



CLINICAL TRIAL PROTOCOL

A Phase 3, Randomized, Double-Blind, Double-Dummy, Multicenter, Prospective Study to Assess the Efficacy and Safety of IV Eravacycline Compared with Ertapenem in Complicated Urinary Tract Infections

Protocol No.: TP-434-021

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EudraCT No.: 2016-002207-26

Version 1.0: 27 July 2016

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.

CONFIDENTIAL

The information in this study protocol is strictly confidential and is available for review to Investigators, study site personnel, the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and the Regulatory Authorities. It will not be disclosed to third parties without written authorization from Tetrphase Pharmaceuticals, Inc. (the Sponsor), except to obtain informed consent from persons participating in the trial. Once the protocol is signed, its terms are binding for all parties.

1. SPONSOR SIGNATURE PAGE

Sponsor: Tetraphase Pharmaceuticals, Inc.
Protocol Number: TP-434-021
Study Medication: IV Eravacycline
Protocol Title: A Phase 3, Randomized, Double-Blind, Double-Dummy, Multicenter, Prospective Study to Assess the Efficacy and Safety of IV Eravacycline Compared with Ertapenem in Complicated Urinary Tract Infections

Date of Issue: 27 July 2016

Approved by:

27 July 2016

Date



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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 [Food and Drug Administration (FDA), European Medicines Agency (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)

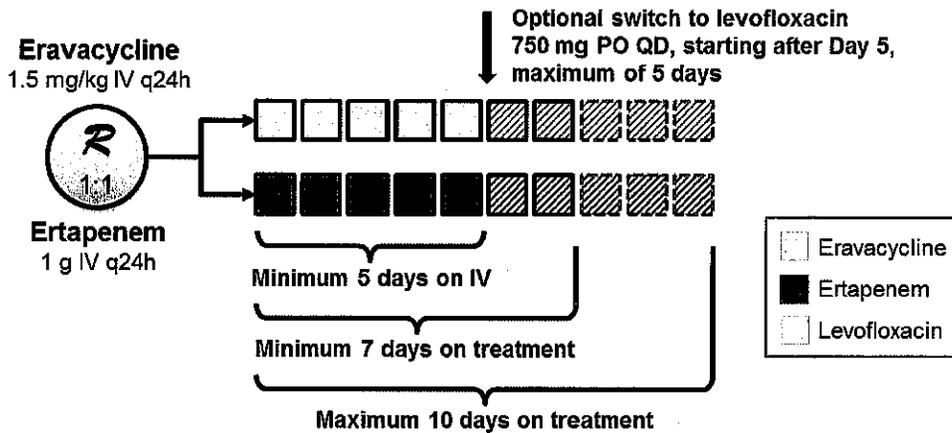
Institution Name

Institution Address

2. TABULATED PROTOCOL SUMMARY

Name of Sponsor/Company:	Tetraphase Pharmaceuticals, Inc.
Name of Finished Products:	Eravacycline (TP-434), Ertapenem (comparator), Levofloxacin (oral drug)
Name of Active Ingredients:	Eravacycline, Ertapenem (comparator), Levofloxacin (oral drug)
Title of Study:	A Phase 3, Randomized, Double-Blind, Double-Dummy, Multicenter, Prospective Study to Assess the Efficacy and Safety of IV Eravacycline Compared with Ertapenem in Complicated Urinary Tract Infections
Indication:	Complicated Urinary Tract Infection (cUTI)
Anticipated Study Period:	4Q 2016 - 4Q 2018
<p>Objectives:</p> <p>Primary Objective:</p> <ul style="list-style-type: none"> The primary objective is to demonstrate that eravacycline is non-inferior to ertapenem in responder outcome (clinical cure and microbiologic success) in the microbiological intent-to-treat (micro-ITT) population at the End of IV (EOI) visit (within 1 day of the completion of IV study drug treatment) and the Test of Cure (TOC) visit (defined as 14-17 days after randomization). NOTE: For the European Medicines Agency (EMA), the primary objective is to demonstrate that eravacycline is non-inferior to ertapenem in microbiological outcome in the microbiological modified ITT (micro-MITT) and microbiologically evaluable (ME) populations at TOC visit. <p>Secondary Objectives:</p> <ul style="list-style-type: none"> To compare responder outcomes in the treatment arms at Day 5 in the micro-ITT population To compare clinical outcomes in the treatment arms at Day 5, EOI, End of Treatment (EOT), TOC, and Follow-up (FU) visits in the following populations: <ul style="list-style-type: none"> ITT population Clinically evaluable (CE) population Micro-ITT population Micro-MITT population ME population To compare microbiologic outcome in the treatment arms at Day 5, EOI, EOT, TOC, and FU visits in the following populations: <ul style="list-style-type: none"> Micro-ITT population Micro-MITT population ME population To assess safety and tolerability of IV eravacycline administration in the safety population. To explore pharmacokinetic (PK) parameters of eravacycline. 	
<p>Methodology:</p> <p>This is a phase 3, randomized, double-blind, double-dummy, multicenter, prospective study to assess the efficacy, safety and pharmacokinetics of eravacycline compared with ertapenem in the treatment of cUTI.</p> <p>Randomization will be stratified based on two criteria: (1) by primary site of infection (pyelonephritis and normal urinary tract anatomy vs all other diagnoses) and (2) by the receipt of a single dose of effective non-study antibiotics for the acute cUTI within 72 hours prior to randomization. An enrollment cap of approximately 50% is planned for subjects with pyelonephritis with normal urinary tract anatomy. Also, an enrollment cap of approximately 20% is planned for subjects who have received a single dose of non-study antibiotics for the acute cUTI within 72 hours prior to randomization.</p> <p>In this study subjects will be enrolled and randomized to one of two treatment arms in a 1:1 ratio: (i) eravacycline intravenously (IV) / levofloxacin (PO), or (ii) ertapenem (IV) / levofloxacin (PO). (</p> <p>Figure 1 below)</p>	

Figure 1: Study Design Schema



Key: IV = intravenous; PO = oral; q24h = every 24 hours; QD = once a day.

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

Subjects will be randomized and enrolled to one of two treatment arms in a 1:1 ratio: (i) eravacycline or (ii) ertapenem. Eravacycline will be dosed at 1.5 mg/kg IV every 24 hours (q24h) for at least the first 5 doses, and ertapenem will be dosed at 1 g IV q24h for at least the first 5 doses. At a minimum, the first five IV doses must be administered in an in-patient hospital setting; subsequent doses may be administered on an out-patient basis. An IV-to-PO transition can occur after dose 5, provided the subject has demonstrated clinical improvement as defined per protocol (Section 11.3.2). After the EOI, oral study drug (levofloxacin) will be dosed through study drug completion. Subjects requiring more than 5 days of IV dosing will have the days of PO dosing reduced to maintain the maximum number of days on treatment at 10 days IV and PO combined. During PO study drug administration subjects will receive 750 mg of levofloxacin once daily. Subjects with documented allergy to levofloxacin or baseline pathogens from blood or urine cultures that are resistant to levofloxacin may receive an alternate PO antibiotic as described in the Pharmacy Manual. Study drugs will be administered daily according to the dosing schedule in Table 1 below:

Table 1: Study Drug Administration

Treatment Arms	For at least the first 5 doses	After EOI through Study Drug Completion
	IV Infusion	Oral Administration
Eravacycline (IV) / Levofloxacin (PO)	Eravacycline 1.5 mg/kg IV and placebo IV q24h	Levofloxacin 750 mg PO QD
Ertapenem (IV) / Levofloxacin (PO)	Ertapenem 1 g IV and placebo IV q24h	Levofloxacin 750 mg PO QD

Key: EOI = End of IV; IV = intravenous; PO = oral; q24h = every 24 hours; QD = once a day.

Ertapenem dose will be adjusted for subjects with creatinine clearance ≤ 30 mL/min as described in the prescribing information. Levofloxacin dose will be adjusted for subjects with creatinine clearance < 50 mL/min as described in the prescribing information.

Appropriate urine specimens for culture will be collected from a mid-stream urine specimen, a newly-placed urinary catheter, cystoscopy, suprapubic aspiration, or a properly disinfected collection port prior to the start of study drug therapy. These specimens will be cultured and quantified in the local laboratory or a reference regional laboratory. The purified pathogen(s) will be sent to a central microbiology laboratory for confirmation of species identification and

susceptibility testing.

Aerobic and anaerobic blood cultures will be obtained at two separate sterile venipuncture sites prior to initiation of study drug therapy. Upon knowledge of a positive culture for a pathogen, blood cultures should be repeated until sterile (i.e., 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 (e.g., signs and symptoms of persistence, relapse, or new infection).

Each subject will receive 7-10 doses of study drug (total IV and PO). Visits will be conducted at Day 5, EOI and EOT; the TOC visit will be 14-17 days after randomization, and at least 5 days after the last dose of study drug; the FU visit will take place 21-28 days after randomization. At any time, the Investigator may discontinue the subject from study drug based on the best interests of the subject. Prior to starting non-study antibiotics, the EOT assessments must be performed. The subject should remain in the study and all applicable procedures should be followed through FU.

Table 2: Timeline for Individual Study Subjects

Screening	Randomization	Study Drug Treatment	Day 5 Visit	End of IV (EOI) Visit	End of Treatment (EOT) Visit	Test of Cure (TOC) Visit	Follow-up (FU) Visit
Within 36-h prior to Randomization		Dose Cycles 1-10	5 days after Randomization	Within 1 day of Last IV Dose	Within 1 day of Last Dose (IV or PO)	14-17 days after Randomization & ≥ 5days after Last Dose	21-28 days after Randomization
Establish diagnosis of cUTI Verify eligibility for enrollment Collection of a urine sample for urinalysis and culture Baseline assessment Informed consent must be obtained prior to performing any study specific procedures that are not standard of care	Use IWRS to randomize subject to study drug	Either: Eravacycline 1.5mg/kg IV plus placebo IV q24h with optional transition to Levofloxacin 750 mg PO QD OR Ertapenem 1 g IV plus placebo IV q24h with optional transition to Levofloxacin 750 mg PO QD	Assessments of clinical response and safety Collection of a urine sample for urinalysis and culture Determination of length of treatment; subjects are expected to receive 7-10 days of therapy.	Subjects are to receive at least 5 doses of IV study drug Assessments of clinical response and safety Collection of a urine sample for urinalysis and culture	Subjects are expected to receive 7-10 doses of study drug Assessments of clinical response and safety Collection of a urine sample for urinalysis and culture	Return to Study Center for: Assessment of clinical response and safety Collection of a urine sample for urinalysis and culture	Return to Study Center for: Assessment of clinical response and safety Collection of a urine sample for urinalysis and culture

Key: cUTI = complicated urinary tract infection; EOI = End of IV visit; EOT = End of Treatment visit; IV = intravenous; IWRS = Interactive Web-based Response System; FU = Follow-up visit; PO = oral; TOC = Test of Cure visit; q24h = every 24 hours; QD = once a day.

Number of Subjects:

Approximately 1200 subjects will be randomized to receive study drug.

Investigative sites will be recruited in approximately 130 centers worldwide.

Criteria for Study Entry:

Inclusion Criteria (Subjects must meet all of the following inclusion criteria)

1. Male and female subjects with either:
 - a. Pyelonephritis and normal urinary tract anatomy (approximately 50% of the total population), **OR**
 - b. cUTI with at least one of the following conditions associated with a risk for developing cUTI:
 - i. Indwelling urinary catheter
 - ii. Urinary retention (at least approximately 100 mL of residual urine after voiding)
 - iii. History of neurogenic bladder
 - iv. Partial obstructive uropathy (e.g., nephrolithiasis, bladder stones, and ureteral strictures)

- v. Azotemia of renal origin (not congestive heart failure [CHF] or volume related) such that the serum blood urea nitrogen [BUN] is elevated (> 20 mg/dL) AND the serum BUN:creatinine ratio is < 15
 - vi. Surgically modified or abnormal urinary tract anatomy (e.g., bladder diverticula, redundant urine collection system, etc.) **EXCEPT** urinary tract surgery within the last 30 days (placing of stents or catheters is not considered to be surgical modification)
2. At least 18 years of age at the time of consent
 3. Able to provide informed consent. For subjects with diminished decision-making capacity and where applicable law permits, a Legally Authorized Representative may consent on behalf of a prospective subject to the subject's participation.
 4. At least two of the following signs or symptoms:
 - a. Chills, rigors, or warmth associated with fever (oral, rectal, tympanic, or by temporal artery temperature $> 100.4^{\circ}\text{F} / 38^{\circ}\text{C}$) or hypothermia (oral, rectal, tympanic, or by temporal artery temperature $< 95^{\circ}\text{F} / 35^{\circ}\text{C}$)
 - b. Flank pain (pyelonephritis) or pelvic pain (cUTI)
 - c. Nausea or vomiting
 - d. Dysuria, urinary frequency, or urinary urgency
 - e. Costo-vertebral angle tenderness on physical examination
 5. Urine specimen with evidence of pyuria
 - a. Dipstick analysis positive for leukocyte esterase (where positive result is at least “++” as indicated on the urine dipstick provided in the laboratory kit), **OR**
 - b. ≥ 10 white blood cells (WBCs) per cubic millimeter, **OR**
 - c. ≥ 10 WBCs per high power field
 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 (e.g., condom) 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 (refer to section 11.4.1 for definition of non-childbearing potential), subjects must commit to either:
 - i. Use at least two medically accepted, effective methods of birth control (e.g., 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**
 - c. Sexual abstinence

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

1. Use of systemic antibiotics effective in cUTI within 72 hours prior to randomization **EXCEPT** under the following circumstances:
 - a. Subjects with suspected acute cUTI who have received a single dose of effective non-study antibiotics for the acute cUTI
 - b. Signs and symptoms of cUTI developed while on the antibiotic for another indication
2. History of an ertapenem-resistant urinary tract infection within 1 year of consent. Likely to require > 10 days of antibiotic treatment to cure the acute cUTI or likely to receive ongoing antibacterial drug prophylaxis prior to the FU visit (e.g. Subjects with chronic vesiculo-ureteral reflux).
3. Unlikely to survive at least through the duration of the study
4. Hypotension, systolic blood pressure ≤ 90 mmHg
5. Complicated pyelonephritis with complete obstruction or known or suspected renal or perinephric abscess, emphysematous pyelonephritis, **OR**
Any condition likely to require surgery to achieve cure (this does NOT include procedure to place catheters or obtain diagnosis)
6. Known or suspected urinary fungal infection
7. Uncomplicated lower urinary tract infections
8. Suspected or confirmed active prostatitis, or currently under treatment for prostatitis
9. High risk for cUTI due to *Pseudomonas sp.* (e.g., history of prior cUTIs due to *Pseudomonas*, ≥ 20 mg QD prednisone or equivalent steroid, and other risk factors as perceived by the Investigator)
10. History of renal transplantation

11. Presence of an ileal loop
12. Any history of trauma to the pelvis or urinary tract occurring within 30 days prior to consent
13. Indwelling urinary catheters present at screening which are not expected to be removed or replaced within 72 hours of randomization (e.g., nephrostomy tubes, stents, urethral and suprapubic catheters).
14. Known concomitant HIV infection with CD4 counts below 200 cells/ μ L within six months prior to consent, or an AIDS defining diagnosis within six months prior to consent
15. Neutropenia (ANC < 1,000 PMNs/ μ L)
16. Participation in a study with an experimental drug or device within 30 days prior to consent
17. Known or suspected hypersensitivity to tetracyclines, carbapenems, or β -lactams
18. History of seizures
19. Any other unstable or clinically significant concurrent medical condition (e.g., immunosuppressive therapy, chemotherapy, class IV heart or lung disease, end stage renal disease, or requiring hemodialysis) that would, in the opinion of the Investigator, jeopardize the safety of a subject and/or their compliance with the protocol

Test Product, Dose and Route of Administration:

Eravacycline (TP-434-046) was synthesized under current good manufacturing practices and the IV 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 0.9% NaCl, to generate 0.3 mg/mL eravacycline solutions for 1.5 mg/kg q24h IV infusions. Please refer to Section 16.2 and the Pharmacy Manual for additional information on reconstitution.

Reference Therapy, Dose and Route of Administration:

Ertapenem 1 g administered by IV q24h.

Oral Transition Medication:

Levofloxacin 750 mg PO q24

Duration of Treatment:

Subjects will remain on study drug for at least 7 days. Study drug may be continued for up to 10 days if the subject meets criteria as specified in the protocol (Section 11.3.3). The TOC visit will be 14-17 days after randomization and the FU visit will be 21-28 days after randomization.

Pharmacokinetics:

Maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}), and area under the plasma concentration-time curve (AUC) will be determined following the first dose of IV study drug. Trough plasma concentration will be determined prior to the second and fifth doses of IV study drug.

Statistical Methods and Criteria for Evaluation:**Sample Size Estimation**

For the calculation of sample size it is assumed that 66% of the randomized subjects will be in the micro-ITT population. It is also assumed that the responder rates (clinical cure and microbiological success) at EOI will be 93% and 94% in the eravacycline group and the ertapenem group, respectively and at TOC will be 71% and 72% in the eravacycline group and ertapenem group, respectively. For the EMA, it was assumed that 65% of the randomized subjects will be in the micro-MITT population and 60% in the ME population. The microbiological success rates at TOC are assumed to be 79% and 82% in both treatment groups in the micro-MITT and ME populations, respectively. With these assumptions, utilizing a 10% non-inferiority margin, and the sample size methodology of Farrington-Manning, 790 subjects (395 subjects per group) are required in the micro-ITT population and a total of 1200 subjects will be randomized. This sample size provides at least 80% power for the co-primary efficacy outcomes at EOI and TOC in the micro-ITT population as well as for the co-primary outcomes for the EMA.

Safety

Safety analyses will be conducted on the safety population. Subjects will be analyzed according to the treatments received.

Adverse Events

Verbatim descriptions of adverse events (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 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, coagulation, and urinalysis (where applicable) data will be summarized using shift tables based on toxicity criteria, change from baseline, and the number and percentage of subjects with clinically notable values. Clinically notable values will be specified in the Statistical Analysis Plan.

Other Safety Data

Physical examination data will be reported (as warranted) and analyzed as adverse events. Vital signs will be summarized using descriptive statistics for change from baseline and percentage of subjects with an abnormal value as defined in the SAP.

Efficacy Assessments

Responder rates will be determined for each treatment arm overall and for the randomization stratification factors: (1) primary site of infection (pyelonephritis and normal urinary tract anatomy vs. all other diagnoses) and (2) receipt of a single dose of effective non-study antibiotics for the acute cUTI within 72 hours prior to randomization. The responder rate will be determined as the number of subjects with clinical cure (i.e., complete or significant improvement of signs or symptoms such that no further systemic antibiotic treatment is required) and microbiological success at the respective visit divided by the number of subjects in the analysis population (i.e., overall or by randomization strata). A two-sided 95% CI around the difference in the eravacycline and ertapenem responder rates will be determined using the Miettinen and Nurminen method. If the lower bound of the 95% CI for the difference in responder rates at EOI and TOC in the micro-ITT population is above -10% for both time points, noninferiority of eravacycline to ertapenem will be concluded.

For the EMA, the microbiological success rate will be determined as the number of subjects with microbiological success at the respective visit divided by the number of subjects in the analysis population. Microbiological success rates at TOC will be determined, along with two-sided 99% CIs, by treatment arm for subjects in the micro-MITT and ME populations. If the lower bound of the 99% CI for the difference in microbiological success rates at TOC is above -10% for both the micro-MITT and ME populations, noninferiority of eravacycline to ertapenem will be concluded.

Clinical outcome and microbiological outcome will be summarized by treatment group, time point and analysis population. Two-sided 95% CIs for the difference between treatment groups in clinical cure and microbiological success will be provided.

Microbiology

Purified bacterial pathogens aerobically cultured from urine using a calibrated loop to identify a quantitative count of bacteria at a lower limit of 10^3 CFU/mL and aerobic and anaerobic blood culture pathogens will be evaluated for susceptibility and the emergence of resistance to study drugs and overgrowth of non-susceptible organisms at a central laboratory.

3. SCHEDULE OF ASSESSMENTS

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

See footnotes on following page(s).

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

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

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5. LIST OF ABBREVIATIONS

ADR	Adverse drug reaction	EMA	European Medicines Agency
AE	Adverse event	EOI	End of IV visit
AIDS	Acquired immune deficiency syndrome	EOT	End of Treatment visit
ALT/GPT	Alanine aminotransferase	etc.	Et cetera [<i>Latin</i>], and so forth
ANC	Absolute neutrophil count	°F	Degrees Fahrenheit
AST/GOT	Aspartate aminotransferase	FDA	Food and Drug Administration
AUC	Area under the plasma concentration-time curve	FU	Follow-up visit
AUC ₀₋₂₄	Area under the plasma concentration-time curve from time zero to time 24-h	g	Gram
AUC _{0-24(ss)}	Area under the plasma concentration-time curve from time zero to time 24-h at steady state	GCP	Good Clinical Practice
BID	Twice a day	h	Hour
BLQ	Below the limit of quantification	HIV	Human immunodeficiency virus
B/P	Blood pressure	HR	Heart rate
BUN	Blood urea nitrogen	IB	Investigator's Brochure
°C	Degrees Celsius	ICH	International Conference on Harmonization
CD4	Cluster of differentiation 4: a glycoprotein that is found primarily on the surface of helper T cells	IDSA	Infectious Diseases Society of America
CE	Clinically evaluable (population)	ie	Id est [<i>Latin</i>], that is
CFR	Code of Federal Regulations	IEC	Independent Ethics Committee
CFU	Colony-forming unit	IND	Investigational new drug
CHF	Congestive heart Failure	IRB	Institutional Review Board
CI	Confidence interval	ITT	Intent-to-treat (population)
cIAI	Complicated intra-abdominal infection	IV	Intravenous/intravenously
CK	Creatine kinase	IWRS	Interactive Web-based Response System
C _{max}	Maximum observed plasma concentration	kg	Kilogram
C _{trough}	Minimum observed plasma concentration	L	Liter
CRF	Case report form	LDH	Lactic dehydrogenase
CRO	Contract research organization	MAD	Multiple ascending dose
cUTI	Complicated urinary tract infection	MCH	Mean cell hemoglobin
dL	Deciliter	MCHC	Mean cell hemoglobin concentration
DSMB	Data Safety Monitoring Board	MCV	Mean cell volume
eC _{Cr}	Estimated Cockcroft-Gault creatinine clearance	ME	Microbiologically evaluable (population)
eCRF	Electronic case report form	MedDRA	Medical Dictionary of Regulatory Activities
e.g.	Exempli gratia [<i>Latin</i>], for example	Micro	Microbiological

µg	Microgram	qXh	Every X hours
µL	Microliter	RBC	Red blood cell, erythrocyte count
mg	Milligram	RR	Respiration Rate
MIC	Minimum inhibitory concentration	SAE	Serious adverse event
MIC ₉₀	Minimum inhibitory concentration of at least 90% of clinical isolates tested	SAP	Statistical Analysis Plan
min	Minute	SAS	Statistical Analysis System
mL	Milliliter	SOA	Schedule of assessments
mmHg	Millimeter of mercury	Sponsor	Tetraphase Pharmaceuticals, Inc.
mm ³	Cubic millimeter	SUSAR	Suspected unexpected serious adverse reaction
MITT	Modified intent-to-treat (population)	T _½	Elimination half-life
NA	Not applicable	T _{max}	Time to C _{max}
NaCl	Saline, sodium chloride	TOC	Test of Cure (visit)
ng	nanogram	TEAE	Treatment emergent adverse event
NI	Non-inferiority	U.S.	United States
PHI	Protected health information	TP-434	Eravacycline (active ingredient)
PK	Pharmacokinetic	TP-434-046	Eravacycline (di HCl salt form)
PMN	Polymorphonuclear neutrophils	WBC	White blood cell, leukocyte count
PO	Oral/orally	WFI	Water for infusion
QD	Once a day	Yrs	Years

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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7. BACKGROUND AND RATIONALE

7.1 Complicated Urinary Tract Infections

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

7.2 Properties of Eravacycline

Eravacycline is a novel fluorocycline tetracycline that inhibits bacterial protein synthesis by binding to the 30S-ribosomal subunit, blocking entry of aminoacyl-tRNA molecules into the A site of the ribosome, thus preventing incorporation of amino-acid residues into elongating peptide chains (8). Importantly, eravacycline was designed to be active against the two major acquired tetracycline-specific resistance mechanisms: ribosomal protection where a protein mediates the removal of tetracycline from its binding site on the small ribosomal subunit and drug efflux (8,9). As a fluorocycline, eravacycline is impervious to either mechanism, with equivalent microbiological activity against *E. coli* strains expressing either resistance determinant. Further, eravacycline showed potent mechanism-based activity in a coupled transcription/translation assay ± the addition of Tet(M), a widespread ribosomal protection protein. Thus, eravacycline should be active where legacy tetracyclines doxycycline, minocycline, and tetracycline are not.

The activity of eravacycline was evaluated in an *in vitro* surveillance study against bacteria collected from European and USA hospitals in 2013 – 2014. In this study, the minimum inhibitory concentrations of at least 50%/90% of clinical isolates tested (MIC_{50/90} values) for clinical isolates of *E. coli* (n = 502; 0.12/0.25 µg/mL), *K. pneumoniae* (n = 497; 0.5/1 µg/mL), *E. faecalis* (n = 501; 0.06/0.06 µg/mL), *E. faecium* (n=459; 0.06/0.06 µg/mL) and *S. aureus* (n = 980; 0.06/0.12 µg/mL) were not different or within two-fold when compared to subsets of isolates that were 3rd generation cephalosporin-resistant, *E. coli* (n=92, 0.25/0.5 µg/mL) and *K. pneumoniae* (n = 107; 0.5/2 µg/mL); carbapenem-resistant, *K. pneumoniae* (n=36; 0.5/2 µg/mL); vancomycin-resistant, *E. faecalis* (n = 25; 0.06/0.12 µg/mL) and *E. faecium* (n=254; 0.06/0.6

µg/mL); and methicillin-resistant, *S. aureus* (n=493; 0.06/0.12 µg/mL).(5) Eravacycline had reduced activity against *P. aeruginosa* (n=499; 8/16 µg/mL). The same primary Gram-negative pathogens (i.e., *E. coli* and *K. pneumoniae*) isolated and identified in the complicated intra-abdominal infection (cIAI) phase 2 and phase 3 studies were also the major pathogens in the phase 3 cUTI study. Major Gram-positive pathogens (i.e., *E. faecalis* and *S. aureus*) were also in common between cIAI and cUTI studies. The full description of the *in vitro* antibacterial activity of eravacycline can be found in the Investigator's Brochure (IB).

The efficacy of eravacycline in sepsis, tissue, lung, and pyelonephritis/cUTI murine models of infection has been described by Murphy et.al (3). Eravacycline is effective in reducing the bacterial burden in kidneys from mice that have been infected with a tetracycline-resistant uropathogenic strain of *E. coli* or an extended-spectrum β-lactamase-producing strain of *K. pneumoniae*.

In terms of Gram-positive pathogens, eravacycline has activity against both nosocomial and community-acquired methicillin-susceptible or methicillin-resistant *Staphylococcus aureus* strains, vancomycin-susceptible or vancomycin-resistant *Enterococcus faecium*, and *Enterococcus faecalis*. In cUTIs, enterococci and streptococci can be frequently isolated, and eravacycline consistently exhibits excellent activity against these strains (10).

The high degree and reliability of *in vitro* antibacterial activity against multidrug-resistant Gram-negative pathogens, the efficacy observed with eravacycline in established animal models of infection, and the efficacy and tolerability established in phase 2 and phase 3 studies of cIAIs warrant clinical development of eravacycline as a single daily dose IV treatment option for cUTIs.

7.3 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 pathogens, including multidrug resistant Gram-negative 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 were favorable and the failure was believed to be due 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. No other safety signals have been identified.

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

7.3.1 Phase 1 IV Multiple Ascending Dose Study (TP-434-P1-MAD-1)

TP-434-P1-MAD-1 was a randomized, placebo-controlled, double-blind study to evaluate the safety, tolerability, and pharmacokinetics of multiple ascending doses of IV eravacycline. The observed pharmacokinetic parameters of the 1.5 mg/kg IV dose given over 60 min were: mean area under the plasma concentration-time curve from time zero to time 24-h (AUC_{0-24}) of 7858 ng·h/mL (range: 6400 to 8839 ng·h/mL); maximum observed plasma concentration (C_{max}), 1891.67 ng/mL; and elimination half-life ($T_{1/2}$), 29.34-h.

7.3.2 Phase 1 IV Study in Subjects with Renal Impairment (TP-434-014)

Plasma pharmacokinetics was determined in subjects with end-stage renal disease (ESRD) following administration of a single dose of IV eravacycline. A single dose of 1.5 mg/kg eravacycline was administered to healthy subjects and subjects with ESRD. The geometric mean C_{max} was increased by 4.8% (90% CI: 69.3, 158.5) and the geometric mean $AUC_{0-\infty}$ was decreased by 7.6% (90% CI: 72.1, 118.5) for subjects with ESRD versus healthy subjects. The increased C_{max} in ESRD subjects was not associated with increased rates of AEs or laboratory abnormalities.

7.3.3 Phase 1 IV Study in Subjects with Hepatic Impairment (TP-434-013)

Plasma pharmacokinetics was determined in subjects with hepatic impairment following administration of a single dose of IV eravacycline. A single dose of 1.5 mg/kg eravacycline was administered to healthy subjects and subjects with mild, moderate, or severe hepatic impairment. The geometric mean C_{max} increased by 13.9%, 16.3%, and 19.7% and the geometric mean $AUC_{0-\infty}$ increased by 22.9%, 37.9%, and 110.3% for subjects with mild, moderate, and severe hepatic impairment versus healthy subjects. The increased C_{max} and AUCs in subjects with hepatic impairment were not associated with increased rates of AEs or laboratory abnormalities.

7.3.4 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 rates were reported as 1.9%, 10.7%, and 6.7%; and emesis rates as 5.7%, 1.8%, and 0% 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. These rates are lower than those observed in the phase 1 studies, probably resulting from the decreased dosing concentration used in the phase 2 study.

7.3.5 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 by the investigator as 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.

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

The efficacy of an IV-to-PO transition regimen of eravacycline was evaluated in a phase 3, randomized, double-blind, double-dummy, multicenter, prospective study in subjects with cUTI. In the Lead-in portion of the study, IV eravacycline (1.5 mg/kg q24h) with transition to PO eravacycline at dose of either 200 mg or 250 mg q12h was compared with IV levofloxacin (750 mg q24h) with transition to PO levofloxacin at the same dose. One hundred forty-three subjects were enrolled the Lead-in portion of the study. Based upon similar efficacy and possibly better gastrointestinal tolerability, eravacycline 200 mg q12h was chosen as the PO transition regimen to be tested in the Pivotal portion of the study. A total of 908 subjects were enrolled in the

Pivotal portion of the study. The responder rates (combined clinical cure and microbiological success) at the Post-Treatment visit in the microbiological-intent-to-treat population were 60.4% and 66.9% in the eravacycline and levofloxacin groups, respectively. The between treatment group difference [% (95% CI)] was -6.5 (-14.1, 1.2); non-inferiority was not declared. Detailed post-hoc analysis of study data suggested that lower-than-expected exposures during PO dosing of eravacycline explained the failure to meet the primary efficacy endpoint of the study. In these post-hoc analyses, efficacy outcome measures at the end of IV treatment appeared to favor eravacycline as did results in subjects who did not transition to PO study drug.

Eravacycline was safe and generally well-tolerated in cUTI subjects. The most commonly reported TEAEs were gastrointestinal disorders, including nausea (18.0% and 3.1% in the eravacycline and levofloxacin groups, respectively) and vomiting (5.9% and 1.1% in the eravacycline and levofloxacin groups, respectively). In the eravacycline group, 7 subjects (1.5%) experienced SAEs, compared with 6 subjects (1.3%) in the levofloxacin group. None of the SAEs in the eravacycline group were considered by the investigator as related to treatment. One subject in the eravacycline group died during the study from disseminated intravascular coagulation that was assessed by the investigator as not related to treatment. 15 subjects (3.3%) discontinued study drug due to a treatment-related TEAE in the eravacycline group compared to 10 subjects (2.2%) in the levofloxacin group.

7.3.7 Summary of Known and Potential Risks

Eravacycline is a novel, synthetic fluorocycline of the tetracycline class, a well-known class of antibiotics that has been utilized for over 50 years.

The overall risk to subjects of the present study is deemed to be acceptable, based on 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 emesis were observed in the cIAI phase 2 and phase 3 studies. Higher levels of nausea and emesis 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 multiple ascending dose (MAD) study. The eravacycline dosing concentration was reduced by 25-50% in the cIAI phase 2 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, the Investigator should carefully review the inclusion and exclusion criteria to ensure the appropriate enrollment of subjects. Although not observed in subjects treated with eravacycline in clinical studies, *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. Subjects should also be monitored for tetracycline class effects as described in the eravacycline IB.

Please refer to the latest version of the eravacycline IB for additional information on eravacycline and tetracycline class effects, and the ertapenem and levofloxacin prescribing information for additional information on eravacycline, ertapenem and levofloxacin.

7.4 Dosing Rationale

For this phase 3 study in subjects with cUTI, the eravacycline dose selected is 1.5 mg/kg q24h IV. The justification for this dose is presented below.

The 1.5 mg/kg IV dose was selected based upon the favorable efficacy and safety profile observed in the phase 2 study in cIAI. Data from the phase 2 study was used in a Monte Carlo simulation and the predicted probability of clinical success for this dose of eravacycline was >80% for all pathogens with an minimum inhibitory concentration (MIC) value of 4 µg/mL or less. An analysis of data from subjects who received only IV treatment in the phase 3 study in cUTI also supports the selection of 1.5 mg/kg IV.

The 1.5 mg/kg IV dose of eravacycline also results in urine levels at steady state well over the MIC₉₀ values for all pathogens except *Pseudomonas aeruginosa*. In the phase 1 IV MAD study the urine concentrations of eravacycline following the first dose in the 1.5 mg/kg q24h group were 6.92 ± 1.16 µg/mL for the first 8 hours post-dose and 2.83 ± 1.8 µg/mL for the next 16 hours. This suggests that high drug concentrations are initially delivered that are greater than the highest MIC₉₀ observed in the Gram-negative surveillance panels, and 4- to 8-fold higher for most common Gram-negative and Gram-positive pathogens in cUTI. By steady-state, the trough values were 9.19 ± 4.97 µg/mL, suggesting that values remain at least 2- to 4-fold the highest MIC₉₀ values for Gram-negative pathogens.

The comparator, ertapenem, was chosen as it is a recommended treatment for cUTI according to clinical practice guidelines and is approved by the Food and Drug Administration (FDA) and other regulatory authorities for the treatment of cUTI. Ertapenem will be given at 1 g IV q24h.

Both eravacycline and ertapenem will be administered for a minimum of 5 doses, in accordance with FDA guidance for an investigational drug with only an IV formulation. After 5 doses, subjects may transition to levofloxacin 750 mg PO QD if they meet clinical criteria and do not have a levofloxacin-resistant baseline pathogen or documented allergy to levofloxacin (See Section 11.3.2). Levofloxacin was chosen as the PO transition for both treatment groups as it is

approved by the FDA and other regulatory authorities and is widely used for the treatment of cUTI.

All subjects will receive a minimum of 7 doses of antibiotic treatment (total IV and PO), in accordance with society guidelines for the treatment of cUTI. However, the duration of treatment may be extended up to 10 doses in subjects with risk factors for recurrent infection.

7.5 Population to Be Studied

Approximately 1200 male and female subjects, ≥ 18 years of age with a diagnosis of cUTI will be recruited into this study.

7.6 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.

8. STUDY OBJECTIVES AND ENDPOINTS

8.1 Primary Objective

The primary objective is to demonstrate that IV eravacycline is non-inferior to ertapenem in responder outcome (clinical cure and microbiologic success) in the microbiological intent-to-treat (micro-ITT) population at the End of IV (EOI) visit (within 1 day of the completion of IV study drug treatment) and Test of Cure (TOC) visit (defined as 14-17 days after randomization).

NOTE: For the European Medicines Agency (EMA), the primary objective is to demonstrate that eravacycline is non-inferior to ertapenem in microbiological outcome in the microbiological modified intent-to-treat (micro-MITT) and microbiologically evaluable (ME) populations at the TOC visit. Refer to Section 14.1 for definitions of analysis populations.

8.2 Primary Endpoints

The primary endpoints of the study are the responder rates (clinical cure and microbiologic success) at the EOI and TOC visits in the micro-ITT population.

NOTE: For the EMA, the primary endpoint will be the microbiologic outcome at the TOC visit in the micro-MITT and ME populations.

8.3 Secondary Objectives

The secondary objectives of the study are:

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

8.4 Secondary Endpoints

The secondary endpoints of the study are

- Responder rate at Day 5
- Clinical outcome at Day 5, EOI, EOT, TOC, and FU
- Microbiologic outcome at Day 5, EOI, EOT, TOC, and FU

8.5 Safety Parameters

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

- Physical exams including vital signs
- Adverse events
- Safety labs at specified time points

9. STUDY DESIGN

9.1 Number of Subjects

The planned study enrollment is approximately 1200 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 15.3, based on the expectation that 66% of subjects will have a baseline pathogen identified and be included in the micro-ITT population.

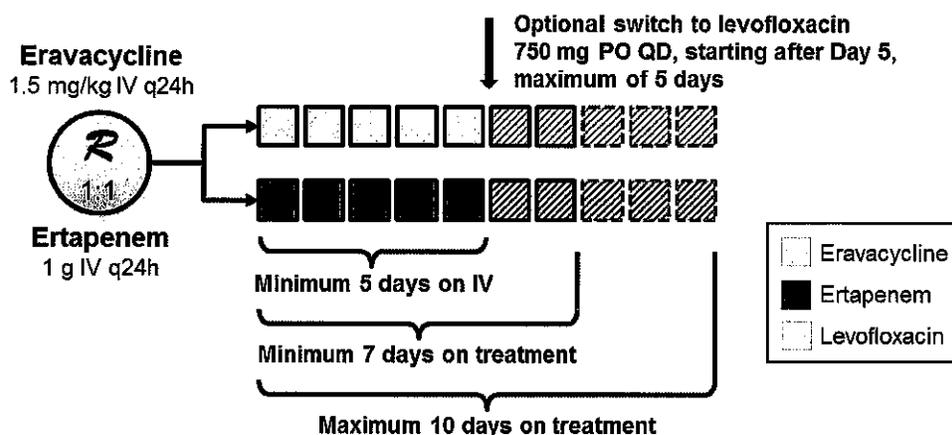
A Data Safety Monitoring Board (DSMB) and the Sponsor will conduct an assessment of the actual number of subjects in the micro-ITT population following the completion of treatment (EOT) of approximately 800 subjects. If there is less than the expected proportion of subjects in the micro-ITT population, the sample size will be adjusted as needed (without a formal protocol amendment) to provide a sufficient number of evaluable subjects.

In addition, the DSMB will conduct an assessment of the overall (aggregated across treatment groups) blinded responder rate (clinical cure and microbiological success) at the TOC visit following the completion of approximately 800 subjects. If the overall blinded responder rate is less than the rate used in the sample size calculation for the eravacycline group, the sample size will be increased as needed (without a formal protocol amendment) to ensure 80% power. The sample size will not be decreased if the overall blinded responder rate is greater than the rate used in the sample size calculation.

9.2 Study Design

This is a phase 3, randomized, double-blind, double-dummy, multicenter, prospective study to assess the efficacy and safety of IV eravacycline compared with ertapenem in the treatment of cUTI. The study will further investigate the pharmacokinetics of eravacycline in subjects diagnosed with cUTI including pyelonephritis.

Subjects will be randomized and enrolled to one of two treatment arms in a 1:1 ratio: (i) eravacycline or (ii) ertapenem. Eravacycline will be dosed at 1.5 mg/kg IV every 24 hours (q24h) for at least the first 5 doses, and ertapenem will be dosed at 1 g IV q24h for at least the first 5 doses. At minimum, the first five IV doses must be administered in an in-patient hospital setting. Subsequent doses may be administered on an out-patient basis. After a minimum of 5 doses of IV study drug, subjects in either treatment arm may transition to levofloxacin 750 mg PO QD until the study drug completion, provided that they demonstrate protocol defined clinical improvement as per the clinical criteria outlined in section 11.3.2. Subjects requiring more than 5 days of IV dosing will have the days of PO dosing reduced to maintain the maximum number of days on treatment at 10 days IV and PO combined. Subjects with documented allergy to levofloxacin or baseline pathogens, from blood or urine cultures, that are resistant to levofloxacin may receive an alternate PO antibiotic as described in the study specific Pharmacy Manual.

Figure 1: Study Design Schema

Key: IV = intravenous; PO = oral; q24h = every 24 hours; QD = once a day.

Dosing in the study arms is described in Table 1 below.

Table 1: Study Drug Administration

Treatment Arms	For at least the first 5 doses	After EOI through Study Drug Completion
	IV Infusion	Oral Administration
Eravacycline (IV) / Levofloxacin (PO)	Eravacycline 1.5 mg/kg IV and placebo IV q24h	Levofloxacin 750 mg PO QD
Ertapenem (IV) / Levofloxacin (PO)	Ertapenem 1 g IV and placebo IV q24h	Levofloxacin 750 mg PO QD

Key: EOI = End of IV; IV = intravenous; PO = oral; q24h = every 24 hours; QD = once a day.

Study drug concentration may be decreased (as long as the infusion volume is ≤ 500 mL per IV bag) and/or infusion times may be increased (up to approximately 120 minutes per IV bag) in order to manage infusion site reactions. Oral study drug will be administered after EOI through EOT.

Urine specimens for culture will be collected from a clean-catch mid-stream urine sample, a newly-placed urinary catheter, cystoscopy, suprapubic aspiration, or a properly disinfected collection port prior to the start of clinical trial drug therapy, and again at Day 5, End of IV, End of Treatment, Test of Cure and Follow-up visits. These specimens will be cultured and quantified using a calibrated loop to identify a quantitative count of bacteria in the local laboratory or a reference regional laboratory. The purified pathogen(s) will be sent to a central microbiology laboratory for confirmation of species identification and antimicrobial susceptibility testing.

Aerobic and anaerobic blood cultures will be obtained at two separate sterile venipuncture sites prior to initiation of study drug therapy. Upon knowledge of a positive culture for a pathogen, blood cultures should be repeated until sterile (i.e., 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 (e.g., signs and symptoms of persistence, relapse, or new infection).

9.3 Measures Taken to Minimize Bias

Subjects will be assigned to treatment arms using computerized randomization. Except for the responsible study site pharmacist or designee, and separate unblinded clinical research staff required, for example, to monitor drug supply and adherence to study drug blinding and randomization procedures, all study staff and participants will be blinded to the treatment arm assignments of subjects.

9.4 Expected Duration of Subject Participation

The expected study duration for any given subject is approximately 4 weeks. Foreseen treatment duration at study entry should be a minimum of five IV doses. The study drug may be discontinued at the discretion of the Investigator at any time. Study drug treatment should be stopped when there is treatment failure or the maximum allowed number of 10 doses has been reached.

Each subject will receive 7-10 doses of study drug (total IV and PO), including at least 5 IV doses. Visits will be conducted at Day 5, EOI, and EOT. The TOC visit will be 14-17 days after randomization, and the FU visit will be 21-28 days after randomization.

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

Table 2: Timeline for Individual Study Subjects

Screening	Randomization	Study Drug Treatment	Day 5 Visit	End of IV (EOI) Visit	End of Treatment (EOT) Visit	Test of Cure (TOC) Visit	Follow-up (FU) Visit
Within 36-h prior to Randomization		Dose Cycles 1-10	5 days after Randomization	Within 1 day of Last IV Dose	Within 1 day of Last Dose (IV or PO)	14-17 days after Randomization & ≥ 5 days after last dose	21-28 days after Randomization
Establish diagnosis of cUTI Verify eligibility for enrollment Collection of a urine sample for urinalysis and culture Baseline assessment Informed consent must be obtained prior to performing any study specific procedures that are not standard of care	Use IWRS to randomize subject to study drug	Either: Eravacycline 1.5mg/kg IV plus placebo IV q24h with optional transition to Levofloxacin 750 mg PO QD OR Ertapenem 1 g IV plus placebo IV q24h with optional transition to Levofloxacin 750 mg PO QD	Assessments of clinical response and safety Collection of a urine sample for urinalysis and culture Determination of length of treatment; subjects are expected to receive 7-10 days of therapy.	Subjects are to receive at least 5 doses of IV study drug Assessments of clinical response and safety Collection of a urine sample for urinalysis and culture	Subjects are expected to receive 7-10 doses of study drug Assessments of clinical response and safety Collection of a urine sample for urinalysis and culture	Return to Study Center for: Assessment of clinical response and safety Collection of a urine sample for urinalysis and culture	Return to Study Center for: Assessment of clinical response and safety Collection of a urine sample for urinalysis and culture

Key: cUTI = complicated urinary tract infection; EOI = End of IV visit; EOT = End of Treatment visit; IV = intravenous; FU = Follow-up visit; IWRS = Interactive Web-based Response System; PO = oral; TOC = Test of Cure visit; q24h = every 24 hours; QD = once a day.

10. SELECTION AND WITHDRAWAL OF SUBJECTS

10.1 Inclusion Criteria

Subjects must meet all of the following criteria:

1. Male and female subjects with either:
 - a. Pyelonephritis and normal urinary tract anatomy (approximately 50% of the total population), **OR**
 - b. cUTI with at least one of the following conditions associated with a risk for developing cUTI:
 - i. Indwelling urinary catheter
 - ii. Urinary retention (at least approximately 100 mL of residual urine after voiding)
 - iii. History of neurogenic bladder
 - iv. Partial obstructive uropathy (e.g., nephrolithiasis, bladder stones, and ureteral strictures)
 - v. Azotemia of renal origin (not congestive heart failure [CHF] or volume related) such that the serum blood urea nitrogen [BUN] is elevated (> 20 mg/dL) AND the serum BUN:creatinine ratio is < 15
 - vi. Surgically modified or abnormal urinary tract anatomy (eg, bladder diverticula, redundant urine collection system, etc.) **EXCEPT** urinary tract surgery within the last 30 days (placing of stents or catheters is not considered to be surgical modification)
2. At least 18 years of age at time of consent
3. Able to provide informed consent. For subjects with diminished decision-making capacity and where applicable law permits, a Legally Authorized Representative may consent on behalf of a prospective subject to the subject's participation.
4. At least two of the following signs or symptoms:
 - a. Chills, rigors, or warmth associated with fever (oral, rectal, tympanic, or by temporal artery temperature $> 100.4^{\circ}\text{F}$ / 38°C) or hypothermia (oral, rectal, tympanic, or by temporal artery temperature $< 95^{\circ}\text{F}$ / 35°C)
 - b. Flank pain (pyelonephritis) or pelvic pain (cUTI)
 - c. Nausea or vomiting
 - d. Dysuria, urinary frequency, or urinary urgency
 - e. Costo-vertebral angle tenderness on physical examination
5. Urine specimen with evidence of pyuria
 - a. Dipstick analysis positive for leukocyte esterase (where positive result is at least “++” as indicated on the urine dipstick provided in the laboratory kit), **OR**
 - b. ≥ 10 white blood cells (WBCs) per cubic millimeter, **OR**
 - c. ≥ 10 WBCs per high power field
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 (e.g., condom) 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 (refer to section 11.4.1 for definition of non-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**
- c. Sexual abstinence

10.2 Exclusion Criteria

Subjects must NOT meet any of the following exclusion criteria:

1. Use of systemic antibiotics effective in cUTI within 72 hours prior to randomization EXCEPT under the following circumstances:
 - a. Subjects with suspected acute cUTI who have received a single dose of effective non-study antibiotics for the acute cUTI
 - b. Signs and symptoms of cUTI developed while on the antibiotic for another indication
2. History of an ertapenem-resistant urinary tract infection within 1 year of consent
3. Likely to require > 10 days of antibiotic treatment to cure the acute cUTI or likely to receive ongoing antibacterial drug prophylaxis prior to the FU visit (eg. Subjects with chronic vesiculo-ureteral reflux).
4. Unlikely to survive at least through the duration of the study
5. Hypotension, systolic blood pressure ≤ 90 mmHg
6. Complicated pyelonephritis with complete obstruction or known or suspected renal or perinephric abscess, emphysematous pyelonephritis, **OR**
Any condition likely to require surgery to achieve cure (this does NOT include procedure to place catheters or obtain diagnosis)
7. Known or suspected urinary fungal infection
8. Uncomplicated lower urinary tract infections
9. Suspected or confirmed active prostatitis, or currently under treatment for prostatitis
10. High risk for cUTI due to *Pseudomonas sp.* (eg, history of prior cUTIs due to *Pseudomonas*, ≥ 20 mg QD prednisone or equivalent steroid, and other risk factors as perceived by the Investigator)
11. History of renal transplantation
12. Presence of an ileal loop
13. Any history of trauma to the pelvis or urinary tract occurring within 30 days prior to consent
14. Indwelling urinary catheters present at screening which are not expected to be removed or replaced within 72 hours of randomization (eg, nephrostomy tubes, stents, urethral and suprapubic catheters).
15. Known concomitant HIV infection with CD4 counts below 200 cells/ μ L within six months prior to consent, or an AIDS defining diagnosis within six months prior to consent
16. Neutropenia (ANC < 1,000 PMNs/ μ L)
17. Participation in a study with an experimental drug or device within 30 days prior to consent

18. Known or suspected hypersensitivity to tetracyclines, carbapenems, or β -lactams
19. History of seizures
20. Any other unstable or clinically significant concurrent medical condition (e.g., immunosuppressive therapy, chemotherapy, class IV heart or lung disease, end stage renal disease, or requiring hemodialysis) that would, in the opinion of the Investigator, jeopardize the safety of a subject and/or their compliance with the protocol

10.3 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 retesting resting B/P parameters. Subjects presenting with hypotension (systolic B/P \leq 90 mmHg) may receive volume replacement and/or be treated with pressors and subsequently retested to establish eligibility.

10.4 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 treatment and/or withdraws prematurely from the study and this information should be recorded on the appropriate page(s) of the electronic case report form (eCRF).

10.4.1 Early Discontinuation from Study Drug Administration

If a subject prematurely discontinues from 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 SOA. The reason for early study drug treatment withdrawal should be recorded on the appropriate page(s) of the eCRF. Reasons for withdrawal from 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 FU visit. Subjects withdrawn secondary to an ongoing study drug-related SAE must be followed clinically until resolution or stabilization (eg, return to baseline or no further improvement expected)
2. Insufficient therapeutic effect requiring rescue/non-study systemic antibacterial treatment for the current cUTI

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.

10.4.2 Withdrawal from Study Protocol

Subjects who wish to withdraw from study drug treatment should be encouraged to complete the EOT, 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

10.5 Replacement of Subjects

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

10.6 Prior and Concomitant Medication

Administration of systemic antibacterial agents effective in cUTI is allowed only in the following circumstances within 72 hours prior to randomization:

- Subjects with suspected acute cUTI who have received a single dose of effective non-study antibiotics for the acute cUTI
- Signs and symptoms of cUTI developed while on the antibiotic for another indication

No concomitant systemic antibacterials effective in cUTI are permitted after the initial dose of study medication until the completion of the FU visit.

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

- Valproic acid and divalproex sodium

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

11. STUDY PROCEDURES

Please also review the entire protocol, including the SOA and appendices, for additional details.

11.1 General Procedures

11.1.1 Temperature

Temperature should be measured orally, rectally, aurally using a tympanic thermometer, or by temporal artery. Axillary temperatures are not allowed. Temperature should be assessed per institution guidelines while in hospital, and the highest daily value recorded in the eCRF.

11.1.2 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 Section 23- Appendix 1 for the complete list of safety laboratory tests.

11.1.3 Urine Cultures

Urine specimens will be collected from a clean-catch mid-stream urine specimen, a newly-placed urinary catheter, cystoscopy, suprapubic aspiration, or a properly disinfected collection port at: (i) Screening, (ii) Day 5, (iii) EOI, (iv) EOT, (v) TOC, and (vi) FU visits.

These specimens will be cultured and quantified using a calibrated loop to identify a quantitative count of bacteria at a lower limit of 10^3 CFU/mL; the species will be identified by the local or regional laboratory. All purified pathogen(s) will be sent to a central reference laboratory 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.

11.1.4 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 (i.e., 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 (e.g., 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 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.

11.1.5 Clinical Outcome

Clinical outcome will be assessed at the Day 5, EOI, EOT, TOC, and FU visits. Clinical outcomes will be classified as cure, failure, indeterminate or missing based on clinical assessments. A favorable clinical outcome is “cure”.

Clinical outcomes are defined as follows:

Clinical Cure

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

Clinical Failure

Subjects are assigned an outcome of clinical failure in the event of:

- Death related to cUTI at any time point
- Persistence of clinical symptoms of cUTI or new symptoms have developed
- Initiation of rescue/non-study antibacterial drug therapy for cUTI

Indeterminate

Study data are indeterminate if the outcome is other than clinical cure or clinical failure. The reason for an “indeterminate” designation must be provided.

Missing

Study data are listed as “missing” if the Investigator did not complete an assessment or if the subject did not complete the study visit.

11.1.6 Microbiologic Outcome

Microbiologic outcome will be assessed at the Day 5, EOI, EOT, TOC, and FU visits. Microbiologic outcomes will be classified as microbiologic successes and microbiologic failures per the Final FDA Guidance for cUTI (11):

Subjects are classified as Microbiologic Successes under the following condition:

- Reduction of the baseline pathogen(s) to $< 10^4$ CFU/mL

Subjects are classified as Microbiologic Failures under the following conditions:

- Blood cultures are positive for the baseline pathogen(s), **OR**
- Urine culture grows $\geq 10^4$ CFU/mL of the baseline pathogen(s)

Subjects are classified as Microbiologic Indeterminate/Missing under the following condition:

- No interpretable culture data are available

11.2 Time Point Specific Procedures

11.2.1 Screening

All potential study participants will undergo a screening evaluation. Clinical assessments and local laboratory results performed during the subject's hospitalization (within 36-h prior to randomization) 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 procedures may occur on the same day (prior to study drug dosing) as Dose 1 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, urine and blood specimens collected during routine 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 signs and symptoms related to current cUTI
 - Complete physical examination including: temperature, resting vital signs, height, and weight
 - Prior and concomitant medication assessment: record medications taken within 1 week prior to randomization, including both day and time for all antibiotics administered in the 72-h prior to randomization and all prescription, over-the-counter, and herbal medications
 - Document any adverse events that have occurred since the time of subject consent. Prior conditions should be documented as medical history
3. Laboratory Assessments:
 - Safety Laboratory Tests (i.e., chemistry, hematology, coagulation, and urinalysis)
NOTE: Local laboratory results should be used to determine eligibility; however, safety laboratory tests must be drawn and sent to the central lab for analysis.
 - Calculate creatinine clearance (Cockcroft-Gault equation [eC_{Cr}]): (13)
$$eC_{Cr}[\text{mL}/\text{min}] = \frac{(140 - \text{Age} [\text{yrs}]) \times \text{Body Weight} [\text{kg}] \times [0.85 \text{ if Female}]}{72 \times \text{Serum Creatinine} [\text{mg}/\text{dL}]}$$
4. Serum pregnancy test (women of childbearing potential only)
NOTE: If a serum pregnancy test is not available or results cannot be received within 4-h of sampling at the investigative site then a urine pregnancy test may be utilized locally for assessment and timely randomization. In addition to the local urine pregnancy test, a serum pregnancy test must be drawn and sent to the central laboratory for analysis. Refer to section 11.4.1 for definition of non-childbearing potential.
5. Obtain blood and urine culture specimens:

- Specific instructions for sample collection, processing, and shipment can be found in the laboratory manual(s) for this study.

6. Determine eligibility

11.2.2 Randomization and Enrollment of Subjects

Once an informed consent is obtained and study eligibility is confirmed, a study site member will obtain a subject number and the pharmacist or pharmacist designee will obtain a study drug assignment for each subject from a computer-generated randomization coding scheme using an Interactive Web-Based/Voice Response system (IXRS).

Subjects will be enrolled and randomized to the eravacycline or the ertapenem treatment arm in a 1:1 ratio.

For this study, enrollment is considered to occur at the time a subject is randomized (i.e., when the Investigator receives notification that the subject has been successfully randomized).

Randomization will be stratified based on two criteria: (1) by primary site of infection (pyelonephritis with normal urinary tract anatomy vs all other diagnoses) and (2) by the receipt of a single dose of effective non-study antibiotics for the acute cUTI within 72 hours prior to randomization. If a subject has abnormal anatomy *AND* pyelonephritis, then they will be classified as "abnormal anatomy" for stratification/analysis purposes and will be randomized to the "all other diagnoses" stratum. An enrollment cap of approximately 50% is planned for subjects with pyelonephritis with normal urinary tract anatomy. Also, an enrollment cap of approximately 20% is planned for subjects who have received a single dose of effective non-study antibiotics for the acute cUTI within 72 h prior to randomization.

The study will include approximately 130 sites globally. No site should enroll more than 50 subjects. Also, each site should ensure that no more than approximately 50% of their study subjects have a diagnosis of pyelonephritis with normal urinary tract anatomy. A site specific change to these randomization guidelines may be granted by the Sponsor as needed.

11.2.3 During Hospitalization ONLY (Day 1 up to Day 10)

If Screening and Day 1 occur on the same day then the signs and symptoms, physical exam, temperature, resting vital signs, and hematology/chemistry do not need to be repeated for the Day 1 visit.

If EOI occurs on the same day as a dosing day during hospitalization then duplicate procedures (e.g., signs and symptoms, physical exam, etc.) do not need to be repeated.

1. Clinical Assessments:

- Record signs and symptoms related to cUTI

- Symptom directed physical exam
- Record temperature
 - Temperature (oral, rectal, tympanic, or by temporal artery) should be assessed per institution guidelines while in hospital, and the highest daily value recorded in the eCRF.
- Resting vital signs
- Concomitant medications
- Calculate creatinine clearance (Day 1 through Day 5, then as clinically indicated, Cockcroft-Gault equation [eC_{Cr}]): (12)

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

- Blood cultures
 - NOTE:** Upon knowledge of a positive culture for a pathogen, blood cultures should be repeated until sterile (i.e., both sets of cultures from two separate venipuncture sites are negative for pathogens) through the FU visit. If baseline cultures or most recently obtained cultures are negative, follow-up cultures should be obtained only if clinically indicated (e.g., signs and symptoms of persistence, relapse, or new infection).
 - AE assessment
 - Plasma PK sampling in accordance with SOA and Section 24 (Day 1, Day 2 and Day 5 only)
2. Study Drug Administration
 - Study drug administration per dosing schedule
 3. Assess readiness for transition to PO anytime after Day 5 study drug administration (see Section 11.3.2 for guidance)

11.2.4 Day 5 Visit

In addition to the assessments required for Day 1 up to Day 10, the following assessments should be performed on Day 5 after randomization.

1. Clinical Assessments:
 - Complete physical exam
 - Urinalysis
 - Urine cultures
 - Clinical outcome assessment
2. Plasma PK sampling in accordance with SOA and Section 24
3. Determination of length of treatment (see Section 11.3.2 for specific criteria)

11.2.5 End of IV Visit (IV-to-PO Transition)

If EOI occurs on the same day as a dosing day during then duplicate procedures (e.g., signs and symptoms, physical exam, etc.) do not need to be repeated.

The following will be performed at the EOI visit:

1. Clinical Assessments:

- Record signs and symptoms related to cUTI
- Complete physical exam
- Record temperature (oral, rectal, tympanic, or by temporal artery)
- Resting vital signs
- Concomitant medications
- Coagulation panel
- Hematology/chemistry safety laboratory tests
- Calculate creatinine clearance (as clinically indicated). Creatinine clearance should be calculated based upon local laboratory results in order to make timely dose adjustments, if needed; however samples are also required to be sent to the central lab for assessment. Creatinine clearance should be calculated using the

Cockcroft-Gault equation [eC_{Cr}](12):

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

- Urinalysis
 - Blood cultures
 - NOTE:** Upon knowledge of a positive culture for a pathogen, blood cultures should be repeated until sterile (i.e., both sets of cultures from two separate venipuncture sites are negative for pathogens) through the FU visit. If the most recently obtained blood cultures are negative, follow-up cultures should be obtained only if clinically indicated (e.g., signs and symptoms of persistence, relapse, or new infection).
 - Urine cultures
 - AE assessment
 - Clinical outcome assessment
- ### 2. Study Drug Administration
- Study drug administration per dosing schedule
- ### 3. Determine PO therapy (levofloxacin vs alternative antibiotic, see Section 11.3.1)

11.2.6 End-of-Treatment Visit

Generally, the EOT visit will occur on the same day as Day 7-10 or the following day, depending on the duration of therapy; however, the EOT procedures are to be performed at premature withdrawal, for treatment failures, and within 1 day of the last dose of study drug.

If EOT occurs on the same day as EOI or a dosing day during then duplicate procedures (eg, Signs and Symptoms, Physical Exam, etc.) do not need to be repeated.

The following will be performed at the EOT visit:

1. Clinical Assessments:

- Record signs and symptoms related to cUTI
- Complete physical exam
- Record temperature (oral, rectal, tympanic, or by temporal artery)
- Resting vital signs

- Concomitant medications
- Hematology/ chemistry safety laboratory tests
- Coagulation panel
- Urinalysis
- Blood cultures
 - NOTE: Upon knowledge of a positive culture for a pathogen, blood cultures should be repeated until sterile (i.e., both sets of cultures from two separate venipuncture sites are negative for pathogens) through the FU visit. If the most recently obtained blood cultures are negative, follow-up cultures should be obtained only if clinically indicated (eg, signs and symptoms of persistence, relapse, or new infection).
- Urine cultures
- AE assessment
- Verify oral study drug compliance
 - NOTE: Subjects should return oral study drug and packaging to the investigative site to verify extent of subject adherence to self-administration. All subjects will be queried about dose schedule adherence and reasons for missed doses.
- Clinical outcome assessment

11.2.7 Test of Cure Visit

The TOC visit will occur 14-17 days after randomization **AND** at least 5 days after the last dose of study drug. The following will be performed at the TOC visit:

1. Clinical Assessments:

- Record signs and symptoms related to cUTI
- Complete physical exam
- Record temperature (oral, rectal, tympanic, or by temporal artery)
- Resting vital signs
- Concomitant medications
- Hematology/ chemistry safety laboratory tests
- Urinalysis
- Blood cultures
 - NOTE: Upon knowledge of a positive culture for a pathogen, blood cultures should be repeated until sterile (i.e., both sets of cultures from two separate venipuncture sites are negative for pathogens) through the FU visit. If the most recently obtained blood cultures are negative, follow-up cultures should be obtained only if clinically indicated (eg, signs and symptoms of persistence, relapse, or new infection).
- Serum pregnancy test (women of childbearing potential only). Refer to section 11.4.1 for definition of non-childbearing potential
- Urine cultures
- AE assessment
 - Clinical outcome assessment

11.2.8 Follow-up Visit

The FU visit will occur 21-28 days after randomization. The following will be performed at the FU visit:

1. Clinical Assessments:

- Record signs and symptoms related to cUTI
- Complete physical exam
- Record temperature (oral, rectal, tympanic, or by temporal artery)
- Resting vital signs
- Concomitant medications
- Hematology/ chemistry safety laboratory tests
- Coagulation panel
- Urinalysis
- Blood cultures

NOTE: Upon knowledge of a positive culture for a pathogen, blood cultures should be repeated until sterile (i.e., both sets of cultures from two separate venipuncture sites are negative for pathogens) through the FU visit. If the most recently obtained blood cultures are negative, follow-up cultures should be obtained only if clinically indicated (eg, signs and symptoms of persistence, relapse, or new infection).

- Urine cultures
- AE assessment
- Clinical outcome assessment

11.3 Study Drug Administration

11.3.1 Study Drug Administration and Dosing Schedule

Eravacycline and ertapenem when prepared for infusion require different infusion volumes and times. For these reasons, this study has been designed using double-dummy methodology.

Study Drug Infusions:

During each 24-h dose cycle on IV administration days, the subject will receive two infusions. The makeup of the infusions is shown in Table 3 below.

Table 3: Study Drug Infusion Specifications

Infusion Specifications	TREATMENT ARM	
	Eravacycline 1.5 mg/kg IV q24h	Ertapenem 1 g IV q24h
Infusion 1		
final volume (mL) ^a	Weight (kg) x 5 mL/kg	Weight (kg) x 5 mL/kg
drug amount (mg)	Eravacycline Weight (kg) x 1.5 mg/kg	Placebo
conc (mg/mL) ^b	0.3	NA
infusion time (min) ^c	60 ± 10 per IV bag	60 ± 10 per IV bag
Infusion 2		

final volume (mL)	60 mL	60 mL
drug amount (mg)	Placebo	Ertapenem 1 g
conc (mg/mL)	NA	Variable
infusion time (min)	30 ± 10 per IV bag	30 ± 10 per IV bag

^a Final infusion volume per IV bag must not exceed 500 mL; Total infusion volume must not exceed 1000 mL

^b Concentration may be decreased as long as the infusion volume does not exceed 500 mL per IV bag

^c Infusion time may be increased to 120 minutes per IV bag

Key: IV = intravenous; q24h = every 24 hours.

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.

Ertapenem dose will be adjusted for subjects with creatinine clearance ≤ 30 mL/min in accordance with the approved prescribing information (see Pharmacy Manual). Subjects with creatinine clearance < 50 mL/min at Screening should have their creatinine clearance recalculated at the Day 1-5 visits, and thereafter as clinically indicated, to allow further dose adjustment of study drug as indicated.

The 24-h interval between IV dose cycles can be shortened (but not prolonged) by up to 2-h (i.e., interval of 22-h to 24-h) from the prior dose cycle during dose cycles 1-3 to adapt to a normal hospital schedule. After the 3rd IV dose cycle, the permitted IV administration window is q24h \pm 90 minutes.

At a minimum, the first 5 IV dose cycles must be administered in an in-patient or hospital setting; subsequent doses may be administered on an out-patient basis.

Study Drug Oral Administration:

After an IV-to-PO transition, subjects will receive PO levofloxacin 750 mg to be administered once daily (approximately 24-h apart). The first PO dose should be taken approximately 24-h \pm 2-h after the start of the last IV infusion of study drug. A one-time dose adjustment may occur with either the first or second oral dose (NOT both) by administering up to 6-h early, in order to adapt to the subject's meal and sleep schedule. All subsequent PO doses should be taken 24-h \pm 2-h after the previous oral dose. Levofloxacin dose will be adjusted for subjects with creatinine clearance < 50 mL/min in accordance with the approved prescribing information (see Pharmacy Manual).

Subjects should be instructed to take PO levofloxacin doses at least two hours before or two hours after antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or didanosine.

Subjects with documented allergy to levofloxacin or baseline pathogens from blood or urine cultures that are resistant to levofloxacin may receive an appropriate alternate oral antibiotic, as

described in the Pharmacy Manual. If no appropriate alternate oral antibiotic is available, IV study drug should be continued for the entire duration of therapy.

11.3.2 Guidance to Investigators for IV-to-PO Transition

An IV-to-PO transition may occur after Day 5 (according to the instructions in Section 11.3.1) provided the subject has demonstrated adequate clinical improvement.

Adequate clinical improvement for an IV-to-PO transition is defined as follows:

- Subject must have adequate appetite and food intake
- Subject must be afebrile for at least 24-h
- Subject must have documented significant improvement or resolution of signs and symptoms present at screening

If the subject qualifies for IV-to-PO transition the Investigator should choose a PO antibiotic as follows:

- If a baseline pathogen was identified and was susceptible to levofloxacin, no baseline pathogen grew, or no antibiotic susceptibility results are available, levofloxacin should be chosen as the PO antibiotic
- If a baseline pathogen was identified and was not susceptible to levofloxacin, or the subject has a documented allergy to levofloxacin, an appropriate alternative PO antibiotic should be chosen, as described in the Pharmacy Manual, OR
- If no appropriate alternative PO antibiotic is available, the subject should continue IV study drug for the entire duration of therapy

11.3.3 Guidance to Investigators for Length of Treatment

The Investigator should choose a length of treatment (regardless of the choice of PO antibiotic or the continuation of IV study drug) as follows:

- Subjects should receive a total of **7 days of treatment** (including IV and PO) if they meet **ALL** of the following criteria assessed **at the Day 5 visit**:
 1. Significant improvement of presenting signs and symptoms and resolution of fever **within 72 h** of start of treatment
 2. No sepsis on presentation
 3. Urinalysis negative (< 10 WBCs/mm³ or < 10 WBCs per high power field or leukocyte esterase “-” on dipstick) at Day 5
 4. No urinary tract device or stone present at Day 5
- Subjects should receive a total of **10 days of treatment** (including IV and PO if they meet **ANY** of the following criteria assessed **at the Day 5 visit**:
 1. Persistence of significant signs and symptoms or fever beyond 72 h of start of treatment
 2. Sepsis on presentation
 3. Urinalysis persistently positive (≥ 10 WBCs/mm³ or ≥ 10 WBCs per high power field or leukocyte esterase “+” or greater on dipstick) at Day 5

4. Urinary tract device or stone present at Day 5
5. Other high risk factor for recurrent infection (Specify, discuss with Medical Monitor)

No subject should receive more than 10 days of study drug therapy. Subjects with persistence of significant signs and symptoms after 10 days of therapy should be considered clinical failures and non-study antibiotics should be administered as appropriate.

11.3.4 Treatment Compliance

The date, start times, stop times, and volumes used in each infusion of study drug will be recorded. These detailed records will be used to document study drug 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. If an infusion has been delayed for ≤ 12 hours, the infusion should be given immediately and the next infusion should be given as scheduled. If an infusion has been delayed for > 12 hours, the infusion should be given immediately and the next infusion should be rescheduled to ensure that the interval between infusions is at least 12 hours.

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 interval of first and last dose.

Subjects should return PO study drug packaging to the investigative site to verify extent of subject adherence to self-administration. All subjects will be queried about dose schedule adherence and reasons for missed doses.

11.4 Specific Restrictions/Requirements

All subjects must have assessments at Day 1-5, EOI, EOT, TOC, and FU unless they have withdrawn consent. Subjects who remain hospitalized beyond Day 5 must have assessments each day they remain hospitalized.

11.4.1 Avoidance of Pregnancy

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 (e.g., condom).

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 study drug treatment and for 14 days afterwards. This is to ensure that the fetus is not exposed to the investigational product in the ejaculate.

Instructions for Female Subjects

Females of non-childbearing potential are defined as those who are at least 12 months post menopause and/or are surgically sterile. All other females are considered of childbearing potential.

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.

11.4.2 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 14 days after the final dose.

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 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.

11.5 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 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 microbiologically evaluability rate of blood and/or urine samples

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Quality Control

12.1.1 Monitoring

The Sponsor, or designee(s), will monitor the study to ensure that the rights and well being of the subjects are protected, for compliance with the protocol, for compliance with applicable laws and regulations, and compliance with GCP. 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 and study appropriate facilities and staff are maintained. Monitoring reports will be issued for each monitoring visit.

12.2 Quality Assurance

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

13. ASSESSMENT OF SAFETY

Safety will be assessed through AEs, physical examinations, vital signs, and the collection of central laboratory data (i.e., 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.

13.1 Definitions

13.1.1 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, or intercurrent illness. 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.

Events that result from lack of efficacy of study drug (eg, treatment failure) are not considered AEs.

13.1.2 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.

13.1.3 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 (i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form)
- Requires in-patient 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 in-patient 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) are not considered SAEs (eg, prolonged hospitalizations due to treatment failures will not be considered SAEs).

13.1.4 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 as described in the most recent IB or the product information for ertapenem, levofloxacin (or the alternative PO antibiotic, if applicable).

13.2 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 severity of the event and relatedness to study drug. Follow-up information on the SAE may be requested by the Sponsor 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, appropriate regulatory agencies, all participating Investigators, as well as central IRBs/IECs will be notified on an expedited basis (7 days for fatal or life-threatening serious, unexpected ADRs). Local IRBs/IECs will be notified of all unexpected, serious ADRs involving risk to human subjects in accordance with the rules and regulations of the local IRB/IEC. Details of reporting responsibilities will be outlined in the study-specific Safety Management Plan.

An unexpected event is one that is not reported in the IB or the relevant prescribing information.

Reporting of SAEs and Suspected Unexpected Serious Adverse Reactions (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 on the applicable form.

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

- Subject number, Investigator name, and site number
- SAE information: event term, onset date, severity, and casual relationship
- Basic demographic information (e.g., age, gender, weight, etc.)
- The outcomes attributable to the event [e.g., death, a life-threatening adverse drug experience, in-patient 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 European Union Clinical Trials Directive (14).

13.3 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

13.4 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 (i.e., 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.

13.5 Laboratory Test Abnormalities

All central laboratory data generated by the study will be included in standard Statistical Analysis System (SAS) datasets. 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 laboratory values 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.

13.6 Follow-up of Adverse Events

All AEs (regardless of relationship to study drug) and SAEs determined not to be study drug related (i.e., not related and unlikely related) will be followed through the FU visit and be noted as "Not Recovered/Not Resolved" if not resolved at this visit. Any SAE that is determined to be study drug related (possibly, probably, or definitely related) will be followed until resolution or stabilization.

The outcome of AEs will be rated as:

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

And subjects will be referred to their primary care doctor as needed post-study.

14. EVALUATION OF EFFICACY

14.1 Analysis Populations

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

- ITT population – all randomized subjects
- Micro-ITT population – All subjects in the ITT population who have at least one baseline bacterial pathogen on culture of urine or blood that causes cUTI against which the investigational drug and control drug have expected antibacterial activity. Subjects should not be excluded from this population based upon events that occurred post-randomization (e.g., loss to follow-up)
- Micro-MITT population – All subjects in the micro-ITT population who receive at least one dose of study drug
- CE populations – All subjects in the ITT population who meet key inclusion/exclusion criteria, receive correct study drug, have a clinical outcome assessed, and follow other important components of the trial. Specific details are included in the statistical analysis plan (SAP)
- ME populations – All subjects in the micro-ITT population who meet key inclusion/exclusion criteria, receive correct study drug, have a microbiologic outcome assessed, and follow other important components of the trial. Specific details are included in the SAP
- Safety population – all randomized subjects who receive any amount of study drug

14.2 Efficacy Evaluations

The following primary efficacy evaluations will be performed:

- Responder outcome (clinical cure and microbiological success) at the EOI and TOC visits in the following populations:
 - Micro-ITT
- For EMA: microbiological response at the TOC visit in the following populations:
 - Micro-MITT
 - ME

The following secondary evaluations will be performed:

- Responder outcome at Day 5 in the micro-ITT population
- Clinical outcome at Day 5, EOI, EOT, TOC, and FU visits in the following populations:
 - ITT
 - CE
 - Micro-ITT
 - Micro-MITT
 - ME

- Microbiologic outcome at Day 5, EOI, EOT, TOC, and FU visits in the following populations:
 - Micro-ITT
 - Micro-MITT
 - ME
- To assess safety and tolerability of eravacycline administration in the safety population
- PK parameters after eravacycline infusion, including
 - C_{max} , time to C_{max} (T_{max}), C_{trough} , and area under the plasma concentration-time curve (AUC)

14.2.1 Clinical Outcome

Clinical outcome will be assessed at the Day 5, EOI, EOT, TOC, and FU visits. Clinical outcomes will be classified as cure, failure, indeterminate, or missing (Section 11.1.5). A favorable clinical response is “cure”.

14.2.2 Per Pathogen Microbiological Outcomes

Per pathogen microbiological outcome will be determined for the Day 5, EOI, EOT, TOC, and FU visits. Outcomes will be classified as success, failure, or indeterminate/missing based on the microbiologic response definitions (Section 11.1.7).

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

14.2.3 Per Subject Microbiological Outcomes

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

An overall microbiological outcome will be assessed as success, failure, or indeterminate/missing for each subject. For subjects from whom only one pathogen is isolated, the overall microbiological outcome will be based on the assessment for that pathogen. For subjects from whom more than one pathogen is isolated, the overall microbiological outcome will reflect the worst outcome present amongst all baseline pathogens.

15. STATISTICAL METHODS

A detailed SAP will be used to guide the analysis and reporting of data collected in this study.

15.1 Data Collection and Processing

An IXRS system 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. Demography and end of study pages will be completed for subjects who are randomized but not treated.

15.2 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 most recent value prior to the start of treatment with study drug.

15.2.1 Efficacy Analyses

The co-primary efficacy outcome measures are responder outcome in the micro-ITT population at the EOI and TOC visits (defined as 14-17 days after randomization). The responder rate will be determined as the number of subjects with clinical cure (i.e., complete or significant improvement of signs or symptoms such that no rescue/non-study antibacterial treatment is required) and microbiological success at the respective visit divided by the number of subjects in the analysis population (i.e., overall or by randomization strata). The number and percentage of subjects in each treatment group classified as a responder, non-responder and indeterminate at the EOI and TOC visits will be tabulated by treatment group in the micro-ITT population. Two-sided 95% CIs for the observed difference in responder rates (eravacycline treatment group minus ertapenem treatment group) at the EOI and TOC visits will be calculated using the method without stratification of Miettinen and Nurminen. If the lower limit of both 95% CIs for the difference in responder outcomes in the micro-ITT population exceeds -10%, then non-inferiority of eravacycline to ertapenem will be declared. The primary efficacy outcome will also be assessed across the randomization stratification factors of: (1) primary site of infection (pyelonephritis and normal urinary tract anatomy vs all other diagnoses) and (2) receipt of a single dose of effective non-study antibiotics for the acute cUTI within 72 hours prior to randomization. For each site of infection and prior antibiotic stratum, a 2-sided 95% CI for the observed difference in responder rates at the EOI and TOC visits will be calculated for the micro-ITT population.

For the EMA, the co-primary efficacy outcome measures are microbiological success in the micro-MITT and ME populations at the TOC visit. The microbiological success rate will be determined as the number of subjects with microbiological success at the TOC visit divided by the number of subjects in the analysis population. The number and percentage of subjects in each treatment group classified as a microbiological success, failure and indeterminate at the TOC visit will be tabulated by treatment group in the micro-ITT and ME populations. Two-sided 99% CIs for the observed difference in success rates (eravacycline treatment group minus ertapenem treatment group) at the TOC visit in the micro-MITT and ME populations will be calculated using the method with stratification of Miettinen and Nurminen. If the lower limit of both 95% CIs for the difference in success rates exceed -10%, then non-inferiority of eravacycline to ertapenem will be declared.

The number and percentage of subjects in each treatment group with a secondary efficacy outcome of clinical cure, failure and indeterminate will be presented for Day 5, EOI, EOT, TOC and FU for the ITT, CE, micro-ITT, micro-MITT 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 the stratification factors of primary site of infection and receipt of a single dose of effective non-study antibiotics for the acute cUTI within 72 h prior to randomization.

Per-subject microbiological response will be summarized as success, failure and indeterminate at Day 5, EOI, EOT the EOT and TOC Visits in the micro-ITT, micro-MITT and ME Populations. Two-sided 95% unstratified CIs will be constructed for the observed difference in the rates of microbiological success between the treatment groups for descriptive purposes; no conclusion of NI will be made.

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

Microbiologic outcome by baseline pathogen will be determined as the proportion of subjects with a microbiologic success at EOI and the TOC visits for each pathogen isolated at baseline in the micro-ITT, micro-MITT and ME populations.

15.2.2 Safety Analyses

All safety analyses will be conducted in the Safety population.

Verbatim descriptions of AEs will be coded using 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 an 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. Abnormal physical examination results are recorded as AEs (when appropriate) and thus, physical exam data will not be summarized in a table.

Descriptive statistics for hematology, chemistry, coagulation and where applicable, urinalysis, values and the change from baseline 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.

15.3 Sample Size Considerations

This study is designed to demonstrate non-inferiority of eravacycline to ertapenem in the co-primary efficacy measures of responder outcome at the EOI and TOC visits in the micro-ITT population. An NI margin of 10% will be used which is based on historical data regarding the treatment effect of antibiotics. A 10% NI margin for the efficacy measure of responder outcome is robust and can sufficiently confirm a clinically meaningful treatment effect of eravacycline in the treatment of cUTI.

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

provide sufficient numbers for this study, assuming 66% of enrolled subjects will meet the requirements for inclusion in the micro-ITT population.

For the EMA, it is assumed that 65% of the randomized subjects will be in the micro-MITT population and 60% in ME population. The microbiological success rates at TOC are assumed to be 79% and 82% in both treatment groups in the micro-MITT and ME populations, respectively. With these assumptions, using a non-inferiority margin of 10%, a one-sided alpha of 0.005, and the sample size methodology of Farrington and Manning, there is at least 80% power to show non-inferiority for the co-primary efficacy outcomes. The power calculations are summarized in Table 4 below based on a total of 1200 randomized subjects:

Table 4: Assumptions for Sample Size Calculations

Outcome/Population	Alpha level (one-sided)	Evaluability Rate	Outcome Rates		Total N	Power
			ERV	ERT		
FDA Outcomes						
Responder at EOI/micro-ITT	0.025	66%	93%	94%	790	>99%
Responder at TOC/micro-ITT	0.025	66%	71%	72%	790	80.0%
EMA Outcomes						
Clinical Cure at TOC/micro-MITT	0.005	65%	79%	79%	780	79.8%
Clinical Cure at TOC/ME	0.005	60%	82%	82%	720	84.7%

ERV=Eravacycline; ERT=Ertapenem

15.4 Data Safety Monitoring Board (DSMB)

A DSMB will meet after approximately 300 subjects have reached EOT in the study, and again after approximately 800 subjects have reached EOT. The DSMB will advise the Sponsor regarding the continuation, modification, or termination of the study. The DSMB may meet at other timepoints as necessary.

The DSMB will have access to the following data:

- Incidence of AEs (overall and drug-related)
- Listing of SAEs
- Premature discontinuations from study drug due to an AE
- Safety laboratory data

The DSMB may be provided with additional data if requested.

The DSMB and Sponsor will conduct an assessment of the actual number of subjects in the micro-ITT population, which will be made following the completion of treatment (EOT) of approximately 800 subjects. If there is less than the expected proportion of subjects in the micro-ITT population, the sample size will be adjusted as needed (without a formal protocol amendment) to provide a sufficient number of evaluable subjects.

In addition, the DSMB will conduct an assessment of the overall (aggregated across treatment groups) blinded responder rate (clinical cure and microbiological success) at the TOC visit following the completion of approximately 800 subjects. If the overall blinded responder rate is less than the rate used in the sample size calculation for the eravacycline group, the sample size will be increased as needed (without a formal protocol amendment) to ensure 80% power. The sample size will not be decreased if the overall blinded responder rate is greater than the rate used in the sample size calculation.

A charter for the DSMB, comprised as a separate document, will be available prior to the first meeting. Recommendations from the DSMB will be made in writing and provided to the Sponsor after each data review.

16. STUDY DRUG MATERIALS

16.1 Study Drug Nomenclature

TP-434 is the active ingredient in eravacycline drug product. The chemical name of TP-434-046 (di 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] di-hydrochloride. The molecular formula for the free base is C₂₇H₃₁FN₄O₈, and the molecular weight is 558.56. Eravacycline is a yellow to orange solid that is soluble in water.

16.2 Study Drug Preparation

16.2.1 Reconstitution of IV Study Drug

A trained, unblinded pharmacist/designee will prepare intravenous study drug. Detailed instructions for the preparation of study drug are provided in the Pharmacy Manual.

The eravacycline drug product will be reconstituted using sterile water for infusion (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 unblinded pharmacist/designee will provide the Investigator with ready-to-use blinded infusion solutions covered with an opaque bag for administration at scheduled study drug infusion times. It is the responsibility of the unblinded pharmacist/designee to maintain the blind of the infusion solutions.

16.2.2 Infusion Administration

In the event of discomfort and/or pain due to infusion, the following actions can be taken for the infusion which caused the reaction after confirming vein patency and flow at the Investigators' request (in the recommended order):

- Decrease concentration (by doubling volume, as long as infusion volume does not exceed 500 mL per IV bag)
- Increase length of infusion time (by doubling infusion time, up to 120 minutes per IV bag)

16.3 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.

16.4 Study Drug Comparator

Ertapenem is a carbapenem antibiotic that has been approved for the treatment of cUTI (including acute pyelonephritis) in the US and other countries. Please consult the local prescribing product information for important information regarding warnings, precautions, and AEs reported with the use of this product.

16.5 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.

16.6 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.

16.7 Breaking 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 in the IXRS system. The instructions for unblinding a subject in the IXRS system can be found in the "IXRS User Guidelines".

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.

17. INVESTIGATOR REQUIREMENTS

17.1 Adverse Event 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

17.2 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 (e.g., 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 microbiologically evaluability rate).

17.3 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. Electronic CRFs should be handled in accordance with instructions from the Sponsor or its representative and 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.

17.4 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.

17.5 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 International Conference on Harmonization (ICH) guidelines, GCPs, and the respective United States (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.

17.6 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

18. 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.

18.1 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; however microbiologic specimens collected during routine 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 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 new information becoming available which may cause significant changes to a subject's assessment of safety and potentially, willingness to continue in the study, the subject will be re-consented. A copy of the signed consent document or a second original must be given to the representative/ proxy consentor. 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. 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.

18.2 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.

18.3 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 (e.g., Protected Health Information [PHI] authorization in North America).

The subject will not be identified by name in the eCRF or in any study reports. 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.

19. DATA MANAGEMENT AND MONITORING

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

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

It is the responsibility of the Investigator(s) to assure that essential study documents are available at the investigative/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.

19.1 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.

19.2 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 [CFR, 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.

20. 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.

21. PUBLICATION POLICY

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

22. REFERENCES

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23. APPENDIX 1: CENTRAL SAFETY LABORATORY TESTS

Hematology:

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

Coagulation:

Prothrombin time
 Partial thromboplastin time
 Fibrinogen

Urinalysis:

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

Serum Chemistry:

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

NOTE: *If a serum pregnancy test is not available within 4 hours at the investigative site then a urine pregnancy test may be utilized locally to facilitate timely randomization. A serum pregnancy test must be drawn and sent to the central laboratory for analysis.*

24. APPENDIX 2: PLASMA PK SAMPLING

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

Day 1 - IV Dosing Plasma PK Sampling Schedule

Plasma Sample	Time
i	within 30 minutes before Infusion 1 on Day 1
ii	upon completion of Infusion 1 (± 2 min)
iii	3-h after the start of Infusion 1 (± 10 min)
iv	7-h after the start of Infusion 1 (± 10 min)
v	12-h after the start of Infusion 1 (± 10 min)

Day 2 - IV Dosing Plasma PK Sampling Schedule

Plasma Sample	Time
i	within 30 minutes before Infusion 1 on Day 2

Day 5 - IV Dosing Plasma PK Sampling Schedule

Plasma Sample	Time
i	within 30 minutes before Infusion 1 on Day 5