CLINICAL TRIAL PROTOCOL

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 No.: **TP-434-025**

Sponsor: **Tetraphase Pharmaceuticals, Inc.**
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EudraCT No.: **2016-002208-21**

ClinicalTrials.gov No.: **NCT02784704**

Version 2.0: **20 March 2017**

This study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki, and applicable regulatory requirements.

1. SPONSOR SIGNATURE PAGE

Sponsor:	Tetraphase Pharmaceuticals, Inc.
Protocol Number:	TP-434-025
Study Medication:	Eravacycline
Protocol Title:	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
Date of Issue:	**20 March 2017**

Approved by:

.....	.....
Date	Guy Macdonald Chief Executive Officer Tetraphase Pharmaceuticals, Inc. 480 Arsenal Street, Suite 110 Watertown, MA 02472 USA
.....	.....
Date	Patrick T. Horn MD, PhD Chief Medical Officer Tetraphase Pharmaceuticals, Inc. 480 Arsenal Street, Suite 110 Watertown, MA 02472 USA

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated. This trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable United States federal regulations and International Conference on Harmonization (ICH) guidelines.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.

I will use only the informed consent form approved by the Sponsor or its representative and will fulfill all responsibilities for submitting pertinent information to the Institutional Review Board/Independent Ethics Committee (IRB/IEC) responsible for this study.

I agree that the Sponsor or its representatives shall have access to any source documents from which case report form information may have been generated. I agree that regulatory authorities (FDA, EMA, and other local and country-related agencies) can audit and review source documents.

I further agree not to originate or use the name of Tetraphase Pharmaceuticals, Inc.or any of its employees, in any publicity, news release, or other public announcement, written or oral, whether to the public, press, or otherwise, relating to his protocol, to any amendment hereto, or to the performance hereunder, without the prior written consent of Tetraphase Pharmaceuticals, Inc.

_____ _____

Investigator's Signature Date

_____

Name of Investigator (Typed or Printed)

_____

Institution Name

_____

Institution Address

2. TABULATED PROTOCOL SUMMARY

Name of Sponsor/Company:	Tetraphase Pharmaceuticals, Inc.
Name of Finished Products:	Eravacycline for intravenous administration; and meropenem (comparator)
Name of Active Ingredients:	Eravacycline (TP-434) and meropenem (comparator)
Title of Study:	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
Indication:	Complicated Intra-abdominal Infections (cIAI)
Anticipated Study Period:	3Q 2016-4Q 2017

Objectives:

Primary Objective:

- The primary objective 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
  NOTE: For the EMA, the primary analysis populations will be the all-treated (MITT) and the clinically evaluable (CE) populations

Secondary Objectives:

- 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)
  - Clinically evaluable (CE) population
  - Micro-ITT population (for EOT and FU)
  - Microbiologically evaluable (ME) population
- To compare the microbiologic response in the treatment arms at the EOT and TOC visits in the following populations:
  - Micro-ITT population
  - ME population
- To assess the safety and tolerability of eravacycline administration in the safety population
- To explore pharmacokinetic (PK) parameters of eravacycline

Methodology:

This is a phase 3, randomized, double-blind, double-dummy, multicenter, prospective study to assess the efficacy, safety and PK of eravacycline compared with meropenem in the treatment of cIAIs.

Once an informed consent is obtained and study eligibility is established, subjects will be enrolled and randomized to either the eravacycline (1.0 mg/kg every 12 hours [q12h]) or the meropenem (1 g q8h) treatment arm in a 1:1 ratio. Randomization will be stratified based on primary site of infection (complicated appendicitis versus all other diagnoses). An enrollment cap of approximately 50% complicated appendicitis is planned.

Specified study personnel will remain blinded to the identity of intravenous (IV) study drug until the database has been locked.

Study drug will be administered in 24-h dosing cycles according to Table 1 below:

Table 1: Study Drug Infusion Scheme of a 24-h 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, 1 g q8h	Placebo	Meropenem	Meropenem	Placebo	Meropenem

Eravacycline concentration may be decreased (as long as the total infusion volume is ≤ 500 mL) and/or infusion time may be increased (to 120 minutes per IV bag) to manage infusion site reactions.

Meropenem will be used in accordance with its most recent prescribing information.

The interval between the 1st Doses of adjacent 24-h dosing cycles can be reduced by up to 4 h after each of the first two 24-h dosing cycles. After the third 24-h dosing cycle, the allowable administration window for each infusion is ± 1 h.

The investigator should collect appropriate specimens for culture at the time of the initial procedure and inoculate into appropriate media for aerobes and anaerobes immediately. These specimens will be cultured and quantified in the local laboratory or a reference regional laboratory. The isolate(s) will be sent to a central microbiology laboratory for validation of identification and susceptibility testing.

Aerobic and anaerobic blood cultures will be obtained at two separate sterile venipuncture sites prior to initiation of clinical trial drug therapy. Upon knowledge of a positive culture for a pathogen, blood cultures should be repeated until sterile (ie, both sets of cultures from two separate venipuncture sites are negative for pathogens) through the FU visit. 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).

Each subject will receive 4-14 complete dose cycles of study drug. A complete dose cycle is defined as all five doses for a dosing cycle. Clinical status will be assessed at EOT. A TOC visit will occur 25-31 days after the initial dose of study drug and a FU visit will take place 38-50 days after the initial dose of study drug. At any time, the investigator may discontinue the subject from study drug based on the best interest of the subject. Prior to starting non-study antibiotics the EOT assessments must be performed. The subject will remain in the study and all applicable procedures should be followed though FU.

Table 2: Timeline for Individual Study Subjects

SCREENING Within 48-h of Initial Dose	ENROLLMENT	STUDY DRUG TREATMENT Dose Cycle 1 through EOT	END-OF-THERAPY (EOT) Within 24-h of Last Dose	TEST-OF-CURE (TOC) 25-31 Days after Initial Dose	FOLLOW-UP (FU) 38-50 Days after Initial Dose
Establish diagnosis of complicated intra-abdominal infections (cIAI) Verify eligibility for enrollment	Use IWRS* to randomize to study drug	Infuse study drug, either: • Eravacycline IV 1.0 mg/kg q12h ***OR*** • Meropenem IV 1 g q8h Expected 4 (min) to 14 (max) study drug treatment 24-h dosing cycles.	Review of subjects with Medical Monitor for therapies longer than seven 24-h dosing cycles. EOT assessments should be performed at premature withdrawal or treatment failure and within 24-h of last dose.	Return to study center for assessment of clinical response and safety	Return to study center for assessment of clinical response and safety

* IWRS = Interactive Web-based Response System

Number of Subjects:

Approximately 466 subjects will be randomized to receive study drug.

Investigative sites will be recruited in approximately 75 centers worldwide.

Criteria for Study Entry:

Inclusion Criteria

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

e. Cholecystitis with perforation or abscess
f. 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.

2. At least 18 years of age
3. Evidence of a systemic inflammatory response with at least one of the following:
   a. Fever (oral, rectal, tympanic, or by temporal artery temperature > 100.4˚F / 38˚C) or hypothermia (temperature ≤ 95.9˚F / 35.5˚C)
   b. Elevated WBC (> Upper Limit of Normal (ULN) laboratory range); or proportion of band forms of the WBC differential beyond the ULN laboratory range
   c. Increased pulse (HR > 90 beats per minute)
   d. Increased respiratory rate (> 20 breaths per minute)
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 back or hip, or localized or diffuse abdominal wall rigidity, or mass, or ileus
5. Able to provide informed consent
6. Subjects must agree to use a highly reliable method of birth control
   a. Male subjects must agree to use an effective barrier method of contraception during the study and for 14 days following the last dose if sexually active with a female of childbearing potential
   b. Female subjects must not be pregnant or nursing. For females of childbearing potential, subjects must commit to either:
      i. Use at least two medically accepted, effective methods of birth control (eg, condom, spermicidal gel, oral contraceptive, indwelling intrauterine device, hormonal implant/patch, injections, approved cervical ring, etc.) during study drug dosing and for 14 days following last study drug dose, ***OR***
      ii. Sexual abstinence

And either

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-h

Or

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 in which all communications between the gastrointestinal (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 one dose of effective antibacterial drug therapy post-operatively before randomization

Exclusion Criteria (Subjects must **NOT** meet any of the following exclusion criteria)

1. Considered unlikely to survive the 6-8 week study period
   - Any rapidly-progressing disease or immediately life-threatening illness, including acute hepatic failure, respiratory failure and septic shock
   - Requirement for vasopressors (prior to enrollment) at therapeutic dosages (ie, dopamine > 5 µg/kg/min, any dose of norepinephrine, epinephrine, or phenylephrine) to maintain a systolic blood pressure ≥ 90 mm Hg or a mean arterial pressure ≥ 70 mm Hg following adequate fluid resuscitation
2. Creatinine clearance of ≤ 50 mL/min as estimated by the Cockcroft-Gault equation

$$eC_{Cr}[mL/min] = \frac{(140 - Age\ [yrs])\ \times\ Body\ Weight\ [kg]\ \times\ [0.85\ if\ Female]}{72\ \times\ Serum\ Creatinine\ [mg/dL]}$$

3. Presence or possible signs of significant hepatic disease:
   a. Alanine aminotransferase or aspartate aminotransferase > 5 x ULN, ***OR***
   b. Total bilirubin > 3 x ULN, unless isolated hyperbilirubinemia is directly related to the acute process
4. Immunocompromised condition, including known HIV positivity (requiring anti-retroviral therapy or with CD4 count < 300), AIDS, organ (bone marrow) transplant recipients, and hematological malignancy.

Immunosuppressive therapy, including use of high-dose corticosteroids (eg, > 20 mg prednisone or equivalent per day for greater than 2 weeks)

5. History of moderate or severe hypersensitivity reactions to tetracyclines, carbapenems, β-lactam antibiotics, or to any of the excipients contained in the study drug formulations
6. Participation in any investigational drug or device study within 30 days prior to study entry
7. Known or suspected current central nervous system (CNS) disorder that may predispose to seizures or lower seizure threshold (eg, severe cerebral arteriosclerosis, epilepsy)
8. Antibiotic-related exclusions:
   a. 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 persistent fever and/or clinical symptoms; or the development of a new intra-abdominal abscess after ≥ 72-h of antibiotic therapy], ***OR***
   b. Receipt of meropenem or any other carbapenem, or tigecycline for the current infection, ***OR***
   c. Need for concomitant systemic antimicrobial agents effective in cIAI other than study drug
9. Refusal of mechanical ventilation, dialysis or hemofiltration, cardioversion or any other resuscitative measures and drug/fluid therapy at time of consent
10. Known or suspected inflammatory bowel disease or associated visceral abscess
11. The anticipated need for systemic antibiotics for a duration of more than 14 days
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
13. Known at study entry to have cIAI caused by a pathogen(s) resistant to one of the study drugs
14. Any other unstable or clinically significant concurrent medical condition (ie, class IV heart or lung disease, end stage renal disease, or requiring hemodialysis, etc.) that would, in the opinion of the investigator, jeopardize the safety of a subject, impact their expected survival through the end of the study participation, and/or impact their ability to comply with the protocol

Test Product, Dose and Route of Administration:

Eravacycline was synthesized under current good manufacturing practices, and the drug product contains 50.0 mg (TP-434 free base equivalents) of lyophilized powder in a 10 mL vial. Eravacycline will be reconstituted with 5 mL of sterile water and further diluted with sterile normal saline, to generate 0.3 mg/mL eravacycline solutions for 1.0 mg/kg q12h IV infusions. Please refer to applicable protocol section(s) and the Pharmacy Manual for additional information.

Reference Therapy, Dose and Route of Administration:

Meropenem 1 g administered by IV q8h. Meropenem infusion solutions will be prepared according to the full prescribing information of meropenem (comparator).

Duration of Treatment:

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. Subjects will remain on study drug treatment until symptoms of cIAI have resolved. If study drug is needed for longer than seven 24-h dosing cycles, cases will be reviewed by the Medical Monitor. The TOC visit will be 25-31 days after the initial dose of study drug. The follow-up visit will be conducted 38-50 days after the initial dose of study drug.

Pharmacokinetics:

C_{max}, T_{max}, and AUC_{0-12} will be determined.

Statistical Methods and Criteria for Evaluation:

Sample Size Estimate:

This study is designed to demonstrate non-inferiority of 1.0 mg/kg q12h eravacycline to meropenem, and a 12.5% non-inferiority margin will be used to determine success. A non-inferiority trial with a one-sided alpha of 0.025, 80% power, a non-inferiority margin (delta) of 12.5%, and projected response rates of 84% in the eravacycline group and 85% in the meropenem group would need 161 subjects per arm in the micro-ITT population. A sample size of approximately 466 randomized subjects should provide sufficient numbers for this study, assuming 68.75% of enrolled subjects will meet the requirements for inclusion in the micro-ITT population.

Safety:

Safety analyses will be conducted in the safety population. Subjects will be analyzed according to the treatment received.

Adverse Events

Verbatim descriptions of AEs will be mapped to Preferred Terms and System Organ Classes using Medical Dictionary of Regulatory Activities (MedDRA) and tabulated by treatment arm. The number and percentage of subjects who experience treatment-emergent AEs and serious AEs (SAEs) will be presented by reporting levels for System Organ Class and Preferred Term. Each subject will be counted once for each level of reporting. Tabulations by severity and by relationship to study drug, as reported by the investigators, will also be provided. Deaths and premature discontinuations from study drug due to an AE will be identified.

Laboratory Data

Hematology, chemistry, and coagulation will be summarized using: shift tables based on toxicity criteria; change from baseline; and the number and percentage of subjects with at least a two grade increase from baseline. Detailed listings of all laboratory data collected during the study will be provided.

Other Safety Data

Clinically relevant physical examinations will be performed and clinically significant findings collected as AEs. Vital signs and ECG findings will be summarized using descriptive statistics for change from baseline and percentage of subjects with an abnormal value as defined in the Statistical Analysis Plan.

Efficacy Assessments:

Clinical cure rates will be determined along with 95% CIs for each treatment arm overall and for the randomization stratification factor of primary site of infection. The clinical cure rate will be determined as the number of subjects with Clinical Cure (ie, complete or significant improvement of signs or symptoms such that no additional antibacterial therapy, surgical, or radiological intervention is required) at the respective visit divided by the number of subjects in the analysis population (ie, overall or by randomization strata). A 95% CI around the difference in the eravacycline and meropenem clinical cure rates will be determined using the Miettinen and Nurminen method. If the lower bound of the 95% CI is above -12.5% for the difference in the overall clinical cure rate, noninferiority of eravacycline to meropenem will be concluded.

Per pathogen and per subject microbiological response rates will be determined, along with 95% CIs, by treatment arm. The per pathogen microbiological response rate will be determined as the number of subjects with a favorable response (ie, eradication or presumptive eradication) at the respective visit divided by the number of subjects in the analysis population with that pathogen at baseline. The per subject microbiological response rate will be determined as the number of subjects with a favorable response (ie, eradication or presumptive eradication) at the respective visit divided by the number of subjects in the analysis population.

Microbiology:

Bacterial isolates cultured from aerobic and anaerobic cIAI specimens and blood will be evaluated for susceptibility and the emergence of resistance to study drugs and overgrowth of non-susceptible organisms.

3. SCHEDULE OF ASSESSMENTS

The calendar day on which the first study drug infusion of the first 24-h dosing cycle is administered is Day 1.

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 38-50 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 *as indicated per protocol* →						
Intra-abdominal Cultures[13]	X			X	X	X	X[2]	X	X
Radiologic Examination[14]	X		← X *as clinically indicated* →						
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						

See footnotes on following page(s).

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 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 two 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 two 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 for schedule of PK assessments.
17. Coagulation only. Urinalysis does not need to be performed at the TOC and FU visits.

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LIST OF TABLES AND FIGURES

4. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine aminotransferase
APACHE	Acute Physiology and Chronic Health Evaluation
APS	Acute Physiology Score
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{0-12}	Area under the plasma concentration-time curve from time zero to time 12-h
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to time 24-h
AUC_{0-inf}	Area under the plasma concentration-time curve from time zero to time infinity
$AUC_{0-tau(ss)}$	Area under the plasma concentration-time curve from time zero to time tau over a dosing interval at steady state, where tau is the length of the dosing interval
B/P	Blood pressure
°C	Celsius
CD4	Cluster of differentiation 4: a glycoprotein that is found primarily on the surface of helper T cells
CE	Clinically evaluable
CI	Confidence interval
cIAI	Complicated intra-abdominal infection
CK	Creatine kinase
CL	Clearance
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
Conc	Concentration
CRA	Clinical research associates
CRF	Case report form
CRO	Contract Research Organization
CV	Coefficient of variation, Cardiovascular
CT	Computed tomography
DG	Dose group
dL	Deciliter
ECG	Electrocardiogram
eCRF	Electronic case report form
eg	For example
EMA	European Medicines Agency
EOT	End of Therapy
ESβL	Extended-spectrum β-lactamase(s)
°F	Farenheight
FDA	Food and Drug Administration
FU	Follow-up
g	Gram
GI	Gastrointestinal tract
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
GMP	Good manufacturing practices
GOT	Glutamyl oxaloacetic transaminase
h	Hour(s)
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IAI	Intra-abdominal Infection
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDSA	The Infectious Diseases Society of America
ie	In other words
IEC	Independent Ethics Committee
MITT	Modified intent-to-treat

IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive web-based response system
kg	Kilogram
L	Liter
LAR	Legally Authorized Representative
LDH	Lactic dehydrogenase
MAD	Multiple ascending dose
Max	Maximum
MCH	Mean cell hemoglobin
MCHC	Mean cell hemoglobin concentration
MCV	Mean cell volume
ME	Microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
µmol	Micromolar
mg	Milligram
MIC	Minimum inhibitory concentration
MIC_{90}	MIC of at least 90% of clinical isolates tested
mL	Milliliter
mm Hg	Millimeter of mercury
Min	Minutes, Minimum
Micro-ITT	Microbiological Intent-to-Treat Population
mMITT	Microbiologic modified-intent-to-treat
MRI	Magnetic resonance imaging
N	Number in a group
N/A	Not applicable
ng	Nanogram
PD	Pharmacodynamic
PHI	Protected health information
PK	Pharmacokinetics
qXh	Every X hours
RBC	Erythrocyte count
RR	Respiration Rate
SAD	Single ascending dose
SAE	Serious adverse event
SOA	Schedule of Assessments
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Elimination half-life
TBD	To be determined
T_{max}	Time to C_{max}
TOC	Test-of-cure
ULN	Upper limit of normal
U.S.	United States
λz	Elimination rate constant
WBC	White blood cell (count)
WHODrug	World Health Organization Drug Dictionary
0.9% NaCl	Normal saline

5. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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6. BACKGROUND AND RATIONALE

6.1 Intra-abdominal Infections

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].

6.2 Properties of Eravacycline

Eravacycline is a novel, synthetic, broad-spectrum fluorocycline antibiotic of the tetracycline class. The mechanism of action behind the antibiotic property of eravacycline is related to its ability to bind to the bacterial 30S ribosomal subunit and inhibit protein synthesis [3]. Eravacycline is more potent than legacy tetracyclines and is highly active against clinically important MDR Gram-negative and Gram-positive aerobic and anaerobic pathogens, including Enterobacteriaceae that produce ESBLs and/or carbapenemases from all of the Ambler classes. Eravacycline is also unique among antimicrobials in late-stage development in that it possesses potent activity against CRAB, including those with blaOXA carbapenemases and against Enterobacteriaceae and A. baumannii containing MBLs, and isolates displaying MDR. Eravacycline exhibits potency profiles similar to those of the carbapenems but more broadly covers Gram-positive pathogens like MRSA and enterococci, and is active against carbapenem-resistant Gram-negative bacteria. Eravacycline is being developed for the treatment of cIAIs and has been shown to have in vitro potency and spectrum to provide protection from infection by either monomicrobial or polymicrobial bacteria from the intestinal flora that commonly cause cIAIs [4].

Eravacycline has low to no potential to inhibit or induce cytochrome P450 isoenzymes at the exposure expected in clinical studies. Major metabolites TP-6208 and TP-034 were not potent direct or metabolism-dependent inhibitors of microsomal P450 enzymes. TP-6208 did not induce major CYP enzymes (CYP1A2, CYP2B6, or CYP3A4), but TP-034 induced CYP2B6 and CYP3A4 [5]. In transport studies, eravacycline inhibited MDR1 (P-gp), OATP1B3, and OAT3 activity at 20 µg/mL. Clinically relevant concentrations of TP-6208 or TP-034 did not inhibit any of 11 major transporters. Neither eravacycline (up to concentrations of 5 µg/mL) nor TP-6208 (up to 2.5 µg/mL) were substrates for MDR1, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, and OCT2, but TP-034 was identified as a potential substrate for the efflux transporters P-gp, BCRP, and BSEP [6].

Eravacycline 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 aerugonisa* 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.

6.3 Clinical Experience

Intravenously administered eravacycline has been studied in fifteen completed clinical trials in healthy subjects, in two studies with special populations (subjects with renal impairment and subjects with hepatic impairment), in phase 2 and phase 3 studies in subjects with cIAI, and in a phase 3 study in subjects with cUTI.

The pharmacokinetics of eravacycline is linear and dose-proportional throughout the range of doses to be used clinically. The phase 2 and phase 3 studies in subjects with cIAI confirmed the efficacy of IV eravacycline in the treatment of serious infections caused by Gram-negative, Gram-positive, and anaerobic pathogens, including multidrug resistant pathogens. In the phase 3 study in subjects with cUTI, the primary efficacy endpoint of non-inferiority to levofloxacin in combined clinical and microbiologic response at the Post-Treatment visit, 6-8 days after the completion of therapy, was not met. Outcomes at earlier timepoints and post-hoc analyses of subjects who only received IV eravacycline were favorable and the failure was attributed to inadequate exposures following transition to PO eravacycline.

Throughout the clinical development program for eravacycline, gastrointestinal side effects of nausea and vomiting have been observed at the higher doses of eravacycline administered as both IV and PO formulations.

Please refer to the current IB for details of the eravacycline clinical studies and adverse event (AE) profile.

6.3.1 Phase 2 Study in Subjects with cIAI (TP-434-P2-cIAI-1)

The proof of concept of eravacycline for the treatment of infections was demonstrated in a phase 2 study of subjects with cIAI. The cure rates [% (95% confidence interval [CI])] in the microbiologically evaluable population (ME) population at the Test of Cure (TOC) visit were 92.9 (80.5-98.5), 100 (91.4-100), and 92.3 (74.9–99.1) for the eravacycline 1.5 mg/kg q24h, the eravacycline 1.0 mg/kg q12h, and the ertapenem 1.0 g q24h groups, respectively. There were no SAEs that were considered by the investigator to be related to study drug, and there were no new safety signals for eravacycline identified in this study. Overall, treatment emergent AEs were reported as 35.8%, 28.6%, and 26.7% of subjects in the eravacycline 1.5 mg/kg q24h, the eravacycline 1.0 mg/kg q12h, and the ertapenem 1.0 g q24h groups, respectively. Nausea was reported in 1.9%, 10.7%, and 6.7% of subjects; and vomiting in 5.7%, 1.8%, and 0% of subjects in the eravacycline 1.5 mg/kg q24h, the eravacycline 1.0 mg/kg q24h, and the ertapenem 1.0 g q24h groups, respectively. The incidence of infusion site reactions was 1.9% and 3.6% in the eravacycline 1.5 mg/kg q24h and the eravacycline 1.0 mg/kg q12h groups, respectively, lower than the incidence observed in the phase 1 studies, probably resulting from the decreased dosing concentration used in the phase 2 study.

6.3.2 Phase 3 Study in Subjects with cIAI (TP-434-008)

The efficacy of IV eravacycline for the treatment of cIAI was confirmed in a phase 3, randomized, double-blind, double-dummy, multicenter, prospective study comparing IV eravacycline (1.0 mg/kg q12h [ERV]) with IV ertapenem (1 g q24h [ERT]) in subjects with cIAI. A total of 541 subjects were enrolled in the study. The cure rates in the microbiological intent-to-treat population at the Test of Cure visit were 86.8 and 87.6% in the ERV and ERT groups, respectively. The between treatment group difference [% (95% CI)] was -0.80 (-7.1, 5.5), allowing non-inferiority to be declared and supporting the efficacy of eravacycline in the treatment of cIAI.

Eravacycline was safe and generally well-tolerated in subjects with cIAI. The most commonly reported TEAEs were gastrointestinal disorders, including nausea (8.1% and 0.7% in the ERV and ERT groups, respectively) and vomiting (4.1% and 3.4% in the ERV and ERT groups, respectively). In the ERV group, 17 subjects (6.3%) experienced SAEs, compared with 16 subjects (6.0) in the ERT group. None of the SAEs were considered related to treatment. Three subjects in the ERV group and 6 subjects in the ERT group died during the study. An equal percentage of subjects (1.9%) discontinued study drug due to a treatment-related TEAE.

6.3.3 Phase 3 Study in Subjects with cUTI (TP-434-010)

The efficacy of an IV-to-PO transition regimen eravacycline for the treatment of cUTI was studied in a phase 3, randomized, double-blind, double-dummy, multicenter, prospective study comparing eravacycline (1.5 mg/kg q24h IV followed by 200 mg q12h PO [ERV]) with levofloxacin (750 mg q24h IV followed by 750 mg q24h PO [LEV]) in subjects with cUTI. A total of 908 subjects were enrolled in the study. The IV-to-PO transition regimen of eravacycline was not shown to be noninferior to levofloxacin in combined clinical and microbiological response at the Post-Treatment visit, 6-8 days after the completion of therapy. Additional post-hoc analyses suggested that lower-then-expected eravacycline exposures during PO administration were responsible for the failure to meet the primary endpoint. Outcomes at earlier timepoints and among subjects who received only IV eravacycline (did not transition to PO) all favored eravacycline, supporting the efficacy of IV eravacycline in the treatment of cUTI.

Eravacycline was safe and generally well-tolerated in subjects with cUTI. As in cIAI, the most commonly reported TEAEs were gastrointestinal disorders, including nausea (18.0% and 3.1% in the ERV and LEV groups, respectively) and vomiting (7.3% and 1.3% in the ERV and LEV groups, respectively). These events rarely led to study drug discontinuation. In the ERV group, 1.5% experienced SAEs, compared with 1.3% in the LEV group. None of the SAEs in the ERV group were considered related to treatment.

6.3.4 Summary of Known and Potential Risks

Eravacycline is related to tetracyclines, a well-known class of antibiotics that has been utilized for over 50 years.

The overall risk to the subjects of the present study is deemed to be acceptable, as indicated by the results of the nonclinical toxicology program, the initial phase 1 studies, the phase 2 cIAI study, and the phase 3 cIAI and cUTI studies. As expected for this class of antibiotics, transient gastrointestinal adverse events of mild to moderate intensity were observed at the higher dose levels in the phase 1 studies. Low levels of nausea and vomiting were observed in the cIAI phase 2 study and phase 3 studies. Higher levels of nausea and vomiting were seen in the phase 3 cUTI study; however, few events led to discontinuation of study drug.

Infusion site related adverse events (eg, pain, discomfort, and superficial phlebitis) were observed in the phase 1 MAD study. The eravacycline concentration was reduced by 25-50% in the phase 2 cIAI study, and the reported incidence of infusion site related adverse events was greatly reduced. Low levels of infusion site related adverse events were observed in the phase 3 cIAI and cUTI studies.

In subjects with higher risk for poor outcomes from infections [ie, auto-immune syndrome or Drug Reaction with Eosinophila and Systemic Symptoms (DRESS) syndrome] the investigator should carefully review the inclusion and exclusion criteria to ensure the appropriate enrollment of subjects. *Clostridium difficile* associated infections are seen with all antibiotics. Care should be taken in subjects enrolled in this clinical study, any subject that has signs or symptoms of *Clostridium difficile* (eg, diarrhea or abdominal pain) should be evaluated for this infection.

Please refer to the latest version of the eravacycline IB and the meropenem package insert for additional information on eravacycline and meropenem, respectively.

6.4 Dosing Rationale

Two doses of eravacycline were evaluated in the phase 2 cIAI study based on tolerability and steady-state AUCs achieved in healthy volunteers in the phase 1 MAD study, and the clinical response rates for both doses were similar to the comparator, ertapenem. The eravacycline 1.0 mg/kg (up to a maximum of 150 mg) q12h dose was selected for the phase 3 cIAI study (TP-434-008), since this dose provided higher AUCs and acceptable tolerability. As the efficacy of IV eravacycline for the treatment of cIAI was confirmed in TP-434-008 study, the eravacycline 1.0 mg/kg q12h dose has been selected (with no maximum dose) for this study.

The comparator, meropenem, was chosen because it is approved by the FDA and other regulatory authorities for the treatment of cIAI. It will be given at the recommended dose of 1 g q8h for an expected minimum of four 24-h dosing cycles.

6.5 Population To Be Studied

Approximately 466 acutely hospitalized subjects with a diagnosis of cIAI requiring surgery will be recruited into this study.

6.6 Statement of Compliance

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory and Institutional Review Board (IRB) / Independent Ethics Committee (IEC) requirements.

7. STUDY OBJECTIVES AND ENDPOINTS

7.1 Primary Objective

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.

7.2 Primary Endpoint

The primary endpoint of this study will be the clinical response at the TOC visit in the micro-ITT population.

NOTE: For the EMA, the primary analysis populations will be the all-treated (MITT) and the clinically evaluable (CE) populations.

7.3 Secondary Objectives

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 pharmacokinetic (PK) parameters of eravacycline

7.4 Secondary Endpoints

The secondary endpoints of the study are:

- Clinical response at the EOT, TOC, and FU visits
- Microbiologic response for subjects in the 2 treatment arms at the EOT and TOC visits

7.5 Safety Parameters

The parameters that will be used to assess safety in this study include:

- Vital signs
- Adverse events
- ECGs at specified time points
- Safety labs at specified time points

8. STUDY DESIGN

8.1 Number of Subjects

The planned study enrollment is approximately 466 subjects. For this study, enrollment occurs at the time of randomization, and it is expected that more subjects will be screened than enrolled into the study. This sample size was calculated as described in Section 14.2.3 based on the expectation that 68.75% of subjects will have a baseline pathogen identified and be included in the micro-ITT population.

A pre-specified assessment of the actual number of subjects in the micro-ITT population was made following completion of the 250th subject. This assessment was performed using data blinded to treatment. Since there was less than the expected proportion of subjects in the micro-ITT population, the sample size was increased to a target of approximately 466 to provide a sufficient number of evaluable subjects.

8.2 Study Design

This is a 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 the Table 1 below.

Table 1: Study Drug Infusion Scheme of a 24-h 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, 1 g q8h	Placebo	Meropenem	Meropenem	Placebo	Meropenem

All subjects will remain hospitalized for the complete course of drug therapy.

8.3 Measures Taken to Minimize Bias

Subjects will be assigned to study drug regimens using computerized randomization. Except for the responsible study 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 participants will be blinded to the IV dosing regimens of subjects.

8.4 Expected Duration of Subject Participation

Individual subject participation in this study is expected to last approximately 6-8 weeks. Foreseen treatment duration at study entry is expected to be a minimum of four 24-h dosing cycles, (ie, in accordance with IDSA Guidelines and the Schedule of Assessments (SOA) for study drug administration). However, study drug may be discontinued at the discretion of the investigator at any time. Study drug treatment should be stopped when symptoms of cIAI have resolved or there is treatment failure. A review of subjects requiring longer than 7 dosing cycles is required with the Medical Monitor. (Refer to Section 10.3.4 Guidance to Investigators for Determining When to End Therapy).

The TOC evaluation will be conducted 25-31 calendar days after the first dose of study drug is administered and a follow-up visit will be performed 38-50 calendar days after the first dose of study drug is administered.

The individual subject study timeline is shown in Table 2 below.

Table 2: Timeline for Individual Study Subjects

SCREENING **Within 48-h of Initial Dose**	**ENROLLMENT**	**STUDY DRUG TREATMENT** **Dose Cycle 1 through EOT**	**END-OF-THERAPY (EOT)** **Within 24-h of Last Dose**	**TEST-OF-CURE (TOC)** **25-31 Days after Initial Dose**	**FOLLOW-UP (FU)** **38-50 Days after Initial Dose**
Establish diagnosis of complicated intra-abdominal infections (cIAI) Verify eligibility for enrollment	Use IWRS* to randomize to study drug	Infuse study drug, either: • Eravacycline IV 1.0 mg/kg q12h ***OR*** • Meropenem IV 1 g q8h Expected 4 (min) to 14 (max) study drug treatment 24-h dosing cycles.	Review of subjects with Medical Monitor for therapies longer than seven 24-h dosing cycles. EOT assessments should be performed at premature withdrawal or treatment failure and within 24-h of last dose.	Return to study center for assessment of clinical response and safety	Return to study center for assessment of clinical response and safety

*IWRS = Interactive Web-based Response System

9. SELECTION AND WITHDRAWAL OF SUBJECTS

9.1 Inclusion Criteria for Enrollment

Subjects must meet all of the following criteria:

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

f. 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

2. At least 18 years of age
3. Evidence of a systemic inflammatory response with at least one of the following:
   a. Fever (oral, rectal, tympanic, or by temporal artery temperature > 100.4˚F / 38˚C) or hypothermia (temperature ≤ 95.9˚F / 35.5˚C)
   b. Elevated WBC (> ULN laboratory range); or proportion of band forms of the WBC differential beyond the ULN laboratory range
   c. Increased pulse (HR > 90 beats per minute)
   d. Increased respiratory rate (> 20 breaths per minute)
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 back or hip, or localized or diffuse abdominal wall rigidity, or mass, or ileus
5. Able to provide informed consent.
6. Subjects must agree to use a highly reliable method of birth control
   a. Male subjects must agree to use an effective barrier method of contraception during the study and for 14 days following the last dose if sexually active with a female of childbearing potential
   b. Female subjects must not be pregnant or nursing. For females of childbearing potential, subjects must commit to either:
      i. Use at least two medically accepted, effective methods of birth control (eg, condom, oral contraceptive, indwelling intrauterine device, hormonal implant /patch, injections, approved cervical ring, etc.) during study drug dosing and for 14 days following last study drug dose, ***OR***
      ii. Sexual abstinence

And either

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-h

Or

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 in 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 one dose of effective antibacterial drug therapy post-operatively before randomization

9.2 Exclusion Criteria

Subjects must NOT meet any of the following exclusion criteria:

1. Considered unlikely to survive the 6-8 week study period
   - Any rapidly-progressing disease or immediately life-threatening illness, including acute hepatic failure, respiratory failure and septic shock
   - Requirement for vasopressors (prior to enrollment) at therapeutic dosages (ie, dopamine > 5 µg/kg/min, any dose of norepinephrine, epinephrine or phenylephrine) to maintain a systolic blood pressure ≥ 90 mm Hg or a mean arterial pressure ≥ 70 mm Hg following adequate fluid resuscitation
2. Creatinine clearance ≤ 50 mL/min as estimated by the Cockcroft-Gault equation

$$eC_{Cr}[mL/min] = \frac{(140 - Age\ [yrs]) \times Body\ Weight\ [kg] \times [0.85\ if\ Female]}{72 \times Serum\ Creatinine\ [mg/dL]}$$

3. Presence or possible signs of significant hepatic disease:
   a. Alanine aminotransferase or aspartate aminotransferase > 5 x ULN, ***OR***
   b. Total bilirubin > 3 x ULN, unless isolated hyperbilirubinemia is directly related to the acute process
4. Immunocompromised condition, including known HIV positivity (requiring anti-retroviral therapy or with CD4 count < 300), AIDS, organ (bone marrow) transplant recipients, and hematological malignancy. Immunosuppressive therapy, including use of high-dose corticosteroids (eg, > 20 mg prednisone or equivalent per day for greater than 2 weeks)
5. History of moderate or severe hypersensitivity reactions to tetracyclines, carbapenems, β-lactam antibiotics or to any of the excipients contained in the study drug formulations
6. Participation in any investigational drug or device study within 30 days prior to study entry
7. Known or suspected current central nervous system (CNS) disorder that may predispose to seizures or lower seizure threshold (eg, severe cerebral arteriosclerosis, epilepsy)
8. Antibiotic-related exclusions:
   a. 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 persistent fever and/or clinical symptoms; or the development of a new intra-abdominal abscess after ≥ 72-h of antibiotic therapy], ***OR***
   b. Receipt of meropenem or any other carbapenem, or tigecycline for the current infection, ***OR***
   c. Need for concomitant systemic antimicrobial agents effective in cIAI other than study drug
9. Refusal of mechanical ventilation, dialysis or hemofiltration, cardioversion or any other resuscitative measures and drug/fluid therapy at time of consent
10. Known or suspected inflammatory bowel disease or associated visceral abscess
11. The anticipated need for systemic antibiotics for a duration of more than 14 days
12. Systemic malignancy that required chemotherapy, immunotherapy, radiation therapy or antineoplastic therapy within the previous 3 months or which is anticipated to begin prior to the TOC visit
13. Known at study entry to have cIAI caused by a pathogen(s) resistant to one of the study drugs

14. Any other unstable or clinically significant concurrent medical condition (ie, class IV heart or lung disease, end stage renal disease, or requiring hemodialysis, etc.) that would, in the opinion of the investigator, jeopardize the safety of a subject, impact their expected survival through the end of the study participation, and/or impact their ability to comply with the protocol

9.3 Requalification for Study Entry

Subjects not fulfilling the entry criteria may not be re-screened for participation even if their eligibility characteristics have changed, with the exception of creatinine clearance. Creatinine clearance is the only screening parameter that can be retested in the establishment of eligibility. Volume depleted subjects should first receive volume replacement prior to having their creatinine clearance calculated.

9.4 Subject Withdrawal Criteria

Subjects should be encouraged to complete all study evaluations. However, subjects may withdraw consent to participate in this study at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Every reasonable effort should be made to determine the reason a subject discontinues study drug treatment and/or withdraws from the study prematurely and this information should be recorded on the appropriate page(s) of the electronic case report form (eCRF).

9.4.1 Early Discontinuation from Study Drug Administration

If a subject prematurely discontinues study drug treatment (including withdrawal of consent for study drug treatment), every reasonable effort should be made to adhere to future protocol evaluations and examinations as specified in the Schedule of Assessments.

The reason for early discontinuation of study drug treatment should be recorded on the appropriate page(s) of the eCRF. Reasons for early discontinuation of study drug treatment may include, but are not limited to, the following:

1. Occurrence of an AE, which, in the opinion of the investigator, warrants the subject's permanent withdrawal from study treatment. In the event of withdrawal due to the occurrence of an AE, the regional medical monitor must be notified within 24-h. Subjects withdrawn secondary to an ongoing non-serious AE (regardless of relationship to study drug) or SAE that is not related to study drug treatment must be followed clinically until the follow-up safety visit (Day 38-50). Subjects withdrawn secondary to an ongoing study drug-related SAE must be followed clinically until resolution or stabilization
2. Insufficient therapeutic effect requiring alternative systemic antibacterial treatment for the current IAI

If a subject has been discharged from the hospital and refuses to return to the investigational site for scheduled evaluations, but is willing to undergo follow-up investigations, clinical response data, safety data, and concomitant medication information may be collected by telephone and/or through medical records.

9.4.2 Withdrawal from Study Protocol

Subjects who wish to discontinue study drug treatment should be encouraged to complete the TOC and FU visits after their last study drug administration. If they choose to withdraw from the study completely, the reason for withdrawal should be recorded on the appropriate page(s) of the eCRF. Reasons for withdrawal from the study may include, but are not limited to, the following:

1. Significant subject noncompliance, defined as refusal or inability to adhere to the prescribed dosing and follow-up regimens
2. Subject lost to follow-up
3. At the request of the subject, investigator, or study sponsor

9.5 Replacement of Subjects

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

9.6 Prior and Concomitant Medication

Prior administration of systemic antibacterial agents effective in cIAI is allowed only in the following circumstances:

≤ 24-h of continuous antibacterial drug therapy for cIAI during the 72-h preceding enrollment. However, subjects with documented cIAI (ie, known baseline pathogen) who have received at least 72-h of systemic antibiotic therapy and are considered treatment failures may be enrolled. Treatment failure is defined as persistent fever and/or clinical symptoms; or the development of a new intra-abdominal abscess after ≥ 72-h of antibiotic therapy.

The following concomitant medications are not permitted while on study therapy:

- Valproic acid and divalproex sodium
- Concomitant systemic antibacterials effective in cIAI are not permitted after the initial dose of study medication until the completion of the FU visit.

All other concomitant medications necessary for the health and wellbeing of a subject will be permitted. All concomitant medications will be recorded on the appropriate eCRF page.

10. STUDY PROCEDURES

Please also review the entire protocol, including the Schedule of Assessments and appendices, for additional details.

10.1 General Procedures

10.1.1 Temperature

Temperatures should be recorded orally, rectally, aurally using a tympanic thermometer, or by temporal artery. Axillary temperatures are not allowed. Temperature should be assessed prior to the initial dose of study drug and then q8h ± 1-h while hospitalized until EOT.

10.1.2 Abdominal Examination

A thorough clinical examination of the abdomen is to be performed at specified time points. Abdominal pain, tenderness to palpation, rebound tenderness, guarding, mass, and ascites will be assessed and severity graded as none, mild, moderate, or severe according to the following definitions:

None:	No signs or symptoms
Mild:	Awareness of signs and symptoms, but easily tolerated
Moderate:	Signs or symptoms of enough intensity to cause interference with usual activity
Severe:	Signs and symptoms of enough intensity that incapacitate and interfere with usual activity

Other pertinent findings should be recorded, including inability to tolerate oral or enteral intake and presence or absence of ileus.

The clinical abdominal examination will include an assessment of the surgical wound (if applicable). The surgical wound examination will assess signs of infection such as: skin erythema, induration, tenderness, warmth to touch, fluctuance, swelling, and superficial wound pain. If signs of infection are present, findings will be recorded and graded as mild, moderate, or severe according to the definitions above. If present, the nature of any discharge (eg, purulent, serous, bloody, etc.) will be assessed and the drainage cultured if clinically indicated.

10.1.3 Safety Laboratory Tests

Safety laboratory tests for this study (chemistry, hematology, coagulation, and urinalysis) are to be performed by a central laboratory, and only values from the central laboratory are to be entered into the laboratory section of the study database. Values from local laboratories may be used to determine eligibility for study enrollment and as the basis for clinical decisions. See Appendix 2: Central Safety Laboratory Tests for the complete list of safety laboratory tests.

10.1.4 ECGs

Standard 12-lead ECGs are to be recorded with the subject in the supine position when indicated by the protocol.

10.1.5 Microbiologic Specimen Collection

Appropriate aerobic and anaerobic specimens for culture at the time of the initial surgical procedure (or during re-intervention in the case of prior treatment failures) should be collected from the site of infection and directly inoculated into culture media during the surgical intervention; microbiologic specimens collected during routine operative care prior to subject consent may be used for study purposes. 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. The specimens should be representative of the material associated with the clinical infection. Every effort should be made to collect specimens via a tissue biopsy or aspirate. Samples collected by swabs are allowed only if it is not possible to collect tissue samples or aspirated fluid. Samples collected from superficial swabs and abdominal drains are not allowed. These specimens will be cultured and the species will be identified by the local or regional laboratory. All purified isolate(s) will be sent to a central, reference laboratory at time points determined by the Sponsor for confirmation of

species identification and susceptibility analysis to eravacycline and meropenem. Specific instructions for sample collection, processing, and shipment can be found in the laboratory manual(s) for this study.

10.1.6 Blood Cultures

Aerobic and anaerobic blood cultures will be obtained at two separate sterile venipuncture sites prior to initiation of clinical trial drug therapy. Upon knowledge of a positive culture for a pathogen, blood cultures should be repeated until sterile (ie, both sets of cultures from two separate venipuncture sites are negative for pathogens) through the FU visit. 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).

These specimens will be cultured and the species will be identified by the local or regional laboratory. All purified pathogen(s) will be sent to a central reference laboratory at time points determined by the Sponsor for confirmation of species identification and antimicrobial susceptibility analysis, including to study drugs. Specific instructions for sample collection, processing, and shipment can be found in the laboratory manual(s) for this study.

10.1.7 Radiologic Assessment

Radiologic evaluation may be performed as part of the pre-operative diagnosis or if surgical re-intervention is clinically indicated. Copies of all radiographic study reports will be collected and copies of the films or images may be requested as deemed necessary by the Sponsor.

NOTE: If randomization is planned pre-operatively then radiographic evidence congruent with the diagnosis of cIAI is required.

10.1.8 Clinical Response

Clinical outcome assessments will be made at the EOT, TOC, and FU visits. Clinical responses will be classified as Clinical Cure, Clinical Failure, or Indeterminate/Missing based on clinical outcomes. A favorable clinical response is “Clinical Cure.”

Clinical response categories are defined below.

10.1.8.1 Clinical Cure

Clinical Cure is defined as complete resolution or significant improvement of signs or 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.

10.1.8.2 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 complication or recurrence of cIAI

- Post-surgical wound infections requiring systemic antibiotics
- Initiation of rescue antibacterial drug therapy for treatment of cIAI

Clinical Failures are to be documented by obtaining an appropriately performed wound or deep site culture, if feasible.

10.1.8.3 Indeterminate/Missing

If the subject's outcome is neither Clinical Cure nor Clinical Failure then the outcome should be listed as "Indeterminate/Missing." The reason for an "Indeterminate/Missing" designation must be provided. Study data are listed as "Indeterminate/Missing" if the Investigator did not complete an assessment or if the study visit was not conducted. Deaths not related to cIAI will be considered "Indeterminate/Missing."

10.2 Time Point Specific Procedures

10.2.1 Screening

All potential study participants will undergo a screening evaluation. Clinical assessments and local laboratory results performed during the subject's hospitalization (within 48-h of screening) may be used to establish eligibility. If any of the required screening assessments defined below were not performed, they must be performed prior to determining eligibility. Screening may occur on the first day of dosing and will include the following activities:

1. Obtain a signed informed consent: Procedures performed as standard of care prior to signing the informed consent 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, microbiologic specimens collected during routine operative care prior to subject consent may be used for study purposes.
2. Clinical assessments:
   - Complete pertinent medical history including approximate time of onset and type of symptoms related to current condition (eg, abdominal pain, past surgeries, allergies, and known viral/bacterial diseases)
   - Complete physical examination, including: temperature, resting vital signs, height and weight.
   - Abdominal examination
   - 12-lead ECG
   - Prior and concomitant medication assessment: record both day and time for all antibiotics administered in the preceding 72-h
3. Laboratory Assessments:
   - Safety Laboratory Tests (chemistry, hematology, coagulation, and urinalysis)
   - Calculate creatinine clearance (Cockcroft-Gault formula):
     $$eC_{Cr}[mL/min] = \frac{(140 - Age\ [yrs])\ \times\ Body\ Weight\ [kg]\ \times\ [0.85\ if\ Female]}{72\ \times\ Serum\ Creatinine\ [mg/dL]}$$
4. Serum pregnancy test (women of childbearing potential only)
   NOTE: If a serum pregnancy test is not available at the investigator site then a urine pregnancy test may be utilized locally.
5. APACHE II assessment

- Serum bicarbonate can be used in place of arterial blood gases for the completion of the APACHE II assessment.

6. Microbiological assessments:
   - Obtain specimens for culture and *in vitro* susceptibility testing of all aerobic and anaerobic organisms considered to be pathogens from the following sites:
     - Site of infection during surgical intervention (should be taken with direct inoculation of sample into culture media)
       - Every effort should be made to collect specimens via a tissue biopsy or aspirate. Samples collected by swabs are allowed only if it is not possible to collect tissue samples or aspirated fluid. Samples collected from superficial swabs and abdominal drains are not allowed.
     - Blood cultures

     Specific instructions for sample collection, processing, and shipment can be found in the laboratory manual(s) for this study.
7. Radiologic Assessment (at Investigator's discretion):
   Perform a radiologic evaluation as part of the pre-operative diagnosis (computed tomography (CT) scan, ultrasound, and/or magnetic resonance imaging (MRI) scan), with or without contrast. Radiologic confirmation of cIAI is required in order for a subject to qualify for pre-operative enrollment. Copies of all operative procedure notes, diagnostic study reports, as well as reports associated with percutaneous drainage procedure will be collected.
8. Determine eligibility

10.2.2 Randomization and Enrollment of Subjects

Once an informed consent is obtained and study eligibility is established, a blinded study site member will obtain a subject number and a 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. 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 one site may be granted by the Sponsor.

10.2.3 Dose Cycle 1

If Dose Cycle 1 and Screening occur on the same day the resting vital signs, abdominal examination, and safety laboratories do not need to be repeated.

1. Assessments prior to the First Study Drug Administration:
   - Record temperature
   - Resting vital signs
   - Safety Laboratory tests (chemistry, hematology, coagulation, urinalysis)

- Calculate creatinine clearance (Cockcroft-Gault formula):
$$eC_{Cr}[mL/min] = \frac{(140 - Age\ [yrs])\ \times\ Body\ Weight\ [kg]\ \times\ [0.85\ if\ Female]}{72\ \times\ Serum\ Creatinine\ [mg/dL]}$$
- Abdominal examination
- AE assessment
- Concomitant medication assessment
- PK sampling in accordance with Schedule of Assessments and Appendix 3: Blood PK Sample Collection, Handling, Preparation and Shipping
- Blood cultures (if indicated)

2. IV Study Drug Infusions
   - Study drug administration per dosing schedule
3. Assessments after the First Study Drug Administration:
   - PK sampling in accordance with Schedule of Assessments and Appendix 3: Blood PK Sample Collection, Handling, Preparation and Shipping
   - Resting vital signs
   - Temperature every 8-h
   - AE assessment
   - Concomitant medication assessment
4. Radiologic evaluation (if deemed necessary by the investigator)

10.2.4 Dosing Cycles 2 and 3

1. Clinical Assessments:
   - Temperature every 8-h
   - Resting vital signs
   - Abdominal examination
   - AE assessment
   - Concomitant medication assessment
2. Laboratory Assessments:
   - Safety Laboratory tests (chemistry, hematology)
   - Blood cultures (if indicated)
   - Intra -abdominal cultures (if indicated)
   - Calculate creatinine clearance (Cockcroft-Gault formula):
$$eC_{Cr}[mL/min] = \frac{(140 - Age\ [yrs])\ \times\ Body\ Weight\ [kg]\ \times\ [0.85\ if\ Female]}{72\ \times\ Serum\ Creatinine\ [mg/dL]}$$
3. IV Study Drug Infusions
   - Study drug administration per dosing schedule.
4. Radiologic evaluation (if deemed necessary by the investigator)

10.2.5 Dosing Cycles 4 through 14 - while subject is on study drug

1. Clinical Assessments:
   - Temperature every 8-h
   - Daily resting vital signs
   - Daily abdominal examination
   - AE assessment
   - Concomitant medication assessment
   - Evaluate subject's requirement for continuation of study drug

2. Laboratory Assessments:
   - Safety laboratory tests (chemistry, heamatology) on Dosing Cycle 4 and repeated every 3 dosing cycles while subject is on study drug
   - Calculate creatinine clearance (Cockcroft-Gault formula) on Dosing Cycle 4 and repeated every 3 dosing cycles while subject is on study drug:
     $eC_{Cr}[mL/min] = \frac{(140 - Age\ [yrs])\ \times\ Body\ Weight\ [kg]\ \times\ [0.85\ if\ Female]}{72\ \times\ Serum\ Creatinine\ [mg/dL]}$
   - Blood cultures (if indicated)
   - Intra -abdominal cultures (if indicated)
3. IV Study Drug Infusions
   - Study drug administration per dosing schedule
4. Radiologic evaluation (if deemed necessary by the investigator)

10.2.6 End-of-Therapy (EOT), Test of Cure (TOC) and Follow-Up (FU)

The EOT, TOC, and FU procedures are to be performed at premature withdrawal or treatment failure and within 24-h of the last dose of study drug, 25-31 days after the initial dose of study drug, and 38-50 days after the initial dose of study drug, respectively.

1. Clinical Assessments:
   - Complete physical examination, including temperature and resting vital signs
   - Abdominal examination
   - Clinical response assessment
   - AE assessment
   - 12-lead ECG ***at EOT visit only***
   - Concomitant medication assessment
   - Radiologic evaluation (if deemed necessary by the investigator)
2. Laboratory Assessments:
   - Safety laboratory tests
     - Chemistry, hematology, and coagulation (including fibrinogen)
     - Urinalysis ***at EOT visit only***
   - Serum pregnancy test (women of childbearing potential only)
     NOTE: If a serum pregnancy test is not available at the investigator site then a urine pregnancy test may be utilized locally.
   - Blood culture (if indicated)
   - Intra -abdominal cultures if indicated

10.3 Study Drug Administration

10.3.1 Study Drug Infusions and Dosing Schedule

Both eravacycline and meropenem, when prepared for infusion, are colored solutions. The two drugs require different infusion volumes. The dosing interval for meropenem is every 8-h. For eravacycline, the dosing interval is every 12-h. For these reasons, this study has been designed using double-dummy methodology.

During each 24-h dosing cycle, the subject will receive five infusions according to Table 3 below.

Table 3: Study Drug Infusion Scheme of a 24-h Dosing Cycle

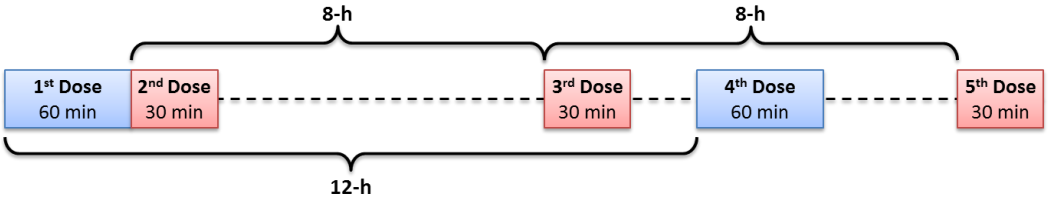
INFUSION	TREATMENT ARM	
	Eravacycline 1.0 mg/kg q12h	**Meropenem 1 g q8h**
1st Dose (of Dosing Cycle)		
final volume (mL)[a]	wt(kg) ÷ 0.3	wt(kg) ÷ 0.3
drug amount (mg)	***Eravacycline*** wt(kg) x 1.0	***Placebo*** N/A
conc (mg/mL)[b]	0.3	N/A
infusion time (min)[c]	60 ± 10	60 ± 10
2nd Dose (of Dosing Cycle)		
final volume (mL)	50	50
drug amount (mg)	***Placebo*** N/A	***Meropenem*** 1000
conc (mg/mL)	N/A	16.7
infusion time (min)	30 ± 5	30 ± 5
3rd Dose (of Dosing Cycle)		
final volume (mL)	50	50
drug amount (mg)	***Placebo*** N/A	***Meropenem*** 1000
conc (mg/mL)	N/A	16.7
infusion time (min)	30 ± 5	30 ± 5
4th Dose (of Dosing Cycle)		
final volume (mL)[a]	wt(kg) ÷ 0.3	wt(kg) ÷ 0.3
drug amount (mg)	***Eravacycline*** wt(kg) x 1.0	***Placebo*** N/A
conc (mg/mL)[b]	0.3	N/A
infusion time (min)[c]	60 ± 10	60 ± 10
5th Dose (of Dosing Cycle)		
final volume (mL)	50	50
drug amount (mg)	***Placebo*** N/A	***Meropenem*** 1000
conc (mg/mL)	N/A	16.7
infusion time (min)	30 ± 5	30 ± 5

[a] Final infusion volume per bag must not exceed 500 mL
[b] Concentration may be decreased as long as the total infusion volume does not exceed 500 mL
[c] Infusion time may be increased to 120 minutes per IV bag

All solutions for infusion will be prepared by an unblinded pharmacist or designee. Specific instructions for preparation of study drugs are included in the Pharmacy Manual for this study.

The eravacycline-matched placebo will consist of sterile normal saline (0.9% NaCl). The meropenem-matched placebo will consist of sterile normal saline (0.9% NaCl).

Figure 1: Study Drug Infusion Scheme of a 24-h Dosing Cycle



The 2nd Dose of a dosing cycle will be started immediately following the completion of the 1st Dose of the dosing cycle. The 3rd Dose of the dosing cycle will be started 8-h following the start of the 2nd Dose of the dosing cycle. The 4th Dose of the dosing cycle will be started 12-h following the start of the 1st Dose of the dosing cycle. The 5th Dose of the dosing cycle will be started 8-h following the start of the 3rd Dose of the dosing cycle. (See Figure 1 above)

The interval between the 1st Doses of adjacent 24-h dosing cycle can be reduced by up to 4 hours after each of the first two 24-h dosing cycles to allow for a more practical infusion schedule for the duration of therapy. After the third 24-h dosing cycle, the allowable administration window for each infusion is ± 1 h.

In the event the Investigator considers the subject a Clinical Cure and it is not necessary to complete the entire dose cycle, study drug can be discontinued at any time after the administration of the 2nd Dose. This is to ensure that the study subject has received one infusion of study drug and its placebo-matched infusion.

10.3.2 Meropenem and Meropenem-Matched Placebo Dose Adjustment

Meropenem dosing should be reduced in subjects with a creatinine clearance of 50 mL/min or less in accordance with the dosage and administration instructions found in the meropenem package insert.

While a creatinine clearance of ≤ 50 mL/min is exclusionary at Screening; it is possible that a subject's creatinine clearance may change while on study. Investigators are instructed to locally calculate creatinine clearance at the Screening Visit, Dose Cycle 1 through Dose Cycle 4, and every three 24-h dosing cycles thereafter while on study drug (eg, Dose Cycle 7, Dose Cycle 10, and Dose Cycle 13).

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. Specific instructions for the dose adjustments of meropenem and/or meropenem-matched placebo are included in the meropenem package insert and the Pharmacy Manual for this study.

10.3.3 Treatment Compliance

The date, start and stop times, and volumes used in each infusion of study drug, will be recorded. These detailed records will be used to document compliance.

If an infusion administration is inadvertently delayed, the infusion must be started as soon as possible. No infusion should be "missed" regardless of how long it may have been delayed.

A complete dose cycle is defined as all five doses for a dosing cycle.

Subjects will be considered compliant with study drug treatment if they do not miss more than 20% of the expected study drug infusions, as defined by the interval between the first and last dose.

10.3.4 Guidance to Investigators for Determining When to End Therapy

In accordance with guidelines, subjects are expected to remain on study drug treatment for a minimum of four 24-h dosing cycles (unless subject is a treatment failure or cure) and for a maximum of 14 dosing cycles. Study drug treatment should be continued until resolution of infection signs and symptoms is documented, such as:

- Maximum temperature (oral, rectal, tympanic, or by temporal artery) has been < 100.4˚F / 38˚C for 24-h
- Improvement of abdominal signs and symptoms presenting at study entry
- A return of bowel function and restoration of oral/enteral intake

Any subject requiring longer than seven 24-h dosing cycles of study drug therapy should be discussed with the Medical Monitor.

10.4 Specific Restrictions/Requirements

Study drug must only be administered while subjects are hospitalized. All subjects must have an EOT assessment, and return to investigational sites for TOC and FU assessments unless they have withdrawn consent.

10.4.1 Avoidance of Pregnancy

10.4.1.1 Instructions for Male Subjects

There is no information on the effects of eravacycline on the development of the fetus in humans. Therefore, it is important that the partners of male subjects do not become pregnant during the study and for a total period of 14 days after the male subject has received the last dose of study drug.

Subjects should avoid fathering a child by either being abstinent or only engaging in intercourse with an effective barrier method of contraception.

Since there is a risk of drug being secreted in the ejaculate, subjects (including men who have had vasectomies) whose partners are currently pregnant should use barrier methods for the duration of the study and for two weeks afterwards. This is to ensure that the fetus is not exposed to the investigational product in the ejaculate.

10.4.1.2 Instructions for Female Subjects

Females of childbearing potential are eligible for enrollment in this study. There is no information on the effects of eravacycline on the development of the fetus in humans. Therefore,

it is important that female subjects enrolled into the study do not become pregnant during the study and for a total period of 14 days after the subject has received the last dose of study drug.

Females of childbearing potential must commit to either: (1) Using at least two medically accepted, effective methods of birth control (eg, condom, spermicidal gel, oral contraceptive, indwelling intrauterine device, hormonal implant /patch, injections, approved cervical ring) during study drug dosing and for 14 days following last study drug dose, or (2) sexual abstinence.

10.4.2 Pregnancy

Pregnancy is considered an immediately reportable event (but not an adverse event), and the investigator will record information concerning the pregnancy on the appropriate form and submit it to the Medical Monitor within 24-h of learning of a subject's pregnancy. Study drug administration will be stopped in any female subject who becomes pregnant while participating, and the subject will be followed to determine the outcome of the pregnancy. All pregnancies in the female partners of male subjects receiving at least one dose of eravacycline will be recorded from first dose to the last study visit.

10.4.2.1 Follow-up in the Event of a Pregnancy

The ethics committee and the Sponsor will be informed of all pregnancies in study subjects and in partners of male subjects.

The subject will be asked to provide information on the outcome of the pregnancy, including premature termination should the case arise. Spontaneous miscarriages and congenital abnormalities will be reported as serious adverse events (SAEs). Information on the status of the mother and child will be forwarded to the Medical Monitor or designee. Generally, follow up will be in accordance with regulatory guidance and at least 6-8 weeks after the estimated delivery date. Any premature termination of the pregnancy will be reported.

10.5 Study Discontinuation/Termination Criteria

The study Sponsor reserves the right to terminate this clinical study or participation of an investigative site at any time. Reasons for study discontinuation/termination may include, but are not limited to, the following:

1. Incidence and/or severity and composition of AEs in this or other studies indicate a potential health hazard to subjects
2. Sponsor's decision to discontinue investigation in a specific therapeutic area
3. Subject enrollment is unsatisfactory
4. An investigator requests to withdraw from participation
5. Serious and/or persistent noncompliance by the investigator with the protocol, clinical research agreement, Form FDA 1572, or applicable regulatory guidelines in conducting the study
6. IRB/IEC decision to terminate or suspend approval for the investigation or an investigator
7. Untimely input of data into eCRFs
8. Low pathogen recovery rate from microbiologic samples

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Quality Control

11.1.1 Monitoring

The Sponsor, or designee(s), will monitor the study for compliance to the protocol, applicable laws and regulations, and Good Clinical Practice. The monitor(s) will verify data on the electronic case report form versus source data. The monitor is also responsible for ensuring that the proper records are maintained. Monitoring reports will be issued for each monitoring visit.

11.2 Quality Assurance

Quality assurance personnel may audit the clinical trial sites and/or study-related materials at any time during the study.

12. ASSESSMENT OF SAFETY

Safety will be assessed through AEs, physical examinations, vital signs, ECGs, and the collection of central laboratory data (ie, chemistry, hematology, coagulation, and urinalysis). The Principal Investigator and designated study staff are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

12.1 Definitions

12.1.1 Adverse Event

An adverse event is any adverse experience in a subject administered a pharmaceutical product, whether or not it is considered drug-related, that occurs during a subject's study participation (defined as after the time of initial informed consent). This would include any side effect, injury, toxicity, sensitivity reaction, intercurrent illness, or sudden death. A pre-existing condition is one that is present at study entry and is reported as part of the subject's medical history. It should be reported as an AE if the frequency, intensity, or character of the condition worsens during study drug treatment. Subjects should be instructed to report all AEs to the investigator or study staff. Adverse events must be appropriately documented in the subject's original source documents and entered into the eCRF. Investigators should report syndromes rather than list symptoms. Treatment failure (e.g. recurrent cIAI) is not considered an AE.

12.1.2 Adverse Drug Reaction (ADR)

An adverse drug reaction (ADR) is any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

12.1.3 Serious Adverse Event (SAE)

An SAE is any AE, occurring at any dose and regardless of causality that:

- Results in death.
- Is life-threatening. Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred (ie, it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form).

- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry, are not considered AEs if the illness or disease existed before the subject was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the study (eg, surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Clarification should be made between the terms "serious" and "severe" since the terms ARE NOT synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as "serious," which is based on subject/event outcome or action criteria described above, and is usually associated with events that pose a threat to a subject's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Events that result from lack of efficacy of study drug (eg, treatment failure, ongoing cIAIs, wound infections requiring antibiotics, recurrence of abscesses) are not considered SAEs and as such prolonged hospitalizations, etc. for these events will not be considered SAEs.

12.1.4 Unexpected Adverse Reactions

An adverse reaction is 'unexpected' if its nature and severity are not consistent with the information about the medicinal product in question set out in the most recent Investigator's Brochure relating to the trial in question or the product information for meropenem.

12.2 AE Collecting and Reporting

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the appropriate page of the eCRF starting from the time of initial informed consent. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded on the appropriate pages of the eCRF starting from the time of initial informed consent. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

All SAEs that occur during the course of the study, as defined by the protocol, must be reported by the Investigator to the Sponsor or its pharmacovigilance designee/contract research organization (CRO) within 24-h from the point in time when the Investigator becomes aware of the SAE. In addition all SAEs, including all deaths, which occur from the time of signing of the informed consent up to and including 30 days after administration of the last dose of study drug, must be reported to the Sponsor or its designated CRO within 24-h. All SAEs and deaths must be reported whether or not considered causally related to the study drug. The information collected will include a minimum of the following: Subject number, a narrative description of the event and an assessment by the Investigator as to the intensity of the event and relatedness to study drug. Follow-up information on the SAE may be requested by Tetraphase or its representative CRO. Detailed instructions for the collecting and reporting of SAEs will be provided in the Investigator Site File.

If there are serious, unexpected ADRs associated with the use of the study drug, the Sponsor or its designated CRO will notify the appropriate regulatory agency(ies) and all participating Investigators on an expedited basis (7 days for fatal or life-threatening serious, unexpected ADRs; 15 days for all other serious, unexpected ADRs). The Sponsor has delegated the responsibility to promptly notify the IRB/IEC of all unexpected serious ADRs involving risk to human subjects in accordance with the rules and regulations of the IRB/IEC to the Principal Investigator.

An unexpected event is one that is not reported in the IB.

Reporting of SAEs and SUSARs

All SAEs must be reported to the designated CRO within 24-h of the investigational site's knowledge of the occurrence. Each investigational site will submit the SAE information to the CRO.

The SAE information transmitted to the CRO will include the following (as available):

- Subject ID, investigator name, and site number
- SAE information: event term, onset date, severity, and casual relationship
- Basic demographic information (eg, age, gender, weight, etc.)
- The outcomes attributable to the event [eg, death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, other important medical event(s)]
- A summary of relevant test results, pertinent laboratory data, and any other relevant medical history
- The first and last dates of study drug administration
- A statement whether study drug was discontinued or study drug administration schedule was modified
- A statement whether event recurred after reintroduction of study drug if administration had been discontinued or withheld
- Supplemental information may include the following hospital records: laboratory results, radiology reports, progress notes, admission and emergency room notes, holding/observation notes, discharge summaries, autopsy reports, and death certificates

The SAE information should be transmitted within 24-h with as much of the above information as available at the time. Supplemental information may be transmitted and should not delay the initial transmission. The Sponsor or CRO may contact the investigational site to solicit additional information or follow-up on the event. Investigational sites will be provided with detailed instructions on the procedures for transmitting SAEs to the CRO.

For regulatory purposes, initial reports of serious ADRs should be transmitted within the prescribed time frame as long as the following minimum information is available: subject identification, suspect study drug, reporting source, and an event or outcome that can be identified as being both serious and unexpected for which, in the investigator's opinion, there is a suspected causal relationship.

A suspected unexpected serious adverse reaction (SUSAR) which is fatal or life-threatening must be reported to the competent authority and ethics committee immediately (within 7 days) after the Sponsor becomes aware of the event. Any additional information must be reported within eight days of sending the first report.

A SUSAR which is not fatal or life-threatening must be reported to the competent authority and ethics committee as soon as possible (within 15 days) after the Sponsor becomes aware of the event.

All SUSARs occurring at the site will be entered into the European database established in accordance with Article 11 of the EU Clinical Trials Directive.

12.3 Grading of Adverse Events

The severity of each AE will be categorized using the following criteria:

Mild	AE usually transient and requires no special treatment and does not interfere with the subject's daily activities.
Moderate	AE produces a low level of inconvenience to the subject and may interfere with daily activities. These events are usually ameliorated by simple therapeutic measures.
Severe	AE interrupts daily activity and requires systemic drug therapy or other medical treatment.

Key: AE = adverse event

12.4 Relationship to Study Drug

For each reported AE, the investigator must make an assessment of the relationship of the event to the study drug using the following scale:

Not Related: An event that is definitely not associated with study drug administration and is judged clearly due to causes other than the study drug.

Unlikely Related: An event that follows a temporal sequence from administration of the study drug, such that, a relationship is not likely and could be reasonably explained by the subject's clinical state, or other modes of therapy administered to the subject.

Possibly Related: An event that follows a reasonable temporal sequence from administration of the study drug, but that, may be due to another cause and could also be reasonably explained by the subject's clinical state, or other modes of therapy administered to the subject.

Probably Related: An event that follows a reasonable temporal sequence from administration of the study drug, that is not easily explained by another cause (such as, known characteristics of the subject's clinical state or other treatment) and is confirmed by improvement on stopping or slowing administration of the study agent (ie, de-challenge, if applicable).

Definitely Related: An event that is clearly associated with study drug administration.

In the event of death, the cause of death should be recorded as the AE. "Death" is an outcome and is NOT the AE. The only exception is "sudden death" when the cause is unknown.

12.5 Laboratory Test Abnormalities

Clinically significant abnormal laboratory findings that are detected during the study or are present at baseline and significantly worsen will be reported as adverse events or SAEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

Clinical significance is at the discretion of the Investigator and ***may*** be defined as those findings which:

- Are directly responsible for discontinuation from the study,
- Require treatment or other therapeutic intervention,
- Require further monitoring, or
- Require further diagnostic evaluation (other than repeat of the same test to confirm the abnormality).

All abnormal laboratory values considered to be clinically significant will be recorded on the adverse event page of the eCRF. Significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant.

All central laboratory data generated by the study will be included in the final study database. Throughout this study, subjects will have samples sent to local laboratories and to the central laboratory. Only the values from the samples sent to the central laboratory will be captured in the study database and used for the safety analysis. Investigators may report AEs based upon local laboratory values. In this event, the actual value and the normal range for the local laboratory should be recorded on the AE form.

12.6 Follow-up of Adverse Events

All AEs (regardless of relationship to study drug) and SAEs determined not to be study drug related (ie, not related and unlikely related) will be followed through the FU visit and be noted as "continuing" if not resolved at this visit. Any SAE that is determined to be study drug related (possibly, probably, or definitely related) will be followed to resolution or stabilization. Subjects will be referred to their primary care doctor for further follow-up as needed post-study.

The outcome of AEs will be rated as:

- Recovered/Resolved
- Recovering/Resolving
- Not Recovered/Not Resolved
- Recovered/Resolved with Sequelae
- Fatal
- Unknown

13. EVALUATION OF EFFICACY

13.1 Analysis Populations

The following definitions will be used in assigning subjects into analysis populations:

- Intent-to-treat (ITT) population – all subjects who are randomized
- All Treated (MITT) Population - all randomized subjects who receive any amount of study drug. Analyses in this population are based on the treatment arm the subject was randomized to.
- Safety Population - all randomized subjects who receive any amount of study drug. Analyses in this population are based on the treatment the subject actually received.
- Microbiological intent-to-treat (micro-ITT) population – all randomized subjects who have at least one baseline bacterial pathogen that causes cIAI and against which the investigational drug has *in vitro* antibacterial activity
- Clinically evaluable (CE) – all subjects in the ITT population who meet key inclusion/exclusion criteria and follow other important components of the trial
- Microbiologically evaluable (ME) – all subjects in the micro-ITT population who meet key inclusion/exclusion criteria and follow other important components of the trial

13.2 Efficacy Evaluations

The primary efficacy evaluation, clinical response at the TOC visit, will be conducted in the micro-ITT population.

The following secondary evaluations will be performed:

- Clinical response at EOT, TOC, and FU visits in the following populations:
  - ITT
  - MITT
  - CE
  - Micro-ITT (EOT and FU)
  - ME
- Microbiologic responses at EOT and TOC visits in the following populations:
  - Micro-ITT
  - ME
- PK parameters after eravacycline infusion, including
  - C_{max}, T_{max}, AUC_{0-12}

13.2.1 Clinical Response

Clinical outcome assessments will be made at the EOT, TOC, and FU visits. Clinical response will be classified by the investigator as Clinical Cure, Clinical Failure, or Indeterminate/Missing. Subjects who are assessed as a Clinical Failure at the EOT Visit will have the failure carried forward to the TOC Visit. Subjects who are assessed as a Clinical Failure at the TOC Visit will have the failure carried forward to the FU Visit. For those subjects reviewed by the Surgical Adjudication Committee (SAC) (see Section 14.2.5), the committee assessment of clinical response will be used for analysis. A favorable clinical response is "Clinical Cure".

13.2.2 Per Pathogen 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 timepoint
- Presumptive eradication – Absence of material to culture in a subject who has responded clinically to treatment (clinical cure)
- 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)
- Indeterminate/Missing – Culture not obtained and clinical response is indeterminate/ missing

These categories will be further classified as follows:

- Favorable
    - Eradicated
    - Presumed eradicated
- Unfavorable
    - Persistence
    - Persistence with decreased susceptibility
    - Presumed persistence
- Indeterminate/Missing

All bacterial isolates cultured from aerobic and anaerobic specimens will be evaluated for susceptibility to study drugs and the emergence of resistance and overgrowth of non-susceptible organisms.

13.2.3 Per-Subject Microbiological Response

Per-subject microbiological response will be determined by the per pathogen microbiological outcomes. 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.

14. STATISTICAL METHODS

A detailed Statistical Analysis Plan (SAP) will be used to guide the analysis and reporting of data collected in this study.

14.1 Data Collection and Processing

An IWRS will be used to allocate treatment assignments to subjects. Creation and validation of the clinical database, data entry, data management, and transfer of central laboratory data will be conducted in accordance with 21 Code of Federal Regulations (CFR) Part 11 and the Guidance for Industry on Computerized Systems Used in Clinical Trials.

eCRFs will be completed for all randomized subjects. Please refer to the CRF Completion Guidelines for instructions on which eCRFs will be completed for subjects who are randomized but not treated.

14.2 Statistical Methodology

All data collected in this study will be presented in data listings and, where indicated, tabulated in summary tables. Data will be presented and summarized using the SAS System (SAS Institute Inc, Cary, NC).

Continuous variables will be summarized with the number of observations, mean, standard deviation, median, minimum, and maximum.

Categorical variables will be summarized with frequencies and percentages. Percentages will be based on non-missing data unless specified otherwise.

Except where indicated in the SAP, Baseline is defined as the closest value prior to the start of treatment with study drug.

14.2.1 Efficacy Analyses

The primary efficacy outcome measure is clinical response at the TOC Visit (incorporating the SAC assessment) in the micro-ITT population. 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% 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. If the lower limit of the 95% CI for the difference in clinical cure rates in the micro-ITT population exceeds -12.5%, then non-inferiority of eravacycline to meropenem will be declared. The primary efficacy outcome will also be assessed across the randomization stratification factor of primary site of infection. For each site of infection stratum, a 2-sided 95% CI for the observed difference in clinical cure rates at the TOC Visit will be calculated for the micro-ITT population. The number and percentage of subjects in each treatment group with a secondary efficacy outcome (the SAC assessment of clinical response will be used, if available) of clinical cure, clinical failure, and indeterminate/missing will be presented for the following time points and analysis populations:

- EOT Visit – ITT, MITT, CE, micro-ITT and ME populations
- TOC Visit – ITT, MITT, CE and ME populations
- FU Visit – ITT, MITT, CE, micro-ITT and ME populations

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

Per-subject microbiological response will be summarized as favorable (eradicated, presumed eradicated), unfavorable (persistence, persistence with decreased susceptibility, presumed persistence), and indeterminate/missing at the EOT and TOC Visits in the Micro-ITT and ME Populations. Two-sided 95% unstratified 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 microbiologic response (eradication or presumed eradication) at the TOC Visit for each pathogen isolated at baseline. The number and percentage of subjects in each treatment group with a microbiologic favorable outcome will be tabulated for the micro-ITT and ME populations.

14.2.2 Safety Analyses

All safety analyses will be conducted in the Safety population.

Verbatim descriptions of AEs will be coded using a current version of MedDRA. Summary tables will be provided for all treatment-emergent adverse events (TEAEs). A treatment-emergent AE is defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug. The number and percentage of subjects reporting a TEAE in each treatment group will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship 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 be summarized by system organ class and preferred term. For all analyses of TEAEs, if the same AE (based on preferred term) is reported for the same 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. Clinically relevant abnormal physical examination results are recorded as AEs and thus, physical exam data will not be summarized in a table.

Descriptive statistics for hematology, chemistry, and coagulation data will be summarized by treatment group and time point, and for the overall worst value post-baseline. Toxicity grades will be determined based on the modified DMID criteria and shift tables will be presented. The number and percentage of subjects with at least a two grade increase from baseline (based on DMID criteria) will be summarized by treatment arm.

Descriptive statistics of the change from baseline for vital signs will be summarized by treatment group and time point. Abnormal values, identified by threshold values defined in the SAP, will be summarized.

Descriptive statistics for ECG parameters at baseline and the EOT Visit, and the change from baseline will be presented by treatment group. QTcB at the EOT Visit and the increase from baseline for QTcB will be categorized and summarized by treatment group.

14.2.3 Sample Size Considerations

This study is designed to demonstrate non-inferiority 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. An 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.

The sample size calculation is based on ensuring sufficient power for the primary efficacy outcome for the FDA as well as the primary efficacy outcome 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. Based upon the results of the pre-specified blinded assessment of the actual number of subjects in the micro-ITT population following completion of the 250th subject, the evaluability rate is assumed to be 68.75%.

Using a 12.5% non-inferiority margin, one-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 466 randomized subjects should provide sufficient numbers for this study, assuming 68.75% 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 one-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 more than 90% power in both the MITT population and the CE population to show non-inferiority with a sample size of 466 enrolled subjects.

14.2.4 Handling of Missing Data

Details of the handling of missing data will be provided in the SAP. For the primary and secondary outcome measures of clinical response, subjects will be defined as an indeterminate/missing response if the investigator cannot determine whether the subject is a clinical cure or failure, including if the subject is lost to follow-up or misses the assessment. By definition, subjects with an indeterminate/missing response are included in the denominator in the microITT and MITT populations and thus, are analyzed in the same manner as clinical failures. Subjects with an indeterminate/missing response are excluded from the CE and ME populations. For microbiologic response, if no post-baseline source specimen is obtained and the subject has an investigator's assessment of clinical response, the microbiologic response is based on the investigator's assessment of clinical response. A microbiologic response will be considered indeterminate/missing only if the clinical response is indeterminate/missing.

14.2.5 Surgical Adjudication Committee (SAC)

Adequate surgical source control is critical to the successful treatment of cIAIs. An independent SAC will be established to review cases for all subjects classified as a clinical failure at any visit and all subjects classified as clinical cure at TOC or FU who undergo a second surgical procedure.

The SAC will review these cases, assess the adequacy of surgical source control, evaluate the investigators' clinical assessments, and either concur with the investigators' assessment of clinical response or re-classify the clinical response in accordance with the rules specified in the SAC Charter.

For additional information regarding the composition of the committee, roles and responsibilities of its members, working procedures, and decision rules refer to the SAC Charter.

14.3 Interim Analysis

No interim analysis is planned for this study.

15. STUDY DRUG MATERIALS

15.1 Study Drug Nomenclature

TP-434 is the active ingredient in eravacycline drug product. The chemical name of TP-434-046 (bis HCl salt form) is: [(4S,4aS,5aR,12aS)-4-(dimethylamino)-7-fluoro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-(2-(pyrrolidin-1-yl)ethanamido)-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide]bis-hydrochloride. The molecular formula for the free base is $C_{27}H_{31}FN_4O_8$, and the molecular weight is 558.56. Eravacycline is a yellow to orange solid that is soluble in water.

15.2 Study Drug Preparation

15.2.1 Reconstitution

All study medications will be prepared for IV infusion by an unblinded pharmacist or his/her designee. Detailed instructions for the preparation of study drug are provided in the Pharmacy Manual for this study.

The eravacycline drug product will be reconstituted using sterile WFI and will be diluted using 0.9% NaCl. Reconstituted eravacycline should be a "clear yellow solution" with no visible particulates in the vial. Once WFI is added to eravacycline vials, swirl each vial gently until the drug dissolves completely (it should take approximately 1 to 2 minutes to achieve a clear yellow solution).

The meropenem drug product will be prepared by the unblinded pharmacist according to the instructions in the meropenem package insert and will use 0.9% sodium chloride for reconstitution and normal saline for dilution.

The unblinded pharmacist or his/her designee will provide the investigator with ready-to-use blinded infusion solutions for administration at scheduled study drug infusion times. It is the responsibility of the pharmacist/designee to maintain the blind of the infusion solutions.

15.2.2 Administration

In the event of discomfort and/or pain due to infusion, the following actions can be taken at the Investigators' request:

For the 1st Dose and 3rd Dose in any dosing cycle (in the following recommended order):

- Decrease concentration (as long as total volume does not exceed 500 mL)
- Increase length of infusion to 120 minutes per IV bag

For the 2nd, 3rd, and 5th Dose in any dosing cycle:

- Follow standard of care and meropenem package insert

15.3 Study Drug Storage

Study drugs must be stored in a restricted access area under the storage conditions indicated on the product label and in the Pharmacy Manual. For further details, please consult the Pharmacy Manual.

15.4 Study Drug Packaging and Labeling

Packaging:

- Eravacycline

  See Section 15.2. Eravacycline will be packaged according to current GMP and GCP guidelines.

- Meropenem

  Meropenem for IV administration will be supplied in bulk in the original vials, which will be repackaged for the purposes of the study. Meropenem will be provided with study

specific labeling. Purchased and repackaged meropenem will be packaged according to current GMP and GCP guidelines.

Labeling:

The study medication will be labeled according to the requirements of local law and legislation as well as current GMP and GCP guidelines. Proof labels, detailing actual label text, will be available in the study files of all participating countries.

15.5 Study Drug Comparator

Meropenem is a carbapenem antibiotic that has been approved for the treatment of cIAI. The recommended dose is 1 g q8h for this indication. Please consult the local prescribing product information for important information regarding warnings, precautions and AEs reported with the use of this product.

15.6 Study Drug Accountability

It is the responsibility of the unblinded pharmacist to ensure that a current record of inventory/drug accountability is maintained. Inventory records must be readily available for inspection by the unblinded study monitor and are open to inspection by the FDA or other regulatory authorities at any time. For further details, please consult the Pharmacy Manual.

15.7 Study Drug Handling and Disposal

Upon the completion or termination of the study, and upon written authorization from the Sponsor or its representative, all unused and/or partially used study drug must be destroyed at the investigative site or returned to a central drug depot, as instructed by the Sponsor or its representative. It is the investigator's responsibility to ensure that the Sponsor or its representative has provided written authorization for study drug destruction, that procedures for proper disposal of the study drug have been established, and that appropriate records of the disposal are documented and maintained.

15.8 Investigator's Breaking of the Blind

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.

16. INVESTIGATOR REQUIREMENTS

16.1 AE Collection and Reporting

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to study treatment
- Determine the seriousness, relationship and severity of each event
- Determine the onset and resolution dates of each event
- Monitor and record all pregnancies and follow up on the outcome of the pregnancy
- Transmit SAE information to the designated CRO within 24-h of the study site staff becoming aware of new information
- Ensure all AE and SAE information are supported by documentation in the subjects' medical records
- Report SAEs to local ethics committees, as required

16.2 Protocol Adherence

Each investigator must adhere to the protocol as detailed in this document and agree that any changes to the protocol must be approved by the Sponsor prior to seeking approval from the IRB/IEC. Each investigator will be responsible for enrolling only those subjects who have met the protocol inclusion and exclusion criteria. The Sponsor and/or its representative reserves the right to close sites when appropriate [eg, in instances where the protocol is not being followed; untimely input of data into eCRFs; under-enrollment (less than 1 subject per quarter); or low microbiological evaluability rate].

16.3 Case Report Forms

Electronic CRFs will be supplied by the Sponsor, or its representative, for the recording of all study data as specified by this protocol. eCRFs should be handled in accordance with instructions from the Sponsor, or its representative. eCRFs must be completed by the designated study personnel. It is the responsibility of the principal investigator to ensure that accurate eCRFs are completed in a timely manner.

16.4 Source Document Maintenance

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, email correspondences, computer printouts, laboratory data, and recorded data from automated instruments. All source documents produced in this study will be maintained by the investigator(s) and made available for inspection by Sponsor representatives and/or regulatory authorities. The original signed informed consent form for each participating subject shall be filed with records kept by the investigator(s) and a copy given to the subject.

16.5 Study Monitoring Requirements

Site visits will be conducted by the Sponsor or authorized Sponsor representatives to inspect study data, subject's medical records, and CRFs in accordance with ICH guidelines, GCPs, and the respective U.S. or foreign regulations and guidelines, as applicable.

The investigator will permit representatives of the Sponsor and/or regulatory authorities the ability to inspect facilities and records relevant to this study.

16.6 Study Completion

The Sponsor requires the following data and materials before a study can be considered complete or terminated:

1. Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period.
2. eCRFs properly completed by appropriate study personnel and signed and dated by the investigator.
3. Complete Drug Accountability records (drug inventory log and an inventory of returned or destroyed clinical material).
4. Copies of protocol amendments and IRB/IEC approval/notification, if appropriate.

17. PROTECTION OF HUMAN SUBJECTS AND GENERAL STUDY ADMINISTRATION

This study will be conducted in compliance with the ICH E6 GCP (consolidated guidelines and the ethical principles of the Declaration of Helsinki), and any additional national or IRB/IEC-required procedures.

17.1 Informed Consent

This study will be conducted in compliance with ICH E6 GCP (consolidated guidelines pertaining to informed consent). At the first visit, prior to initiation of any study-related procedures, subjects will give their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits. Clinical assessments and local laboratory results performed during the subject's hospitalization (within 48-h of screening) may be used to establish eligibility, and microbiologic specimens collected during routine operative care prior to subject consent may be used for study purposes.

For subjects with diminished decision-making capacity and where applicable law permits, a Legally Authorized Representative (LAR) may consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in this research study. Subjects should be re-consented in cases where their capacity to make decisions has returned.

In case of significant changes to safety, the subject will be re-consented. A copy of the signed consent document or a second original must be given to the representative/ proxy consenter. The original signed consent document will be retained by the investigator. Local legal requirements must be observed and informed consent must be sought from the subject as soon as possible

afterwards, if feasible. This procedure must have prior agreement from the IEC/IRB. If applicable, the informed consent will be provided in a certified translation for non-English speaking subjects. Signed consent forms must remain in the subject's study file and be available for verification by Sponsor personnel or regulatory agency at any time.

17.2 IRB/IEC Approval

This protocol, the informed consent document, and all relevant supporting data must be submitted to the IRB/IEC for approval. IRB/IEC approval of the protocol, informed consent document, and any advertisement used to recruit study subjects must be obtained before the study may be initiated.

17.3 Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (eg, Protected Health Information [PHI] authorization in North America).

The subject will not be identified by name in the eCRF or in any study reports, and these reports will be used for research purposes only. The Sponsor and designee(s) and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

18. DATA MANAGEMENT AND MONITORING

Training sessions, regular monitoring of investigators by sponsor-designated personnel, instruction manuals, data verification, cross-checking, and data audits will be performed to ensure quality of all study data. Investigator meetings will be performed to prepare investigators and other study personnel for appropriate collection of study data.

The Sponsor will perform internal and/or external audits of study data.

It will be the responsibility of the investigator(s) to assure that essential laboratory and pharmacy manuals are available at the investigator/institutional site. Any or all of these documents may be subject to, and should be available for, audit by the Sponsor's auditor and/or inspection by regulatory authorities.

18.1 Direct Access to Source Data/Documents

The investigator agrees by his/her participation that the results of this study may be used for submission to national and/or international registration and supervising authorities. If required, these authorities will be provided with the names of investigators, their addresses, qualifications, and extent of involvement. It is understood that the investigator is required to provide the Sponsor with all study data, complete reports, and access to all study records.

Data generated by this study must be available for inspection by any regulatory authorities, by the Sponsor, and the IRB/IEC as appropriate. At a subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Subject medical information obtained during the course of this study is confidential and disclosure to third parties other than those noted above is prohibited.

18.2 Retention of Records

U.S. Investigational New Drug (IND) exemption regulations require that records and documents pertaining to the conduct of this study and the distribution of investigational drugs including CRFs, consent forms, laboratory test results, and medication inventory records must be kept on file by the principal investigator for a minimum of two years after notification by the Sponsor that a marketing application has been approved for eravacycline [Code of Federal Regulations, Title 21, Part 312, Section 62(c)]. If no application is filed or approved, these records must be kept for two years after the investigation has been discontinued and the U.S. FDA and applicable foreign authorities have been notified. The Sponsor will notify the investigator of these events. No study records should be destroyed without prior authorization from the Sponsor. This study will be conducted under a U.S. IND; for study sites outside the United States, the investigator must comply with U.S. FDA IND regulations and with those of the relevant national and local regulatory authorities.

19. FINANCING AND INSURANCE

The financing and insurance for this study are outlined in the Clinical Trial Agreement and must comply with all local and national rules and regulations.

20. PUBLICATION POLICY

The publication policy is outlined in the Clinical Trial Agreement. The data generated in this clinical trial are the exclusive property of Tetraphase Pharmaceuticals Inc. and are confidential. Written approval from Tetraphase is required prior to disclosing any information related to this clinical trial.

21. REFERENCES

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[3] Brown, R. and B. Bhyravbhatla, "Computational analysis of eravacycline binding to the ribosome A-site," Xtal Biostructures, Natick, MA, July 24, 2008.

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APPENDIX 1: APACHE II SCORE

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

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

Age Points	
Age	**Points**
≤44	0
45-54	2
55-64	3
65-74	5
≥75	6
Total Age Points	**B**

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

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

APPENDIX 2: CENTRAL SAFETY LABORATORY TESTS

Hematology:

- Hemoglobin
- Hematocrit
- Erythrocyte count (RBC)
- Mean cell volume (MCV)
- Mean cell hemoglobin (MCH)
- Mean cell hemoglobin concentration (MCHC)
- Leukocyte count (WBC)
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils
- Platelets

Coagulation:

- Prothrombin time
- Partial thromboplastin time
- Fibrinogen

Urinalysis:

- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Urine microscopy (RBC, WBC, crystals, and casts)

Clinical Chemistry:

- Magnesium
- Bicarbonate
- Sodium
- Potassium
- Phosphorus
- Chloride
- Calcium
- Alkaline phosphatase
- Gamma-glutamyl transferase (GGT)
- Alanine aminotransferase (ALT/GPT)
- Aspartate aminotransferase (AST/GOT)
- Creatine kinase (CK)
- Lactic dehydrogenase (LDH)
- Total and indirect bilirubin
- Total cholesterol
- Glucose, non-fasting
- Total protein
- Albumin
- Creatinine
- Urea nitrogen
- Uric acid
- Amylase
- Lipase
- Serum pregnancy test *(women of childbearing potential only)*

NOTE: *If a serum pregnancy test is not available at the investigator site then a urine pregnancy test may be utilized locally.*

APPENDIX 3: BLOOD PK SAMPLE COLLECTION, HANDLING, PREPARATION AND SHIPPING

The timelines and procedures for PK sampling, handling, dispatch, and analysis are detailed in the Central Laboratory Manual.

Dose Cycle 1 - PK Sampling Schedule

Time	PK Sample Number
30 – 0 min prior to the start of the 1st Dose of Dose Cycle 1	1
End of infusion of the 1st Dose of Dose Cycle 1 (± 2 min)	2
+3-h post the start of the 1st Dose of Dose Cycle 1[a]	3
+7-h post the start of the 1st Dose of Dose Cycle 1[a]	4
30 – 0 min prior to the start of the 4th Dose of Dose Cycle 1	5

[a] PK sample must be collected within ± 10 minutes of target time.