjects should provide sufficient numbers for this study, assuming 66% of enrolled subjects will meet the requirements for inclusion in the micro-ITT population.

For the EMA, it is assumed that 65% of the randomized subjects will be in the micro-MITT population and 60% in ME population. The microbiological success rates at TOC are assumed to be 79% and 82% in both treatment groups in the micro-MITT and ME populations, respectively. With these assumptions, using an NI margin of 10%, a one-sided alpha of 0.005, and the sample size methodology of Farrington and Manning, there is at least 80% power to show NI for the co-primary efficacy outcomes. The power calculations are summarized in Table 3 based on a total of 1200 randomized subjects.

Table 3 Assumptions of Sample Size Calculations

			Outcome Rates			
Outcome/Population	**Alpha level (one-sided)**	**Evaluability Rate**	**ERV**	**ERT**	**Total N**	**Power**
FDA Outcomes						
Responder at EOI/ micro-ITT	0.025	66%	93%	94%	790	>99%
Responder at TOC/ micro-ITT	0.025	66%	71%	72%	790	80.0%
EMA Outcomes						
Microbiological Success at	0.005	65%	79%	79%	780	79.8%

TOC / micro-MITT						
Microbiological Success at TOC / ME-TOC	0.005	60%	82%	82%	720	84.7%

Key: ERV = Eravacycline; ERT = Ertapenem; EMA = European Medicines Agency; FDA = Food and Drug Administration; ITT = Intent-to-Treat; ME = Microbiologically Evaluable; Micro-MITT = Modified Microbiological Intent-To-Treat; TOC = Test of Cure.

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.

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 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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 (ULN) 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. Values that are out of range will be marked as ‘H’ or ‘L.’

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 or higher, 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 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 cUTI 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 outcome measure of clinical response:
        - Subjects will be defined as an indeterminate if the Investigator cannot determine whether the subject is a clinical cure or failure. Outcome will be defined as missing if the Investigator did not complete the assessment,

or if the subject did not complete the study visit. For the purposes of analysis missing data will be considered indeterminate, and by definition, subjects with an indeterminate response are included in the denominator for analyses in the ITT, micro-ITT and micro-MITT analysis sets, and thus, are considered failures. Subjects with an indeterminate response are excluded from the CE and ME populations.

- For outcome measure of microbiologic response:
  - If no interpretable post-baseline specimen is available, the microbiological response is considered indeterminate. By definition, subjects with an indeterminate response are included in the denominator for analyses in the micro-ITT and micro-MITT populations and thus, are considered failures. Subjects with an indeterminate response are excluded from the ME populations.
- 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 800 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.

A blinded assessment of the overall (aggregated across treatment groups) responder rate (clinical cure and microbiological success) at the TOC visit will be conducted following the completion of approximately 800 subjects. If the overall blinded responder rate is less that the rate used in the sample size calculation for the eravacycline group (71%), the sample size will be increased as needed to ensure 80% power. The sample size will not be decreased if the overall blinded responder rate is greater than the rate used in the sample size calculation. No adjustment to the overall alpha level is required since the sample size adjustment is based on the overall (aggregated across treatment groups) responder rate.

A separate analysis plan will be developed for the interim analysis.

4.8. Visit Windows

Visits will be planned to occur during the visit windows defined in Table 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.

Table 4 Derived Analysis Visits for Efficacy and Safety Analyses

Visit	ITT, micro-ITT, and micro-MITT Efficacy Analysis Window[1]	CE and ME Efficacy Analysis Window	Safety Analysis Window[2]
Day 5	N/A	4-6 Days after Randomization	4-6 Days after Randomization
EOI	N/A	Within 1 day of last dose of IV study drug	Within 1 day of last IV dose of study drug
EOT	N/A	Within 1 day of last dose of study drug (IV or PO)	Within 1 day of last dose of study drug (IV or PO)
TOC	N/A	13 – 18 Days after Randomization & >=5 Days after last dose	14-17 Days after Randomization & >=5 Days after last dose
FU	N/A	20-29 Days after Randomization	21-28 Days after Randomization

Key: EOI = End of IV; EOT = End of Treatment; FU = Follow-up; ITT = Intent-to-Treat; MITT = Modified Intent to Treat
IV = Intravenous; N/A = Not Applicable; PO = Per Oral; TOC = Test of Cure.

1. For ITT, micro-ITT, and micro-MITT 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, micro-MITT, CE-Day 5, CE-EOI, CE-EOT, CE-TOC, CE-FU, ME-Day 5, ME-EOI, ME-EOT, ME-TOC, ME-FU) will be summarized by treatment group, geographic region and country. Regions are as follows: European Union (Austria, Bulgaria, Estonia, Hungary, Latvia, Poland, Romania, Slovakia), Non-European Union Europe (Republic of Moldova, Russia, and Ukraine, Georgia), and North America (United States). Tables 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, micro-ITT, micro-MITT and ME-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, micro-ITT, micro-MITT and ME-TOC populations. A table will present the subject demographics (eg, gender, age, ethnicity and race) and baseline characteristics (height, weight, BMI, and creatinine clearance) 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). Creatinine Clearance will be summarized as both a continuous and categorical (<15ml/min, 15 - <60ml/min, >=60, >=130ml/min) 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 ITT and micro-ITT populations. Subjects reporting the same SOC or preferred term more than once will be counted only once for that SOC and preferred term.

The primary site of infection at baseline (pyelonephritis and normal urinary tract anatomy, cUTI with indwelling urinary catheter, urinary retention, neurogenic bladder, partial obstructive uropathy, with azotemia of renal origin or with surgically modified/abnormal urinary tract anatomy, or other diagnosis) will be summarized by treatment group for the micro-ITT, micro-MITT and ME-TOC populations.

Signs and symptoms related to the cUTI (chills rigors, fever, hypothermia, flank pain, pelvic pain, nausea, vomiting, dysuria, urinary frequency, urinary, urgency, cost-vertebral angle

tenderness) will be summarized as none, mild, moderate or severe at baseline by treatment group for the micro-ITT, micro-MITT and ME-TOC populations. Descriptive statistics (mean, SD, median, minimum and maximum value) for baseline temperature (highest daily temperature) will also be presented by treatment group.

5.4. Baseline Microbiology

The microbiological assessment of the baseline blood and urine specimens will be summarized by treatment group for the micro-ITT, micro-MITT and ME-TOC populations. The number and percentage of subjects with a suitable urine specimen obtained, the number of isolates obtained and whether or not the culture was interpretable will be summarized by treatment group. The distribution of the urine collection methods will also be presented.

The pathogenic organisms identified from the baseline blood culture or urine culture specimens 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, micro-MITT and ME-TOC populations overall and by primary site of infection (pyelonephritis and normal urinary tract anatomy vs. all other diagnoses). The same pathogen identified from both the blood and the urine 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, micro-MITT and ME-TOC populations. The number and percentage of subjects with levofloxacin resistant and ertapenem resistant organisms will also be presented. 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 urine culture.

Several tables providing the frequency distribution of the minimum inhibitory concentrations (MIC) by pathogen as reported by the central laboratory will be provided for the micro-ITT, micro-MITT and ME-TOC populations:

- The MIC distribution to eravacycline of the baseline pathogens.
- The MIC distribution to ertapenem of the baseline pathogens.
- The MIC distribution to levofloxacin 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, MIC50 and MIC90) for baseline pathogens to the study drug received. Range will be reported for all pathogens, MIC50 and MIC90 will only be reported for those pathogens with at least 10 isolates in either treatment group.

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 effective in cUTI taken prior to the first dose of study drug (micro-ITT, micro-MITT and ME-TOC populations)
- Systemic antibacterial medications (excluding study drug) taken between first dose of study drug and the TOC visit (micro-ITT, micro-MITT and ME-TOC populations)
- Non-antibacterial medications prior to the first dose of study drug (ITT and Safety 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 (IV and oral) will be characterized by the total duration of treatment (IV and oral), duration of IV treatment, the number of infusion days, the number of active doses (IV only), total IV dose received, the average daily dose over all infusion days, duration of PO treatment, and the number of PO days. Descriptive statistics for each measure of exposure to study drug will be summarized by treatment group for Safety, micro-ITT, and micro-MITT 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). Total duration of treatment (IV and PO), Duration of IV treatment and Duration of PO treatment will be calculated separately.

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.

Number of PO days would be calculated as:

Number of PO days = [Duration of PO days – Number of days dose was missed]

Study drug (IV only) is administered in mg/kg for the eravacycline arm and in g for the ertapenem 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) = 1.5 * weight (kg) * (total volume of drug administered for dose) / (total volume of drug prepared for dose)

For ertapenem:

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

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 1.5 mg/kg.

The average daily dose of ertapenem, 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 (IV and oral) 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. 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 Safety, micro-ITT, micro-MITT and ME 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 outcome measure is a responder outcome derived from both clinical response and microbiological response at the EOI and the TOC Visit in the micro-ITT population.

<u>Clinical Response:</u>

Clinical response is based on the Investigator Responses on the CRF and is not derived programatically. Clinical response is classified by the Investigator as cure, failure or indeterminate based on the following definitions:

- Clinical Cure: Clinical cure is defined as complete resolution or significant improvement of signs and symptoms of the infection such that no rescue/non-study antibacterial therapy is required to treat the cUTI that presented at study entry

- Clinical Failure: Subjects are classified as a clinical failure based on:
    - Death related to cUTI at any time point
    - Persistence of clinical symptoms of cUTI or new symptoms have developed
    - Initiation of rescue/non-study antibacterial drug therapy for cUTI
- Indeterminate/Missing: If the subject's outcome is neither clinical cure nor clinical failure, then the outcome should be listed as indeterminate/missing, including death where the cUTI is clearly noncontributory. If the Investigator did not complete an assessment or if the subject did not complete the study visit, the outcome is considered missing

Subjects who are assessed as a clinical failure at the EOT visit or beyond will have the failure carried forward to all subsequent visits.

Data for all subjects will be reviewed to ensure the Investigators are following the protocol defined criteria for clinical response and queries will be issued as needed to clarify any response that does not meet the protocol definition.

Microbiologic Response:

Per-subject microbiological response is defined as follows:

- Microbiological success:
    - Reduction of the baseline pathogen(s) to <10^4 CFU/mL
- Microbiological failure:
    - Blood cultures are positive for the baseline pathogen(s), or
    - Urine culture grows ≥10^4 CFU/mL of the baseline pathogen(s)
- Microbiological Indeterminate/Missing: No interpretable urine culture data are available

The primary efficacy outcome is defined in Table 5.

Table 5 Primary Efficacy Outcome

Primary Efficacy Outcome		
Clinical Response	**Microbiological Response**	**Responder Outcome**
Cure	Success	Responder
Cure	Failure	Non-responder
Cure	Indeterminate / Missing	Indeterminate
Failure	Success	Non-responder
Failure	Failure	Non-responder
Failure	Indeterminate / Missing	Non-responder
Indeterminate / Missing	Success	Indeterminate
Indeterminate / Missing	Failure	Non-responder
Indeterminate / Missing	Indeterminate / Missing	Indeterminate

For the micro-ITT population, the proportion of micro-ITT subjects with a response is defined using the following formula (where the denominator adds to the total number of subjects in the micro-ITT population):

$$\frac{\text{Number of subjects with response}}{\text{(Number of subjects with a response + Number of subjects with a non-response + Number of subjects with an indeterminate response)}}$$

The primary efficacy analyses will be based on the micro-ITT population. The NI test will be a one-sided hypothesis test performed at the 2.5% level of significance. This NI test will be based on the lower limit of the two-sided 95% confidence interval (CI) for both EOI and TOC Visits. The primary efficacy outcome is the percentage of subjects with an outcome of responder (clinical cure and microbiological success) at the EOI and TOC Visits. The primary analysis is unadjusted.

The number and percentage of subjects in each treatment group defined as a responder, non-responder and indeterminate/missing will be tabulated. 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 p1 is the responder rate in the eravacycline treatment group, p2 is the responder rate in the ertapenem treatment group, and Δ is the NI margin of 10%. Note: For H_0, outcomes at both EOI and TOC visits will be considered. For H_1, outcomes at EOI or TOC visits will be considered.

To test the null hypothesis, two-sided 95% CIs for the observed difference in responder rates (eravacycline treatment group minus ertapenem treatment group) will be calculated for the micro-ITT population for the EOI and TOC Visits. If the lower limit of both (EOI and TOC Visits) 95% CIs for the difference in responder rates in the micro-ITT analysis set exceeds –10%, then the null hypothesis will be rejected and the NI of eravacycline to ertapenem will be declared.

The two-sided 95% CIs for NI testing based on the difference of responder rates at the EOI and TOC Visits, will be computed using the method proposed without stratification by Miettinen and Nurminen (Miettinen 1985). For notation purposes, assume 1 represents the eravacycline group (Group 1) and 2 represents the ertapenem 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 average proportion in the eravacycline group (Group 1), $\hat{p}_2$ is the observed average proportion in the ertapenem 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 ertapenem group (Group 2), and $\tilde{p}_1$ and $\tilde{p}_2$ are the maximum likelihood estimators for the responder rates in the eravacycline and ertapenem 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 non-inferior to ertapenem, superiority of eravacycline to ertapenem will be assessed. A step-wise analysis will be conducted in which superiority at TOC will be tested first. If the lower bound of the 2-sided 95% CI is greater than 0, superiority of eravacycline for response (clinical cure and microbiological success) at the TOC visit will be concluded and superiority at EOI will be tested. If the lower bound of the 2-sided 95% CI is greater than 0, superiority of eravacycline for response (clinical cure and microbiological success) at the EOI visit will be concluded. If superiority is not concluded at the TOC visit, superiority at the EOI visit will not be tested.

The reasons for non-response and for an indeterminate response at the EOI and TOC visits will be summarized by treatment group for the micro-ITT population. The primary efficacy outcome will also be assessed separately across the randomization stratification factors of primary site of infection and receipt of a single dose of effective non-study antibiotics. For each infection site stratum and each antibiotic stratum, a 2-sided 95% CI for the observed difference in the responder rate at the EOI and TOC visits will be calculated for the micro-ITT population using the same method as for the primary efficacy analysis. 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 response rate at the EOI and TOC visits 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 and receipt of a single dose of effective non-study antibiotics). A 2-sided stratified 95% CI will be computed for the difference in responder rate at the EOI and TOC visits between the eravacycline and ertapenem treatment groups using the method of Miettinen and Nurminen (9). 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 ertapenem 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 responders. Additional sensitivity analyses will be stratified analyses for the following combinations: primary site of infection and geographic region, primary site of infection and receipt of a single dose of effective non-study antibiotics, and geographic region and receipt of a single dose of effective non-study antibiotics. Two-sided 95% CIs will be computed for the difference in responder rate at the EOI and TOC visits between the eravacycline and ertapenem treatment groups within each stratum using the method of Miettinen and Nurminen.

5.7.2. Secondary Efficacy Analyses

Responder outcome will also be analyzed at the Day 5 visit. A 2-sided 95% CI for the observed difference in the responder rate at the Day 5 visit will be calculated for the micro-ITT population using the same method as for the primary efficacy analysis.

The number and percentage of subjects in each treatment group with an outcome 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:

- Day 5 - ITT, CE-Day 5, micro-ITT, micro-MITT, ME-Day 5 populations
- EOI Visit - ITT, CE-EOI, micro-ITT, micro-MITT, ME-EOI populations
- EOT Visit – ITT, CE-EOT, micro-ITT, micro-MITT, ME-EOT populations
- TOC Visit – ITT, CE-TOC, micro-ITT, micro-MITT, ME-TOC populations
- FU Visit – ITT, CE-FU, micro-ITT, micro-MITT, ME-FU populations

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 infection site and receipt of a single dose of effective non-study antibiotics in the ITT and CE-TOC populations.

Per-subject microbiological response will be summarized as success, failure and indeterminate at the Day5, EOI, EOT, TOC and FU visits in the micro-ITT, micro-MITT and ME populations. Two-sided 95% unadjusted CIs will be constructed for the observed difference in the success rates between the treatment groups for descriptive purposes; no conclusion of NI will be made.

Time to resolution of signs and symptoms is defined as the number of days from the start of study treatment to the visit where all signs and symptoms are reported as absent or have at least a 2-grade decrease in severity (chills, rigor or warmth associated with fever or hypothermia, flank or pelvic pain, nausea or vomiting, dysuria, urinary frequency or urinary urgency, costo-vertebral angle tenderness on physical examination). Subjects who discontinue the study prior to having all signs and symptoms resolved will be censored at the last evaluation at which sign and symptoms were assessed.

Time to resolution of signs and symptoms will be analyzed using Kaplan-Meier methods in the micro-ITT population. The median, 25th and 75th percentile will be presented by treatment group and Kaplan-Meier curve will be presented by treatment group.

5.7.3. Additional Efficacy Analyses

5.7.3.1. Intravenous Only Responder Outcome

Responder outcome will be analyzed at the EOT, TOC and FU visits in the micro-ITT population among subjects who only received IV study drug and did not transition to PO study drug for any reason (including treatment failures who did not receive PO study drug). The analysis will be conducted using the same methods as the primary efficacy analysis.

5.7.3.2. Responder Outcome in Subjects with and without Levofloxacin-Resistant Baseline Pathogens

Responder outcome will be analyzed at the EOI and TOC visits in subjects with levofloxacin-resistant baseline pathogens. A 2-sided 95% CI for the observed difference in the responder rate at the EOI and TOC visits will be calculated for the micro-ITT population using the same method as for the primary efficacy analysis.

5.7.3.3. Responder Outcome in Subjects with and without Ertapenem-Resistant Baseline Pathogens

Responder outcome will be analyzed at the EOI and TOC visits in subjects with ertapenem-resistant baseline pathogens. A 2-sided 95% CI for the observed difference in the responder rate at the EOI and TOC visits will be calculated for the micro-ITT population using the same method as for the primary efficacy analysis.

5.7.3.4. Clinical Outcome Measures

A summary (number and percentage of subjects) of the shift from baseline to each visit (Day 5, EOI, EOT, TOC and FU Visits) in the signs and symptoms of cUTI will be presented by treatment group for the micro-ITT population.

5.7.3.5. Microbiological Outcomes

Microbiologic response by baseline pathogen will be determined as the proportion of subjects with a microbiological success at the EOI (micro-ITT and ME-EOI populations) and TOC (micro-ITT and ME-TOC populations) visits for each pathogen isolated at baseline. Microbiologic response for levofloxacin resistant and ertapenem resistant baseline pathogens will also be presented.

For subjects with baseline pathogens obtained from blood culture (ie, for bacteremic subjects), microbiologic success by baseline pathogen will also be summarized separately for the micro-ITT population.

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 for each pathogen.

Per-pathogen microbiological success 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 urine 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 urine 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 continued presence of the baseline pathogen at ≥10^4 CFU/mL with 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 Table 6), 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 6. Clinical laboratory values will be expressed in System International (SI) units. Box plots showing the minimum, maximum, and quartile values will be presented for all visits by treatment group.

Table 6 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

Key: ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; GGT = Gamma-Glutamyl Transferase; LDH = Lactate Dehydrogenase.

Baseline is defined as the value closest to but prior to the start of study drug administration. Analyses will utilize assessments occurring during safety analysis windows (see Table 2). Thus, if a subject has a visit outside the window, for example, a TOC visit on Day 11, 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 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 Day 5, EOI, 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 Division of Microbiology and Infectious Diseases (DMID) criteria in Table 7. 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 7 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	≤80%	>80%-90%	>90-95%	>95%	--

Key: WBC = White Blood Cell Count.

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

Key: BUN = Blood Urea Nitrogen; ULN = Upper Limit of Normal.

* 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

Key: ALT (SGPT) = Alanine Aminotransferase (Serum Glutamic Pyruvic Transaminase); AST (SGOT) = Aspartate Aminotransferase (Serum Glutamic Oxaloacetic Transaminase); GGT = Gamma-Glutamyl Transferase; ULN = Upper Limit of Normal.

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

Key: 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 table 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 table 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.

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

A summary of abnormal values, identified by the threshold levels provided in Table 8 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 8 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	-

Key: CTCAE = Common Terminology Criteria for Adverse Events, Version 4.0

Detailed patient listings of all vital signs results will be provided.

6. CHANGES TO PLANNED ANALYSES

This is Version 1.0 of the SAP.

7. REFERENCES

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