CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211109Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	505(b)(1) NDA Type 1 NME
Application Number(s)	211,109
Priority or Standard	Priority
Submit Date(s)	December 28, 2017
Received Date(s)	December 28, 2017
PDUFA Goal Date	August 28, 2018
Division/Office	DAIP/OAP
Review Completion Date	See DARRTS electronic signature page
Established Name	Eravacycline
(Proposed) Trade Name	XERAVA
Pharmacologic Class	Tetracycline
Code name	TP-434
Applicant	Tetraphase Pharmaceuticals, Inc
Formulation(s)	50 mg eravacycline powder in a single-use 10 mL vial for injection
Dosing Regimen	1.0 mg/kg by intravenous infusion every 12 hours for 4 to 14 days
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with complicated intra-abdominal infections (cIAI)
Regulatory Action	Approval
Indication/Population	Treatment of adult patients with complicated intra-abdominal infections (cIAI)

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OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
OPV= Division of Pharmacovigilance
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DMPP= Division of Medical Policy

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2	Office of Scientific Investigations – Division of Clinical Compliance Evaluation	Trial integrity	Aisha Johnson, MD, MPH, MBA Janice Pohlman, MD Susan Thompson, MD Kassa Ayalew, MD, MPH
3	Office of Prescription Drug Promotion	Labeling	David Foss, PharmD, MPH Jim Dvorsky, Pharm D, RAC
4	Office of Surveillance and Epidemiology - Division of Medication Error Prevention and Analysis	Proprietary Name and Labeling	Sevan Kolejian, PharmD, MBA Otto Townsend, PharmD
5	Office of Surveillance and Epidemiology – Division of Pharmacovigilance	Postmarketing Safety	Page Crew, PharmD, MPH Kelly Cao, PharmD Robert Levin, MD
6	Office of Surveillance and Epidemiology – Division of Risk Management	REMS/Safety	Cynthia LaCivita, PharmD Elizabeth Everhart, MSN, RN, ACNP Mei Yen Chen, PharmD

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	Consulting Team	Issue	Reviewers
7	Pediatric Review Committee (PeRC)	PREA PMR and Agreed Initial Pediatric Study Plan	Jacqueline Yancy, PhD PeRC Members

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Glossary

AC	Advisory committee
AE	Adverse event
APACHE II	Acute Physiology and Chronic Health Evaluation II
AR	Adverse reaction
ATS	America Thoracic Society
AUC	Area under the curve (drug concentration versus time)
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
cIAI	Complicated intra-abdominal infection
CMC	chemistry, manufacturing, and controls
CR	Carbapenem-resistant
CrCl	Creatinine clearance
CRE	Carbapenem-resistant Enterobactericeae
CRF	Case report form
CSR	Clinical study report
cUTI	Complicated urinary tract infection
DAIP	Division of Anti-Infective Products
ECG	Electrocardiogram
ERT	Ertapenem
ERV	Eravacycline
ESBL	Extended spectrum beta-lactamase
ETP	Ertapenem (alternative abbreviation)
eCTD	Electronic common technical document
FDA	Food and Drug Administration
GCP	Good clinical practice
GNR	Gram-stain negative rod
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ITT	Intent to treat
IDSA	Infectious Disease Society of America
MDR	Multiple drug resistant
MedDRA	Medical Dictionary for Regulatory Activities
MER	Meropenem
MIC	Minimum inhibitory drug concentration of microbial growth
Micro-ITT	Microbiological intent to treat
mITT	Modified intent to treat
NDA	New drug application
NME	New molecular entity
NOAEL	No observed adverse effect level

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OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	Pharmacodynamics
PI	Prescribing information or package insert
PK	Pharmacokinetics
PMC	Postmarketing commitment
PMR	Postmarketing requirement
PSUR	Periodic Safety Update report
PT	Preferred term
PTA	Probability of target attainment
q8h	Every 8 hours
QIDP	Qualified infectious disease product
REMS	Risk evaluation and mitigation strategy
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	(Body) system organ classification
SRP	Surgical review panel
TOC	Test of cure
TEAE	Treatment emergent adverse event

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1. Executive Summary Office Level Concurrence

1.1. Product Introduction

Eravacycline (XERAVA™) is a synthetic tetracycline class antibacterial drug. The proposed indication is for cIAI patients aged 18 years or more with a dosing regimen of 1 mg/kg by intravenous infusion every 12 hours for 4 to 14 days.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness to support approval of XERAVA for the treatment of cIAI in adult patients. This new drug application provided data from two adequate and well-controlled, randomized clinical trials to conclude noninferiority of XERAVA relative to comparators in the treatment of cIAI. In Trial 008, eravacycline was compared to ertapenem. The difference in clinical response rates was -0.8% (95% CI: -7.1%, 5.5%). In Trial 025, the comparator was meropenem and the difference in clinical response rates was -0.5% (95% CI: -6.3%, 5.3%). Noninferiority was concluded in both trials since the lower 95% confidence limits of the clinical response rates (-7.1% and -6.3%) were within the pre-specified noninferiority limits of -10% and -12.5%, respectively. Supportive evidence was provided from a randomized active-controlled Phase 2 dose ranging study that was not powered for statistical inference testing. The efficacy analyses are presented in detail in Section 7 of this review.

1.3. Benefit-Risk Assessment

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Benefit-Risk Summary and Assessment

In NDA 211109, the Applicant is seeking approval of eravacycline for the treatment of complicated intra-abdominal infections (cIAI) in adults. Eravacycline is a synthetic tetracycline class antibacterial drug. cIAIs are serious and potentially life-threatening infections for which antibacterial therapy as well as surgical intervention play an important role. The proposed dose regimen is 1 mg/kg every 12 hours for 4 to 14 days by intravenous (IV) infusion over 60 minutes.

Data from two noninferiority (NI) Phase 3 studies (TP-434-008 and TP-434-025) support the efficacy of IV eravacycline for the treatment of cIAI in adults. Study TP-434-008 and Study TP-434-025 evaluated the primary endpoint of clinical response at Test-of-Cure (Day 25 to 31) in the micro-ITT population using NI margins of 10% and 12.5%, respectively. The micro-ITT population was defined as all randomized patients with a valid baseline pathogen against which eravacycline has antibacterial activity. No baseline pathogens were resistant to the respective comparator in each of the trials and so this definition was considered acceptable as eravacycline was being compared to effective comparators in both NI trials. In both trials, NI of eravacycline to comparator therapy (ertapenem in Study TP-434-008 and meropenem in Study TP-434-025) was demonstrated. Differences in clinical response rates between eravacycline and comparator were -0.8% (95% CI: -7.1%, 5.5%) in Study TP-434-008 and -0.5% (95% CI: -6.3%, 5.3%) in Study TP-434-025. Since the lower 95% confidence limits of -7.1% and -6.3% were within the pre-specified NI margins of -10% and -12.5%, respectively, NI was demonstrated in both trials. Secondary analyses which considered clinical response at different time points (i.e., at end of therapy, at study completion) and in different analysis populations (ITT-based and evaluable populations) were consistent with the primary analysis findings. Various sensitivity analyses produced similar conclusions as the primary analysis findings. Subgroup analyses did not raise concerns that NI inferences may not be valid in selected groups of patients. Supportive evidence was provided from a randomized active-controlled Phase 2 dose ranging study (TP-434-P2-cIAI-1).

The Phase 3 studies and the Phase 2 dose-ranging study support the safety of IV eravacycline for the treatment of cIAI in adults. A similar safety profile was observed across studies. The proposed dose was evaluated in the Phase 2 and Phase 3 cIAI studies. Treatment Emergent Adverse Events (TEAEs) occurred at a higher rate in subjects who received eravacycline compared to those who received comparator. The increase was driven primarily by increased rates of gastrointestinal events (i.e., nausea and vomiting) and infusion site reactions (i.e., phlebitis, thrombophlebitis, infusion site pain/erythema/swelling). These events were mostly mild or moderate in severity and infrequently led to discontinuation of eravacycline. Gastrointestinal side effects including nausea and vomiting have been reported for tetracycline class antibacterial drugs. Serious adverse events (SAEs) were infrequent and generally balanced among treatment arms. Mortality rates were balanced among treatment arms in the two Phase 3 cIAI studies (8 deaths [1.5%] in the eravacyline group versus 7 deaths [1.7%] in the comparator group); no deaths occurred in the patients who received the proposed dose of eravacyline in the Phase 2 cIAI study. Based on our review of the case narratives, none of the SAEs (including fatal events) could be directly attributed to eravacycline treatment. The reported SAEs generally occurred in patients with comorbidities. The AEs that occurred were generally consistent with that of the tetracycline class of

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antibacterial drugs. The major risks associated with eravacycline use include life-threatening hypersensitivity reactions, tooth discoloration and enamel hypoplasia, inhibition of bone growth, *Clostridium difficile*-associated diarrhea, and tetracycline-class adverse reactions (photosensitivity, pseudotumor cerebri, and anti-anabolic action which has led to increased blood urea nitrogen, azotemia, acidosis, hyperphosphatemia, pancreatitis, and abnormal liver tests).

Overall, eravacycline demonstrated a favorable benefit-risk profile for the treatment of cIAI. The risks associated with eravacycline use will be adequately addressed through the product labeling and routine post-marketing surveillance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• cIAIs are invasive infections that extend beyond the hollow viscus of origin into the peritoneal space and are associated with either abscess formation or peritonitis and systemic signs and symptoms of illness. • The most common types of cIAI include complicated appendicitis, cholecystitis, and post-operative infection. • Infections are typically polymicrobial and the major pathogens involved are usual residents of the gastrointestinal tract, including Enterobacteriaceae, streptococci, and certain anaerobes (particularly *Bacteroides fragilis*). Healthcare-associated cIAI arising post-operatively during hospitalization commonly involve more resistant organisms. • Management of cIAIs involves surgical and/or percutaneous drainage, removal of diseased tissue, and adequate source control in conjunction with broad spectrum antimicrobials. • Duration of antimicrobial therapy of cIAI is usually between 4 to 14 days.	cIAI is a serious bacterial infection that can cause significant morbidity and can be fatal in some circumstances. cIAIs are generally polymicrobial and often seen in patients with multiple comorbidities.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• The increasing rate of drug resistance among Enterobacteriaceae in cIAI can limit use of currently available treatments as a single agent alone. • Eravacycline is active against gram negative and gram positive aerobic and anaerobic pathogens, Enterobacteriaceae, *Staphylococcus aureus*, enterococci, and anaeobes.	While treatment are options available for cIAI, the existing armamentarium of drugs is expected to decline in utility over time due to the emergence and spread of resistant organisms. In addition, it is important to have treatment options for patients who are intolerant of other available therapies.
Benefit	• The efficacy of eravacycline in the treatment of cIAI was evaluated in two Phase 3 NI studies that used either ertapenem or meropenem as the active control. Ertapenem and meropenem are both approved for the treatment of cIAI and are considered standards of care for this indication. • In one Phase 3 study, eravacycline was noninferior to ertapenem in the treatment of patients with cIAI with respect to the primary endpoint of clinical cure at TOC in the Micro-ITT population. Differences in clinical response rates between eravacycline and ertapenem was -0.8% (95% CI: -7.1%, 5.5%). • In a second Phase 3 study, eravacycline was noninferior to meropenem in the treatment of patients with cIAI with respect to the primary endpoint of clinical cure at TOC in the Micro-ITT population. Differences in clinical response rates between eravacycline and meropenem was -0.5% (95% CI: -6.3%, 5.3%).	Eravacycline was noninferior to acceptable comparators in two adequate and well-controlled trials in adults with cIAI.
Risk and Risk Management	• Key safety concerns for eravacycline include hypersensitivity reactions, tooth discoloration and enamel hypoplasia, inhibition of bone growth, *Clostridium difficile*-associated diarrhea, and tetracycline class adverse reactions. Overall, the safety profile of	The risks associated with eravacycline are consistent with that of the tetracycline class antibacterial drugs. These risks will be communicated in appropriate sections of

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	eravacycline was consistent with that of the tetracycline class antibacterial drugs.	labeling, including the Warnings and Precautions and Adverse Reactions sections of the package insert. Routine postmarketing surveillance activities will suffice at this point. There are no safety signals/potential for safety issues that require a Risk Evaluation and Mitigation Strategy (REMS) at this time.

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1.4. Patient Experience Data

Clinical outcome assessments were performed in the Phase 2 and Phase 3 cIAI studies (TP-434-P2-cIAI-1, TP-434-008, and TP-434-025). Throughout the study, the investigator assessed whether the signs and symptoms of the index infection completely resolved/significantly improved, were persistent/recurred, or resulted in death. In the Phase 3 cIAI studies, selected clinical responses (i.e., cases recorded as failures or cases with second procedures recorded as cures) were reviewed by a Surgical Adjudication Committee (SAC) of surgeons and radiologists. These assessments were performed prior to unblinding and database lock. Please see Section 7.2 for study endpoints

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	X □ Clinical outcome assessment (COA) data, such as	Section 7.2 study endpoints
	□ □ Patient reported outcome (PRO)	
	□ □ Observer reported outcome (ObsRO)	
	□ □ Clinician reported outcome (ClinRO)	
	□ □ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	

2. Therapeutic Context

2.1. Analysis of Condition

Complicated intra-abdominal infections (cIAI) extend beyond the hollow viscus of origin into the peritoneal space and are associated with either abscess formation or peritonitis and systemic signs and symptoms of illness. This disease classification encompasses several infectious processes, including (but not limited to) the following: 1) appendicitis with perforation or periappendiceal abscess; 2) intra-abdominal abscess(es); 3) peritonitis; 4) perforation of stomach or intestine; 5) diverticulitis with perforation, peritonitis, or abscess; and 6) cholecystitis with perforation or abscess. Patients of any age or gender can be affected. cIAI is a serious condition as inappropriate or ineffective therapy may lead to sepsis and death. The infections are typically polymicrobial and caused by the diverse bacteria that normally reside in

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the gastrointestinal tract. The major pathogens responsible for community-acquired cIAI are Enterobacteriaceae (especially *Escherichia coli*) and anaerobes (especially *Bacteroides fragilis*). More resistant flora are often associated with exposure to recent antibacterial therapy or exposure to the health-care environment. The management of cIAIs involves surgical interventions for source control (i.e., open laboratory, laparoscopy, percutaneous drainage of an abscess) in conjunction with broad spectrum antimicrobials. The course of antibacterial therapy ranges from 4 to 14 days, depending upon the clinical response of the patient, as judged by the resolution of all signs and symptoms of the disease.

2.2. Analysis of Current Treatment Options

Currently available treatments for cIAI by antibacterial class is presented in Table 1.

Table 1: Currently Available Treatments for cIAI by Antibacterial Class

Generic name	Trade name	Comments
Extended-spectrum penicillins		
Piperacillin	Pipracil	Unlikely to be used alone without tazobactam
Cephalosporins (parenteral 2nd, 3rd and 4th generation)		
Cefotetan	Cefotan	
Cefoxitin	Mefoxin	
Cefotaxime	Claforan	Use as empiric monotherapy has declined with emergence of multi-drug resistant gram-negative bacilli
Ceftazidime	Fortaz, Tazicef	
Ceftriaxone	Rocephin	
Cefepime	Maxipime	
β-lactam/β-lactamase Inhibitor Combinations		
Ticarcillin clavulanate	Timentin	
Ampicillin-sulbactam	Unasyn	
Piperacillin-tazobactam	Zosyn	
Ceftolozane-tazobactam	Zerbaxa	
Ceftazidime-avibactam	Avycaz	
Fluoroquinolones		Risk of tendonitis, tendon rupture, QTc prolongation, exacerbation of myasthenia gravis, CNS effects, peripheral neuropathy
Ciprofloxacin	Cipro	
Moxifloxacin	Avelox	
Carbapenems		
Imipenem-cilastatin	Primaxin	
Meropenem	Merrem	
Ertapenem	Invanz	
Doripenem	Doribax	
Monobactams		Treatment guidelines recommend addition of an agent against gram-positive cocci. Although used in patients with allergy to penicillins/cephalosporins, there are concerns about cross-reactivity with ceftazidime
Aztreonam	Azactam	
Aminoglycosides		
Gentamicin		
Amikacin		
Tobramycin		

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Glycylcyclines		Vancomycin-resistant *Enterococcus faecium* (VREF) activity, but *Pseudomonas aeruginosa* is intrinsically resistant to tigecycline
Tigecycline	Tygacil	
Other		
Clindamycin	Cleocin	Prevalence of resistance to *B. fragilis* group
Metronidazole	Flagyl	Treatment guidelines recommend in combination for patients with high-severity cIAI

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Eravacycline is is not currently marketed in the US or in any other country.

3.2. Summary of Presubmission/Submission Regulatory Activity

Eravacycline injection formulation has been studied under IND 104839 which was opened August 20, 2009. The following is a summary of the key regulatory interactions and proceedings with respect to the clinical development program:

- May 28, 2009: A pre-Investigational New Drug (IND) meeting was held. The Agency agreed that the microbiology information from animal models of infection and the pre-clinical studies were adequate to support the Phase 1 clinical program.
- January 25, 2013: An End-of-Phase 2 meeting was held. The Agency agreed that the microbiology information from animal models, the completed pre-clinical studies, and the completed Phase 1 and 2 studies were adequate to support the Phase 3 clinical program.
- July 9, 2013: Qualified Infectious Disease Product (QIDP) was granted for IV eravacycline for the indications of cIAI and cUTI.
- March 27, 2014: Fast track designation was granted for IV eravacycline for the indications of cIAI and cUTI.
- November 4, 2015: A Type B pre-NDA meeting was held. The clinical trial for the cUTI indication did not demonstrate efficacy, but the cIAI trial was successful. The Agency therefore requested that the Applicant either conduct a second adequate and well-controlled study in cIAI. The clinical data available at the time was reviewed to determine the potential of eravacycline to address an unmet medical need.
- February 17, 2016: A face-to-face meeting was held. The Agency ruled that the evidence presented to satisfy an unmet medical need were insufficient; thus, the Applicant agreed to conduct a second Phase 3 cIAI study (TP-434-025). Discussion at this meeting plus various email communications provided input from the Agency into the design of the second Phase 3 cIAI study. Agreements were reach with respect to the use of meropenem as the active-comparator and a -12.5% noninferiority margin for the

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primary endpoint.

- November 10, 2017: An initial pediatric study plan (iPSP) was submitted and agreed to by the Agency. The iPSP included a waiver for the pediatric population less than 8 years of age due to the risks of tetracycline-associated bone and tooth staining, and a deferment of pediatric studies in subjects aged 8 to 17 years until safety and efficacy data were obtained in the adult population.
- October 13, 2017: A Pre-NDA meeting was held to discuss and reach agreement on the content, organization, and regulatory filing strategy to support the eravacycline NDA submission
- December 28, 2017: NDA 211109 submission for the treatment of adult patients with cIAI was received.

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4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) conducted an inspection of four clinical sites from the Phase 3 cIAI studies (sites No. 072, No. 081, No. 118, and No. 107). Site No. 72 was selected due to high enrollment (Study TP-434-008), high treatment efficacy (for serious infections) in both treatment arms, and high evaluability rates (low occurrence of protocol violations). Site No. 081 was selected due to high enrollment (Study TP-434-025), high treatment efficacy rates, and relatively scant reporting of protocol violations and adverse events. Site No. 118 was selected due to participation in both studies and higher number of adverse events and serious adverse events in the study treatment arm in Study 025. Site No. 107 was selected due to participation in both studies and was chosen as representative US site. OSI also inspected Tetraphase Pharma. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued. Based upon these findings OSI determined that the study data derived from these clinical sites are considered reliable.

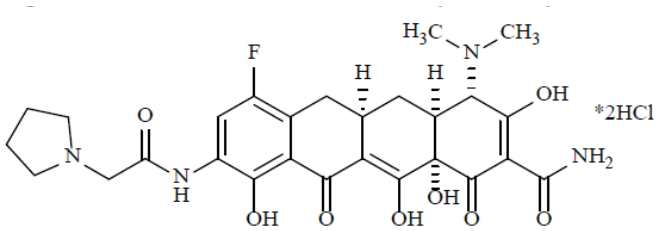
4.2. Product Quality

Novel excipients: No
Any impurity of concern: No
Sufficient controls to insure safety and efficacy of the commercial product: Yes

Provided below is a brief summary of the product quality assessment from the Office of Pharmaceutical Quality (OPQ). Details of the review findings are referred to the Integrated Quality Assessment (IQA).

Eravacycline is a synthetic, broad-spectrum fluorocyclic antibacterial drug belonging to the tetracycline class and has the following structural formula:

Figure 1 Structure of Eravacycline



Molecular Formula: $C_{27}H_{31}FN_4O_8$

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The overall information provided in the NDA for the drug substance, including the (b) (4) proposed specification, was found acceptable by the drug substance reviewer. Available stability data in the NDA support a retest period of (b) (4) months for the drug substance stored (b) (4)

The drug product, eravacycline for injection, 50 mg is a lyophilized powder for intravenous administration presented in a USP (b) (4) glass vial with rubber stopper and aluminum seal. An overfill of (b) (4) mg of eravacycline is used to allow withdrawal of the labeled amount of eravacycline. The excipients used in the formulation (see table below) include mannitol (b) (4) sodium hydroxide and hydrochloric acid (pH adjusters), (b) (4) are of compendial standards. (b) (4)

Table 2 Components and Composition of Eravacycline drug product

Component	Theoretical Quantity per Vial[2]	Function	Reference to Standard
Eravacycline[1]	50 mg	Active Pharmaceutical Ingredient	In-house
Mannitol	150 mg	(b) (4)	Ph. Eur., USP, JP
Sodium Hydroxide (NaOH)	As needed to adjust pH to target	pH adjustment	Ph. Eur., NF
Hydrochloric acid (HCl)	As needed to adjust pH to target	pH adjustment	Ph. Eur., NF
(b) (4)			

Ph. Eur. = European Pharmacopoeia; USP = United States Pharmacopeia; NF = National Formulary; JP = Japanese Pharmacopeia; NA = Not Applicable

[1] = The drug substance is a salt, eravacycline dihydrochloride. (b) (4)

[2] = (b) (4)

[3] = (b) (4)

The drug product specification (see table below) includes quality attributes relevant for the proposed dosage form such as appearance, identification, assay, impurities, content uniformity, pH, particulate matter, reconstitution time, endotoxins and sterility. The proposed acceptance limits and the analytical procedures were found acceptable. The NDA

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provided 18-months long-term and 6-month accelerated stability data for three full commercial batches manufactured at the proposed commercial manufacturing site. The stability data supports the proposed expiration date of 24-month for the drug product when stored under refrigerated conditions of 5° ±3° C. The applicant has provided in-use stability studies to support the label recommendation to use 0.9% saline. (b) (4)

Table 3 Drug Product Specification

Test	Test Method	Acceptance Criteria	
		In-house Release Specifications**	**Shelf life and Regulatory Specifications**
Appearance of Lyophilisate*	Visual	(b) (4) yellow to orange lyophilised cake	
Appearance of container	Visual	Clear glass vial with a rubber stopper with aluminum crimp free of external defect	
Appearance of Reconstituted Solution[1]*	Ph. Eur. 2.2.1, Ph. Eur. 2.2.2, Ph. Eur. 2.9.20, USP <1>	Clear solution from pale yellow to orange colour, free of visible particles	
Visible Particles[1]	Ph. Eur. 2.9.20 USP <790>, USP <1>	For each vial tested, the solution has to be practically free from particles or foreign material that can be observed by visual inspection	
Identification	HPLC (Retention time)	Retention time of principal peak is (b) (4)% of average retention time of bracketing standard injections	
Identification	HPLC (UV Spectrum)	UV spectrum of sample matches that of the standard by visual comparison	
Assay[2]*	HPLC (%w/w)	(b) (4) of total vial content	(b) (4) of total vial content
Impurities*	HPLC (area%)	Identified specified (b) (4)	
		Each Individual unspecified unidentified (b) (4)	
		Total[3]	
Content Uniformity	USP <905> Ph. Eur. 2.9.40	Conforms	

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Test	Test Method	Acceptance Criteria	
		In-house Release Specifications**	**Shelf life and Regulatory Specifications**
[redacted] (b) (4)			
pH of Reconstituted Solution[1,5]*	Ph. Eur. 2.2.3	5.5 to 7.0	
Particulate Matter (Microscopy)*	Ph. Eur. 2.9.19 USP <788>	ø ≥10µm: (b) (4) per vial ø ≥25µm: (b) (4) per vial	
Endotoxins*	Ph. Eur. 2.6.14 USP <85>	(b) (4) EU/mg	
Sterility*	Ph. Eur. 2.6.1 USP <71>	Sterile	
Reconstitution Time*	Visual	(b) (4) min	

[1] Reconstituted with 5 mL of (b) (4) water
[2] (b) (4)
[3] Total impurities include the DS process impurities (b) (4)
[4] (b) (4)
[5] Test performed as per Ph. Eur. which is more restrictive the corresponding USP method (USP<791>)
*Tests also performed on stability
**In compliance with *ICH Q6A Guidance "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (October 1999),* Section 2.2, Tetraphase considers the shelf-life specifications provided in *Table 1*, as the eravacycline DP regulatory specifications. The more restrictive in-house release specifications are provided herein for information only.

A risk assessment according to ICH Q3D has been performed to establish control of elemental impurities. The Applicant analyzed four drug product batches and the levels of all elements (Class 1, 2A, 2B, and 3) were <30% of the respective PDEs.

The Applicant's claim of categorical exclusion under 21 CFR 25.31(b) and statement of no extraordinary circumstance have been found acceptable.

The facilities supporting the NDA were evaluated and based on the information available, the Office of Process and Facilities has found the proposed manufacturing facilities adequate to support the NDA.

There are no outstanding product quality issues. OPQ recommends **Approval** of the NDA from product quality perspective.

4.3. Devices and Companion Diagnostic Issues

There were no companion devices or diagnostic instruments in this application

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5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Safety pharmacology studies evaluated potential for effects on the cardiovascular, respiratory, and neurological systems. Cardiovascular/respiratory findings were limited to dose-dependent increases in heart rate, blood pressures, respiratory rate and core body temperature in telemetered beagle dogs during dosing with 15 or 30 mg/kg and within 30-60 minutes after the end of the infusion, returning to baseline within 4 hours of infusion start. The ECG recordings were within normal limits. Neurofunctional assessment in rats revealed histaminergic reactions and significant Functional Observational Battery (FOB) changes at 30 and 60 mg/kg within 5 minutes of dosing and resolving by 24 hours post-dosing. No Adverse Effect Level (NOAEL) doses in those studies were 5 mg/kg (dogs, human equivalent dose (HED) = 2.5 mg/kg) and 4 mg/kg (rat, HED = 0.6 mg/kg).

After intravenous administration, eravacycline was widely distributed, including into fetal tissues and milk. Exposure was generally greater than dose-proportional, and there was evidence of accumulation with repeated dosing. Protein binding varied between species, and was inversely related to concentration. Quantitative whole body autoradiography in pigmented rats suggested binding to melanin-containing structures. No gender differences were apparent. Elimination took place in urine and feces, with some evidence of biliary and intestinal secretion. The elimination half-life ranged from approximately 5 hours in the rat to 6-14 hours in dogs and monkeys.

GLP-compliant general toxicology studies included 2-week studies in rats, dogs, and cynomolgus monkeys and 3-month studies in rats and cynomolgus monkeys. Effects consistent with histaminergic reactions were seen in rats and dogs at all doses. Irritation at the injection site was seen at all three species, and in high dose monkeys (2-week study) was severe enough to result in impaired use of hind limbs. Targets of toxicity in the rat appeared to be erythrocytes (decreased, associated with bone marrow hypoplasia, increased total bilirubin in serum, hemosiderin in the spleen or lymph nodes, and/or increased MCH, indicating possible decreased production and hemolysis), lymphoid tissue (decreased circulating lymphocytes, lymphoid depletion in thymus, lymph nodes and/or GALT), liver (evidence of decreased synthesis of protein, albumin, cholesterol, and/or triglycerides), testis/epididymis (seminiferous tubule degeneration, oligospermia, abnormal sperm), and bone (discoloration).

In the dog, toxicity was dose-limiting, resulting in death or early termination of all animals in the mid- and high doses (12 and 20 mg/kg/day). Targets of toxicity included the gastrointestinal tract (including hemorrhage), bone marrow (red and white blood cell elements, decreased circulating cells), lymphoid tissue (atrophy, lymph node hemorrhage, decreased circulating lymphocytes), liver (decreased apparent synthesis of protein and albumin, hepatocyte vacuolation), bone (discoloration), heart (cardiac hemorrhage and necrosis, 2nd

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degree AV block), and testes (cytoplasmic vacuolation and/or degeneration of seminiferous tubules)

Targets of toxicity in the cynomolgus monkey also included erythrocytes (decreased red cell parameters), liver (decreased total protein, albumin A/G ratio, and/or cholesterol), lymphoid tissue (decreased spleen and thymus weights, lymphoid depletion), increased serum BUN and bilirubin, decreased serum calcium (tetracyclines are known to bind), mucosal tissues (mucosal atrophy in the gastrointestinal tract, erosion of mucosal surfaces), and bone (discoloration). A T-cell dependent antibody response assay was conducted in the 3-month study and demonstrated impaired immune function.

Table 4 LOAEL or NOAEL doses in non-clinical studies

Species	**Duration**	**NOAEL/LOAEL dose (mg/kg/day)**	**Sex**	**AUC (ng*hr/mL)**		
				Day 1	**Day 14**	
Rat	2 week	4 (LOAEL)	male	9105	14455	$AUC_{0\text{-}inf}$
			female	9955	15938	
Dog	2 week	2 (LOAEL)	male	4062	6833	$AUC_{0\text{-}last}$
			female	3586	7302	
Monkey	2 week	4 (LOAEL)	male	30900	45700	$AUC_{0\text{-}24h}$
			female	31400	49000	
				Day 1	**Day 91**	
Rat	13 week	4	male	16100	24800	$AUC_{0\text{-}t}$
			female	13300	17700	
Monkey	13 week	4 (LOAEL)	male	33500	44800	$AUC_{0\text{-}24h}$
			female	39700	50600	

For comparison, the proposed labeling indicates that the IV clinical dose is 1 mg/kg q 12h, and the AUC = 4305 (Day 1) or 6309 (Day 10) ng*hr/mL.

Results of genetic toxicology testing were negative, although eravacycline and at least one metabolite were toxic to bacterial strains used in the reverse mutation assay. In developmental and reproductive toxicology tests, testicular effects were again noted and resulted in impaired male fertility; effects were reversible after a relatively long recovery period. The NOAEL for male fertility was 4 mg/kg/day. The NOAEL for female fertility and early embryonic development was 20 mg/kg/day, the highest dose tested, although that study did not test to maternal toxicity.

Embryo-fetal development studies in rats demonstrated total litter resorption and increased post-implantation loss at 20 and 40 mg/kg/day and decreased fetal body weights at 10 and 20 mg/kg/day in a dose range-finding study. In the definitive study, decreased fetal body weights

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and decreased or delayed skeletal ossification were seen at 10 mg/kg/day; this study did not test to maternal toxicity. The developmental NOAEL was 5 mg/kg/day.

In rabbit embryo-fetal development studies, total litter loss was seen in high dose (12 mg/kg/day) dams. In the definitive study, at the high dose (4 mg/kg/day), increased late resorptions, increased post-implantation loss, one litter with a dead fetus, decreased fetal body weights, and decreased ossification of limbs were seen. The developmental NOAEL was 2 mg/kg/day.

A peri- and post-natal development study was conducted in rats. While the study did not test to maternal toxicity, it did demonstrate concentrations of eravacycline and metabolites in milk. Pre-weaning assessment of pups revealed decreased pup body weight on post-natal Day 1 (PND 1) and a trend toward stillborn pups or pups found dead during lactation. Post-weaning assessment did not reveal any remarkable findings, with the exception of decreased absolute testis and epididymis weights in male pups in the high maternal dose group (10 mg/kg/day). The NOAEL for reproduction in the F0 generation dams and for viability, growth, and reproduction in the F1 generation rats was considered to be 10 mg/kg/day (highest dose level tested).

From a Pharmacology/Toxicology standpoint, this application is approvable. The nonclinical data support the safety of the proposed clinical use.

5.2. Referenced INDs, NDAs, BLAs, DMFs

IND 104839 (IV)
(b) (4)

5.3. Pharmacology

Primary pharmacology

Eravacycline (TP-434) is a semi-synthetic tetracycline. As a class, tetracyclines bind to the bacterial ribosome 30S subunit and inhibit bacterial protein synthesis. Activity is bacteriostatic. Details of primary pharmacology studies conducted with eravacycline can be found in the Nonclinical Microbiology Section 8.1.

Safety Pharmacology

Potential for cardiovascular effects was evaluated in a hERG assay in human embryonic kidney cells (**Study no. 081230.UQQ**) at nominal concentrations of 9.2, 17.8, 22.2, and 91.6 µM. The test article inhibited hERG current by 0.9 % at 9.2 µM, 5.6% at 17.8 µM, 8.3% at 22.2 µM, and 6.9% at 91.6 µM. The IC_{50} was not calculated due to insolubility of the compound (precipitate was reported at 22.2 µM, approximately 12.4 µg/mL), but was considered to be greater than 22.2 µM.

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A cardiovascular and respiratory safety pharmacology study of eravacycline was conducted in telemetered beagle dogs (**Study no. EQC00001**). Doses were vehicle (0.9% saline USP), 5, 15, or 30 mg/kg eravacycline administered as a 30 minute IV infusion of a volume of 5 mL/kg. Systolic, diastolic and mean arterial pressures, ECG, respiratory rate, and core body temperature were recorded for 24 hours before the start of each infusion through 24 hours after the start of the infusion for each session. Arterial blood samples were collected for blood gas and pH measurements. Blood samples were taken for plasma drug concentrations, and clinical observations and body weight were monitored. At all doses, acute histamine-like skin reactions were observed. At 5 mg/kg, heart rate, respiratory rate, blood pressures, ECG, blood gas, and core body temperature were not affected. At 15 and 30 mg/kg, dose-dependent increases in heart rate, blood pressures, respiratory rate and core body temperature were observed during dosing and within 30-60 minutes after the end of the infusion, and returned to baseline within 4 hours of infusion start. The ECG recordings were within normal limits.

Neurofunctional assessment following a single IV bolus (over 1-2 minutes) dose of vehicle (0.9% NaCl), 4, 30, or 60 mg/kg eravacycline (10 mL/kg) was conducted in Sprague-Dawley rats (**Study no. EQC00004**). A functional observational battery (FOB) consisting of five domains (Central nervous system (CNS) activity and excitability, Autonomic nervous system, Sensorimotor function, Neuromuscular function, Physiologic effects) was conducted. No clinical signs or FOB changes were noted at 4 mg/kg. Histaminergic signs were noted at 30 and 60 mg/kg. Significant FOB changes were reported at 30 and 60 mg/kg within 5 minutes of dosing. These included decreased home cage activity, flattened posture, lower reactivity during handling and removal, slower or irregular respiration, decreased rearing counts and activity/arousal in open field testing, muscle fasciculation or slight tremors, miosis and absence of pupillary reflex, ocular discharge, slight salivation, prolonged tail flick response, decreased muscular tone, gait pattern abnormalities, slight to severe ataxia, impaired surface and air righting ability, decreased mean landing foot splay, decreased forelimb grip strength and decreased body temperature. While findings at 30 and 60 mg/kg were similar, greater incidence and severity were seen at the higher dose. All were comparable to controls at the 24 hour assessment. The NOAEL was concluded to be a single IV dose of 4 mg/kg (HED = 0.67 mg/kg, or 40 mg for a 60 kg human).

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
	Single dose PK parameters are summarized in the Applicant's Table 3 below (Study numbers are provided in footnotes).

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Type of Study | **Major Findings**

Table 3 Pharmacokinetic / Toxicokinetic Parameters for TP-434 in the Rat, Rabbit, Dog, Monkey, and Humans Following a Single Intravenous Dose of Eravacycline

Species	Dose (mg/kg)	C_0 or C_{max} (µg/mL)	$T_{½}$ (h)	AUC_{0-t}, AUC_{0-24} or AUC_{last} (µg-h/mL)	AUC_{inf} (µg-h/mL)	CL (L/h/kg)	V_d (L/kg)
Sprague Dawley rat[a]	1	3.58	5.28	3.02	3.11	0.343	1.64
Rabbit[b]	1.63	7.29	7.2	8.59	8.74	0.188	0.97
	2.90	15.1	12.7	19.9	20.2	0.145	1.07
	10.53	64.1	13.0	101	102	0.104	0.75
Beagle dog[c]	1 (portal)	2.75	13.9	6.05	6.49	0.155	2.25
	1 (cephalic)	2.86	14.2	5.98	6.43	0.157	2.24
Beagle dog[a]	1	1.21	14.2	3.09	4.06	0.247	3.91
Beagle dog[d]	5	5.45	10.1	15.53	18.18	0.285	4.04
	15	35.64	9.02	94.03	104.63	0.274	3.55
	30	131.58	6.39	549.73	584.27	0.153	1.71
Cynomolgus monkey[a]	1	5.27	7.90	4.39	4.75	0.225	1.65
Cynomolgus monkey[e]	1	0.319	16.7	1.89	2.14	0.487	10.9
	3.15	3.61	14.1	12.50	12.8	0.258	5.42
	12	54.6	15.9	163	165	0.075	1.71
	36	327.0	12.3	1320	1330	0.028	0.49
Human[f]	1.0, BID	2.13	8.64	5.11	5.63	0.18	2.22 (V_z)
Human[g]	1.0	1.04	14	4.32	4.59	3.90 (ml/min/kg)	3.57
Human[h]	1.0	1.17	15	4.10	5.38	3.20 (mL/min/kg)	2.85

AUC_{inf} = area under the plasma concentration-time curve extrapolated through infinity;
AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours post-dose;
AUC_{last} = area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; AUC_{0-t} = area under the concentration-time curve from time zero to time t (the last measurable concentration); BID = twice daily; C_0 = plasma concentration at time zero; C_{max} = maximum observed plasma concentration; CL = clearance; h = hour(s); $T_{½}$ = terminal elimination half-life; V_d = volume of distribution;
- = not applicable.
Note:
Values represent the average of means for males and females.
[a] = *Report PK15-01*,
[b] = *Report* (b) (4) *PK-002 Phase 1.*
[c] = *Report 47704-10-431.*
[d] *Report EOC00001*; V_z
[e] *Report* (b) (4) *912001*; V_z
[f] = *Study TP-434-P1-MAD-1*, Day 1 values.
[g] = *Study TP-434-016*, single dose.
[h] = *Study TP-434-020*, single dose.

Reviewer's comment: These AUC values are higher than those reported in the original IND in rat, dog, and monkey after a single dose.

- No apparent gender differences were reported.
- Cmax and AUC increased with increasing dose.

- Clearance exceeded GFR.

Distribution

- Plasma protein binding was highly variable and inversely related to concentration (**Reports** (b) (4) **-001, AD09-06, AD15-4, and TET-R4384**). According to the nonclinical overview, in cynomolgus monkeys, free drug

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Type of Study	Major Findings
	ranged from 0.4% free at 100 µg/mL to 5.1% free at 0.1 µg/mL. The plasma binding of 1 µg/mL eravacycline was highest in cynomolgus monkey plasma (1.7% free) and lowest in rabbits (18.6% free); the mean free fraction was 14.0% in human plasma. • A Quantitative Whole Body Autoradiography (QWBA) study (**Report TTP-01**) demonstrated rapid and widespread distribution, with Tmax in most tissues at 6 minutes post-dose. Highest radioactivity was seen in the first 2 hours after dosing and was concentrated in trachea, adrenal, liver and aorta. Radioactivity was below the level of quantitation (BLQ) 21 days post-dose, with the exception of the uveal tract, bone, thyroid, and pigmented fur, reflecting binding of eravacycline to melanin-containing structures and slow elimination from calcified tissues. Placental transfer and fetal plasma exposure were demonstrated in dose range-finding embryo-fetal development (EFD) studies in rats (**Report 20013499**) and rabbits (**Report 20013501**)
Metabolism	
	• TP-434 was reported to be metabolically stable in vitro • In vivo metabolism was by CYP3A4, FMO 1, 3, and 5, and glucuronide conjugation • TP-434 is metabolized to the C4 epimer, TP-498 • Exposure to major human metabolites, TP-6208 and TP-034, was minimal in animals, but was qualified in toxicology studies where the metabolites were administered. Comparative metabolism is shown in the Applicant's Figure 2 below.

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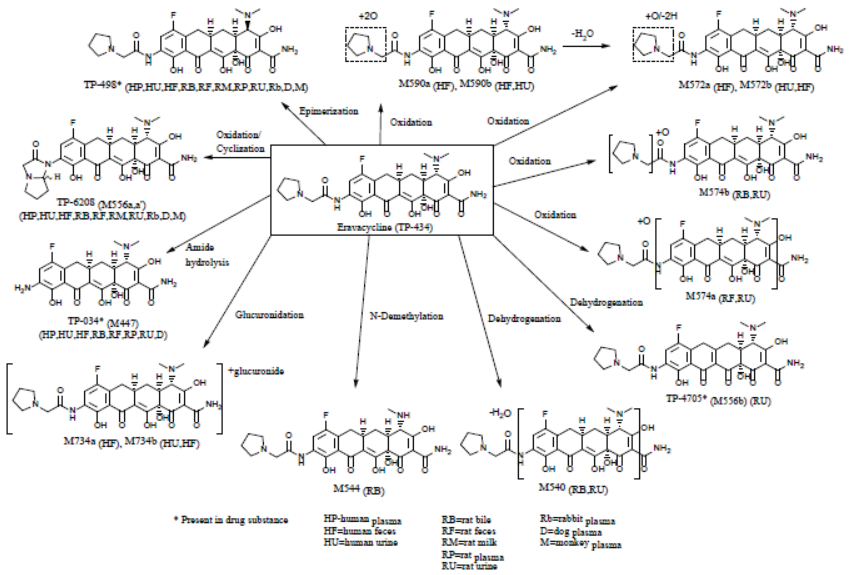
Type of Study	Major Findings
	Figure 2 Eravacycline (TP-434) Comprehensive Schematic of Metabolic Pathways in Humans and Animals 
Excretion	
	• Primary elimination routes were feces (66%) and urine (25%) in rats and urine (34%), bile (23%), and feces (17%) in bile duct-cannulated rats, suggesting combination of biliary excretion and secretion into the gastrointestinal tract from the blood. • TP-434 and metabolites TP-498 (epimer) and TP-6208 were detected in rat milk • TP-434, TP-498, and TP-6208 were found in fetal blood in rats (**Study no. 20013499**) and rabbits (**Study no. 20013501**)
TK data from general toxicology studies	Rat T1/2: 4.43-5.38 hours in the 2-week study (**Study no. EQC00010**); 4.64-5.57 hours on Study Day (SD) 1 of the 3-month study (**Study no. 20048026**) and 4.75-8.17 hours on SD 91 Accumulation: Evidence of some accumulation in the 2-week study and in the 3-month study Dose proportionality: AUC was approximately dose proportional for doses of 4, 20, and 40 mg/kg/day for 2 weeks, but was greater than dose-proportional in the 3-month study at doses of 2, 4, 8, and 16 mg/kg/day. TK parameters from the 2-week rat study:

Type of Study	Major Findings

Day 1 (Males)

Group No.	Dose Level (mg/kg)	Cp0 (ng/mL)	$AUC_{(0\text{-}last)}$ (ng•h/mL)	$AUC_{(0\text{-}\infty)}$ (ng•h/mL)
2	4	11358	8848	9105
3	20	75934	102696	103572
4	40	199891	240597	242751

Day 1 (Females)

Group No.	Dose Level (mg/kg)	Cp0 (ng/mL)	$AUC_{(0\text{-}last)}$ (ng•h/mL)	$AUC_{(0\text{-}\infty)}$ (ng•h/mL)
2	4	11006	9790	9955
3	20	73867	113884	114947
4	40	135667	208243	210918

Day 14 (Males)

Group No.	Dose Level (mg/kg)	Cp0 (ng/mL)	$AUC_{(0\text{-}last)}$ (ng•h/mL)	$AUC_{(0\text{-}\infty)}$ (ng•h/mL)
2	4	14162	14230	14455
3	20	62507	134089	135608
4	40	113912	244200	247609

Day 14 (Females)

Group No.	Dose Level (mg/kg)	Cp0 (ng/mL)	$AUC_{(0\text{-}last)}$ (ng•h/mL)	$AUC_{(0\text{-}\infty)}$ (ng•h/mL)
2	4	12237	15737	15938
3	20	94633	163626	164591
4	40	190384	280171	282203

TK parameters from the 3-month rat study:

Text Table 18
Selected Toxicokinetic Parameters for Eravacycline

Dose Group	Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{(0\text{-}t)}$ (ng·hr/mL)	$t_{1/2}$ (hr)
DS 1						
2	2	M	2450	0.100	5810	5.57
		F	1990	0.100	4470	4.98
3	4	M	10400	0.100	16100	5.05
		F	8740	0.100	13300	4.85
4	8	M	26500	0.100	44200	4.96
		F	26600	0.100	36400	4.70
5	16	M	67600	0.100	112000	5.26
		F	72800	0.100	95500	4.64
DS 91						
2	2	M	4560	0.100	8160	6.61
		F	1410	0.500	3900	NC
3	4	M	17000	0.100	24800	7.73
		F	10700	0.100	17700	5.04
4	8	M	44100	0.100	70800	8.17
		F	33600	0.100	50100	5.15
5	16	M	101000	0.100	175000	5.95
		F	97900	0.100	169000	4.75

NC = Not Calculated

<u>Monkey</u>

T1/2: 14.5-19.5 hours in the 2-week study (**Study no. (b) (4)-912002**)
In the 3-month study (**Study no. (b) (4)-912005**), clearance decreased with increasing dose, ranging from approximately 0.06-0.5 L/h/kg on Day 0.

Reference ID: 4312284

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>
Accumulation: Evidence of some accumulation in the 2-week study and in the 3-month study

Dose proportionality: Greater than dose-proportional exposure for doses of 2, 4, and 18 mg/kg/day for 2 weeks and for doses of 1, 2, 4, and 8 mg/kg/day for 3 months

TK parameters from the 2-week monkey study:
Table 1. Overall Mean (±SD) Toxicokinetic Summary Data; Sorted by Analyte, Day, Group, and Nominal Dose of TP-434
<table>
<tr><th>Analyte</th><th>Day</th><th>Group</th><th>Nominal Dose of TP-434 (mg/kg)</th><th>C_{max} (µg/mL)</th><th>T_{max} (h)</th><th>AUC_{0-24h} (µg*h/mL)</th></tr>
<tr><td rowspan="6">TP-434</td><td rowspan="3">0</td><td>2</td><td>2</td><td>6.04 (1.96)</td><td>0.083 (0.00)</td><td>8.74 (2.18)</td></tr>
<tr><td>3</td><td>4</td><td>23.2 (4.99)</td><td>0.083 (0.00)</td><td>31.1 (4.74)</td></tr>
<tr><td>4</td><td>18</td><td>297 (46.9)</td><td>0.083 (0.00)</td><td>541 (103)</td></tr>
<tr><td rowspan="3">13</td><td>2</td><td>2</td><td>10.3 (1.68)</td><td>0.083 (0.00)</td><td>14.5 (1.78)</td></tr>
<tr><td>3</td><td>4</td><td>30.7 (4.62)</td><td>0.083 (0.00)</td><td>47.4 (4.89)</td></tr>
<tr><td>4</td><td>18</td><td>275 (53.8)</td><td>0.083 (0.00)</td><td>585 (79.5)</td></tr>
<tr><td rowspan="6">TP-498</td><td rowspan="3">0</td><td>2</td><td>2</td><td>0.341 (0.119)</td><td>0.0997 (0.0528)</td><td>0.688 (0.122)</td></tr>
<tr><td>3</td><td>4</td><td>1.21 (0.214)</td><td>0.083 (0.00)</td><td>2.20 (0.204)</td></tr>
<tr><td>4</td><td>18</td><td>10.9 (1.64)</td><td>0.0997 (0.0528)</td><td>24.7 (4.29)</td></tr>
<tr><td rowspan="3">13</td><td>2</td><td>2</td><td>0.271 (0.0422)</td><td>0.083 (0.00)</td><td>0.936 (0.103)</td></tr>
<tr><td>3</td><td>4</td><td>0.614 (0.074)</td><td>0.083 (0.00)</td><td>2.13 (0.320)</td></tr>
<tr><td>4</td><td>18</td><td>6.55 (1.44)</td><td>0.083 (0.00)</td><td>25.3 (3.39)</td></tr>
<tr><td rowspan="6">TP-6208</td><td rowspan="3">0</td><td>2</td><td>2</td><td>0.0218 (0.00402)</td><td>2.00 (0.00)</td><td>0.212 (0.044)</td></tr>
<tr><td>3</td><td>4</td><td>0.039 (0.0106)</td><td>2.00 (0.00)</td><td>0.518 (0.143)</td></tr>
<tr><td>4</td><td>18</td><td>0.202 (0.0657)</td><td>2.41 (2.06)</td><td>3.15 (0.842)</td></tr>
<tr><td rowspan="3">13</td><td>2</td><td>2</td><td>0.0216 (0.00469)</td><td>1.81 (0.606)</td><td>0.306 (0.0726)</td></tr>
<tr><td>3</td><td>4</td><td>0.0452 (0.0098)</td><td>0.500 (0.794)</td><td>0.680 (0.194)</td></tr>
<tr><td>4</td><td>18</td><td>0.801 (0.120)</td><td>2.00 (0.00)</td><td>13.2 (2.29)</td></tr>
</table>

TK parameters from the 3-month monkey study:
Text Table 2. Summary of Toxicokinetic Parameters for Eravacycline (TP-434)
<table>
<tr><th rowspan="2">Dosage</th><th colspan="2">AUC_{0-24hr} (ng•hr/mL)</th><th colspan="2">CL (L/hr/kg)</th><th colspan="2">V_{ss} [a] (L/kg)</th></tr>
<tr><th>Day 0</th><th>Day 90</th><th>Day 0</th><th>Day 90</th><th>Day 0</th><th>Day 90</th></tr>
<tr><td colspan="7">Eravacycline (TP-434)</td></tr>
<tr><td><u>Males</u></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>1 mg/kg/day</td><td>2000</td><td>3650</td><td>0.501†[2]</td><td>0.283</td><td>1.64†[2]</td><td>0.949</td></tr>
<tr><td>2 mg/kg/day</td><td>8550</td><td>12,100</td><td>0.270†[5]</td><td>0.171</td><td>1.14†[5]</td><td>0.995</td></tr>
<tr><td>4 mg/kg/day</td><td>33,500</td><td>44,800</td><td>0.110†[3]</td><td>0.0929</td><td>0.400†[3]</td><td>0.387</td></tr>
<tr><td>8 mg/kg/day</td><td>124,000</td><td>194,000</td><td>0.0630†[4]</td><td>0.0417</td><td>0.246†[4]</td><td>0.225</td></tr>
<tr><td><u>Females</u></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>1 mg/kg/day</td><td>2180</td><td>3300</td><td>0.514†[3]</td><td>0.307</td><td>1.88†[3]</td><td>0.895</td></tr>
<tr><td>2 mg/kg/day</td><td>9720</td><td>11,900</td><td>0.241†[2]</td><td>0.174</td><td>0.992†[2]</td><td>0.569</td></tr>
<tr><td>4 mg/kg/day</td><td>39,700</td><td>50,600</td><td>0.0970†[3]</td><td>0.0836</td><td>0.382†[3]</td><td>0.451</td></tr>
<tr><td>8 mg/kg/day</td><td>129,000</td><td>187,000</td><td>0.0638†[2]</td><td>0.0437</td><td>0.243†[2]</td><td>0.240</td></tr>
</table>
[a] = V_{ss} on study day 90 was estimated using MRT_{last}
N = 6 except where noted as $\dagger^{N}$.
</td></tr>
<tr><td>TK data from reproductive toxicology studies</td><td><u>Rat</u>
AUC: 13200 ng*hr/mL on Day 1 (14100 on Day 5) for the NOAEL for male fertility (4 mg/kg/day) determined in a separate PK study (Study no.8309245 – PK study in male rats after 5 days of dosing)</td></tr>
</table>

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Type of Study	Major Findings
	AUC: 113884 ng*hr/mL on Day 1 (163626 on Day 14) for the NOAEL for female fertility (20 mg/kg/day), determined in unmated females in the 2-week general toxicology study (**Study no. EQC00010** – PK data from the 2-week general toxicology study in rats) AUC: 21.5 µg*hr/mL on Gestation Day (GD) 7, the first day of dosing (27.4 on GD 17) for the NOAEL for embryo-fetal developmental toxicity (5 mg/kg/day co-administered with TP-6208) (**Study no. 20013500**) <u>Rabbit</u> AUC: The NOAEL for embryo-fetal developmental toxicity in the rabbit EFD study was 2 mg/kg/day. AUC from a separate PK study in pregnant rabbits (**Study no. 20059976**) at 2 mg/kg day was 20600 ng*hr/mL on GD 11 (25800 on GD 15).

5.5. Toxicology

5.5.1. General Toxicology

Most toxicology studies have been reviewed previously under IND 104839 and are summarized under "General Toxicology – additional studies." One new general toxicology study is reviewed here:

Study title/ number: A 13-week GLP-compliant toxicity and toxicokinetic study of eravacycline (TP-434) by intravenous injection in rats with at 7-week recovery period (Study no. 20048026)

<u>Key Study Findings</u>

Evidence of histaminergic reactions were reported at 8 and 16 mg/kg/day in males and at 16 mg/kg/day in females during the dosing period. Decreased body weights and body weight gains were reported in 16 mg/kg/day males.

Hematology findings included one or more decreased RBC parameters at 16 mg/kg/day (may correlate with hemosiderin deposits in the popliteal lymph node at 8 and 16 mg/kg/day and increased MCH, suggestive of hemolysis), decreased lymphocytes and other WBC at 8 and 16 mg/kg/day; serum chemistry suggestive of decreased synthetic ability in the liver. Most values were within or near the historical control range for the laboratory.

Post-mortem changes included yellow bone discoloration in the 8 and 16 mg/kg/day groups at the end of treatment and persisting in the high dose animals at the end of the recovery period. Decreased testis weights in high dose males correlated with seminiferous

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tubule degeneration in the 8 and 16 mg/kg/day males. Decreased epididymis weights in the 8 and 16 mg/kg/day males correlated with decreased and abnormal sperm in those groups. Decreased thymus weight correlated with decreased lymphoid cellularity in the thymus at 8 and 16 mg/kg/day, as well as in lymph nodes and GALT at all doses.

The no-observed-adverse-effect level (NOAEL) of eravacycline in male rats was considered to be 4 mg/kg/day, which correlated with mean Study Day 91 $AUC_{(0-t)}$ and C_{max} values of 24800 ng•h/mL and 17000 ng/mL, respectively. The NOAEL for female rats was reported to be 16 mg/kg/day (highest dose tested), although that dose was associated with decreased lymphoid cellularity and some minor hematology and clinical chemistry changes. The 16 mg/kg/day dose in females correlated with mean Study Day 91 $AUC_{(0-t)}$ and C_{max} values of 169000 ng•h/mL and 97900 ng/mL, respectively.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (vehicle), 2, 4, 8, or 16 mg/kg/day eravacycline once daily for 13 weeks
Route of administration:	Intravenous injection over 1-2 minutes
Formulation/Vehicle:	0.9% Sodium Chloride Injection, USP, pH adjusted to 6.5 ± 0.2 (b) (4)
Species/Strain:	Crl:CD(SD) rats
Number/Sex/Group:	10 (main study) and 5 (recovery)
Age:	Approximately 62 days (males) and 56 days (females) upon arrival at the test facility
Satellite groups/ unique design:	3/sex for control and 6/sex for treated groups for toxicokinetics
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No test article-related mortality
Clinical Signs	During treatment: Swollen snout, swollen limbs/paws, excess salivation (histaminergic response) in 8 and 16 mg/kg/day males and 16 mg/kg/day females; reddened ears in 16 mg/kg/day males; mild

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	dehydration in 16 mg/kg/day males. No test article-related signs were reported during the recovery period.
Body Weights	Average body weights and body weight gains in 16 mg/kg/day males were significantly lower than controls during the dosing period. During the recovery period, body weights in high dose males remained significantly lower than controls through SD 113, but there was a rebound increase in body weight gain in that group. Female body weight gains during the recovery period were significantly increased relative to control in all treated groups.
Ophthalmoscopy	No test article-related effects were reported.
Hematology	End of treatment (Study Day 92): 2 or 4 mg/kg/day: No treatment-related effects were reported. 8 mg/kg/day: -26.3% lymphocytes (males) 16 mg/kg/day: -16.2% RBC (males), -11% (males) and -5.6% (females) hemoglobin, -10.9% HCT (males), up to +6.3% MCV and MCH (males), -28.9 WBC (males, NSD), -33.1% lymphocytes (males), -59.9% eosinophils (males), -54.7% basophils (males) Mid-recovery (SD 115) 16 mg/kg/day: -10.2 to -10.4% RBC (males), +9.8% MCH (males), +7.2% MCV (males, NSD) End of recovery (SD 142 ± 2) No treatment-related effects were reported, although changes in some parameters appeared to persist but were NSD, and some exhibited a slight rebound. In general, values at all time points were within or near the range of historical controls.
Clinical Chemistry	End of treatment (Study Day 92): 2 or 4 mg/kg/day: No treatment-related effects were reported, however, -25.5% triglyceride (males, NSD), -30-36% triglycerides in females (NSD at 2 mg/kg, statistically significant at 4 mg/kg) 8 mg/kg/day: -29.3% triglyceride (males), -23.0% triglyceride (females, NSD), -7.4% globulin (males) 16 mg/kg/day: -10.5% total protein (males), -16.5% globulin (males), +16.1% phosphorus (males), -10.6% albumin (females), -25% triglyceride (males, NSD) and -34.2% triglyceride (females), and -17.7% (males, NSD) and -23.4% cholesterol (females) Mid-recovery (SD 115) No treatment-related effects were reported, however, NSD decreases in cholesterol (males and females), decreased triglyceride in all treated male groups and 4 and 16 mg/kg females, decreased total protein (-12 to 15%) in all treated male groups and (-8.8 to 11.6%) in 4-16 mg/kg females, decreased globulin (-15.8 to -19.1%) in all treated male groups End of recovery (SD 142 ± 2)

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	No treatment-related effects were reported, however, NSD decreases persisted in cholesterol, triglyceride, and globulin in all treated groups In general, values at all time points were within or near the range of historical controls. Changes may reflect normal variation, or could reflect alteration to the synthetic capability of the liver.
Urinalysis	End of treatment (Study Day 92): • Statistically significant changes in blood in urine at all doses • increased incidence of female rats with RBC in urine sediment at 8 and 16 mg/kg/day • Increased incidence of female rats with casts in urine sediment at 4, 8, and 16 mg/kg/day End of recovery (SD 142 ± 2) • Ketones in urine in males at 2, 8, and 16 mg/kg/day (not dose-dependent, but could be related to changes in body weight at the higher doses) • Increased urine pH in females at 4, 8, and 16 mg/kg/day
Gross Pathology	End of treatment (Study Day 92): Yellow bone discoloration in male and females at 8 and 16 mg/kg/day with dose-related incidence End of recovery (SD 142 ± 2): Yellow bone discoloration persisted in 16 mg/kg/day animals. In all treated groups, the number of females that appeared normal at necropsy was significantly reduced, primarily due to observations of dark red lungs and/or large thymus. The significance of this is unclear.
Organ Weights	End of treatment (Study Day 92): • Decreased epididymis and thymus weights in 8 and 16 mg/kg/day males • Decreased testis and liver weights in 16 mg/kg/day males. • Thyroid weights were increased in high dose males and were "slightly" greater than the upper limit of the historical control range, but may be of more significance since thyroid weights in all groups, including control, were reported to be lower than the average historical control. End of recovery (SD 142 ± 2) No treatment-related effects were reported.
Histopathology **Adequate battery:** Yes for the end of treatment set, but the recovery set was limited to ten "target" tissues and would have missed any delayed effects in a tissue not affected at the end of treatment	End of treatment (Study Day 92): • Seminiferous tubule degeneration in the testes in the 8 and 16 mg/kg/day male dose groups, characterized by decreased release of residual bodies, decreased uptake of residual bodies by Sertoli cells, spermatid retention in the seminiferous tubules, increased spermatid head retention in Sertoli cells, and vacuolation of Sertoli cells. • Epididymides in the 8 and 16 mg/kg/day male dose groups: decreased sperm, cribriform change, abnormally shaped sperm and increased cell debris (secondary to testicular changes). • Increased incidence and/or severity of decreased lymphoid cellularity and/or decreased number and/or size of germinal centers in thymus of males at 8 and 16 mg/kg/day and in lymph

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	nodes and GALT in males and females at all doses. • Increased hemosiderin deposits in the popliteal lymph node in the 8 and 16 mg/kg/day female dose groups and in one 16 mg/kg/male (possible evidence of hemolysis). • Mixed cell inflammation at the intravenous injection site in the ≥ 4 mg/kg/day male dose groups. End of recovery (SD 142 ± 2) Partial or complete recovery of most findings was reported.
[Other evaluations]	

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control.
+: indicates increase in parameters compared to control.
NSD: no statistically significant difference from control.

Toxicokinetics

Toxicokinetic parameters are summarized for eravacycline and its epimer TP-498 in the tables below reproduced from the study report.

Text Table 18
Selected Toxicokinetic Parameters for Eravacycline

Dose Group	Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{(0-t)}$ (ng·hr/mL)	$t_{1/2}$ (hr)
DS 1						
2	2	M	2450	0.100	5810	5.57
		F	1990	0.100	4470	4.98
3	4	M	10400	0.100	16100	5.05
		F	8740	0.100	13300	4.85
4	8	M	26500	0.100	44200	4.96
		F	26600	0.100	36400	4.70
5	16	M	67600	0.100	112000	5.26
		F	72800	0.100	95500	4.64
DS 91						
2	2	M	4560	0.100	8160	6.61
		F	1410	0.500	3900	NC
3	4	M	17000	0.100	24800	7.73
		F	10700	0.100	17700	5.04
4	8	M	44100	0.100	70800	8.17
		F	33600	0.100	50100	5.15
5	16	M	101000	0.100	175000	5.95
		F	97900	0.100	169000	4.75

NC = Not Calculated

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Text Table 19
Selected Toxicokinetic Parameters for TP-498

Dose Group	Eravacycline Dose Level (mg/kg/day)	Sex	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{(0-t)}$ (ng·hr/mL)	$t_{1/2}$ (hr)
DS 1						
2	2	M	403	0.100	673	2.50
		F	310	0.100	371	NC
3	4	M	1590	0.100	2360	2.02
		F	1020	0.100	1890	1.73
4	8	M	3560	0.100	4610	NC
		F	2340	0.100	3760	1.79
5	16	M	9000	0.100	14700	7.10
		F	6830	0.100	12300	4.44
DS 91						
2	2	M	810	0.100	1870	5.71
		F	325	0.500	855	NC
3	4	M	2960	0.100	4620	10.4
		F	1930	0.100	3980	4.82
4	8	M	7110	0.100	11300	NC
		F	5240	0.100	7970	7.12
5	16	M	17200	0.100	27900	8.20
		F	17100	0.100	26000	5.63

NC = Not Calculated

General toxicology; additional studies

1. Study no. (b) (4)-912005: A 3-month GLP-compliant intravenous toxicity and toxicokinetic study of eravacycline (TP-434) administered via vascular access ports with a 6-week recovery period in cynomolgus monkeys

Eravacycline (TP-434) was administered by intravenous infusion (over a 1-2 minute period) for up to 91 consecutive days to groups of 6/sex cynomolgus monkeys at doses of 0 (vehicle), 1, 2, 4, and 8 mg/kg/day. No mortality or clinical signs were reported. Decreased body weight and body weight gains were seen in male monkeys at 4 and 8 mg/kg/day. Decreased albumin and total protein values were reported in the 8 mg/kg/day dose group during the dosing period on Study Days 29/27 (males/females) and 83. These findings were not reported in animals evaluated during the recovery period. Gross pathology findings included test article-related yellow discoloration of the bone at all doses at the end of treatment necropsy on Study Day 91. That finding persisted at the end of recovery necropsy on Study Day 133 in the 4 and 8 mg/kg/day animals. Microscopic evidence of minimal to moderate lymphoid depletion in the spleen and lymph nodes (mandibular and mesenteric) was noted in the 8 mg/kg/day group males and females at the end of treatment, but was not reported at the recovery necropsy. Impairment of immune function was evident as test article-related decreased anti-KLH IgG antibody levels in the T-cell dependent antibody response (TDAR) assay in the 8 mg/kg/day group on multiple days during the dosing period, consistent with the lymphoid depletion seen

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on histopathological examination. Exposure to eravacycline, (b) (4) a metabolite (TP-6208) was evaluated.

Based on these observations, the NOAEL would be (b) (4) mg/kg/day, based on decreased body weight at 4 mg/kg/day and bone discoloration. However the body weight finding was reversible, and it is unclear whether or not there would be adverse effects relative to the observed bone discoloration based on this study. Therefore, this study may still support a clinical dose equivalent to 4 mg/kg/day (LOAEL)in the cynomolgus monkey (HED = 1.33 mg/kg/day for 3 months). The report states that this dose corresponded to mean plasma eravacycline $AUC_{0\text{-}24hr}$ values of 44,800 and 50,600 ng•hr/mL and mean C_0 values of 56,900 and 46,900 ng/mL on study day 90 in male and female cynomolgus monkeys, respectively. $AUC_{0\text{-}24hr}$ values on study day 90 for the (b) (4) ng•hr/mL in males and females, respectively. $AUC_{0\text{-}24hr}$ values on study day 90 for the metabolite (TP-6208) at this dose were 701 and 568 ng•hr/mL in males and females, respectively.

2. Study no. EQC00010: TP-434: A 14-day intravenous toxicity study in Sprague-Dawley rats with a 3-week recovery period

Doses of 4, 20, and 40 mg/kg/day of the free base, TP-434 were administered IV. Three high dose animals were euthanized in the second week due to treatment-related effects. Clinical signs included skin erythema (consistent with histaminergic response) and stereotypic behavior (circling and chasing the tail, considered to be related to irritation at the dose site) at all doses; swelling, lacrimation, ataxia, salivation, and nasal and/or tail discharge at the mid- and high doses, and loss of body temperature, labored breathing, vocalization, facial edema, and hunched posture at the high dose. Decreased body weights were seen at 20 and 40 mg/kg/day, and food consumption was decreased at the high dose. Dose-dependent decreases in red blood cell parameters were seen at the mid- and high doses, and correlated with hypoplasia of erythroid elements in the bone marrow. Mean lymphocyte count was decreased at the high dose, correlating with marked lymphoid depletion in the thymus and reduction of thymus weight. Decreases in total protein, albumin, A:G ratio, cholesterol, and triglycerides at the mid- and/or high doses, may have been indicative of decreased synthetic capability of the liver. Liver weights were decreased at all doses, with statistical significance only at the mid- and high doses. Microscopic findings included cytoplasmic vacuolation of hepatocytes at the high dose. Total bilirubin was increased in high dose animals on Day 15, possibly due to erythrocyte loss. At termination on Day 15, spleen weights were increased at the high dose with microscopic findings of hemosiderin pigment and macrophage hyperplasia. Dose-related decreases in prostate and seminal vesicle weights were seen at all doses, but were statistically significant only at the high dose. Microscopic findings included atrophy and decreased secretions. Testis and epididymis weights were reported to be decreased at Day 15, but microscopic correlates were not reported. Dose-related decreases in thymus weights were seen at the mid- and high doses, but only statistically significant in the latter. This correlated with the histological finding of marked lymphoid depletion. Lesions at the administration site were more severe in high

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dose animals than in controls and consisted of fibrosis, chronic-active inflammation, and vasculopathy. Increased mean fibrinogen was seen at all doses and was considered to be reflective of the inflammatory changes at the administration site. On Day 36, most of the Day 15 findings were fully or partially recovered. However, new findings of degeneration in the testis and oligospermia in the epididymis at the mid- and high doses appear to indicate a delayed adverse effect on the male reproductive tract. (N.B. Only tissues from control and high dose animals underwent histological examination on Day 15. On Day 36, the only tissues examined from low and mid-dose animals were testis and epididymis.) Spleen weight increases at the high dose and liver weight decreases at all doses persisted, but without microscopic correlates.

The lowest dose, 4 mg/kg/day for 2 weeks (HED = 0.7 mg/kg/day; $AUC_{0\text{-}inf}$ = 9100-16,000 ng*hr/mL) could be considered a LOAEL, with findings limited to histaminergic signs, inflammatory changes at the administration site, and decreased prostate, seminal vesicle, and liver weights (not statistically significant).

3. Study no. EQC00008: TP-434: A 14-day toxicity study in beagle dogs with a 21-day recovery

Three beagle dogs per sex were administered 2, 12, or 20 mg/kg/day IV of TP-434 free base. Doses of ≥ 12 mg/kg/day were not tolerated; they were associated with moribundity, acute skin reactions that were probably histamine-mediated, and severe gastrointestinal toxicity (including intestinal hemorrhage), dehydration, body weight loss, and decreased food consumption. All mid-dose animals and one high dose animal were terminated early, and the high dose treatment was terminated on Day 7. Bone marrow (red and white cell elements) and lymphoid organ atrophy, with related decreases in circulating cell populations, were seen. Only leukocyte counts were partially recovered in high dose animals. Total protein, albumin, and globulin were decreased, consistent with inhibition of protein synthesis by the test article or to decreased hepatic synthetic capability. Spleen and thymus weights were decreased, and only partially reversible at the high dose. Additional microscopic changes included bone discoloration, hepatocyte vacuolation, lymph node hemorrhage, cardiac hemorrhage and necrosis, and cytoplasmic vacuolation and/or degeneration of the seminiferous tubules in the testes. Second degree AV block was seen at the high dose. At the administration site, subcutaneous hemorrhage and chronic active inflammation were found, indicative of irritation due to the test article. The lowest dose, 2 mg/kg/day (HED = 1 mg/kg/day, $AUC_{(0\text{-}tlast)}$ = 3500-7300 ng·hr/mL) may be considered to be the LOAEL. Findings at that dose were limited to reversible hematology and splenic weight changes consistent with findings at higher doses.

4. Study no. (b) (4)-912002: A 14-Day Intravenous Toxicity and Toxicokinetic Study of Eravacycline (TP-434) Administered as a Bolus Intravenous Injection with a 21-Day Recovery Period in Cynomolgus Monkeys

Reference ID: 4312284

Eravacycline was administered by intravenous (bolus) injection to cynomolgus monkeys for 14 consecutive days at doses of 2, 4, and 18 mg/kg/day. At 18 mg/kg/day, animals lost weight and showed clinical signs as a result of the eravacycline-related effects on the gastrointestinal tract (e.g. diarrhea, emesis, inappetance). Sporadic gastrointestinal signs were also noted in the lower dose groups. Local effects at the injection site, consisting of swelling, redness, and impaired use of hind limbs were noted in high dose animals.

Test article-related hematology findings on Day 12 included decreased red blood cell parameters (red blood cell count, hemoglobin, and hematocrit), platelet and/or reticulocyte counts and increased clotting times (APTT) in high dose animals. Test article-related clinical chemistry findings included decreased albumin, total protein, A/G ratio, calcium (consistent with known effects of tetracyclines), and cholesterol, as well as increased BUN, and increased total, direct, and indirect bilirubin in high dose animals. Decreased urine pH in was reported for high dose animals on Day 12. These changes appeared to be reversible in recovery animals. Gross pathological findings at the end of treatment were seen in high dose animals and included small spleen, small thymus, and dark red area in the stomach. These correlated with lower organ weights, lymphoid depletion, and mucosal erosion in the stomach. Additional histopathological findings in high dose animals included generalized lymphoid depletion in the lymph nodes and Peyer's patches, bone marrow depletion (correlating with hematology findings). With the exception of findings in the thymus, these findings were reversible. Mucosal atrophy was noted in the gastrointestinal tract in mid- and high dose animals. Test article-related acute inflammation in the kidneys, duodenum, and cecum in mid- and high dose animals, and erosion, ulceration, and/or fungal hyphae in the tongue (the latter was considered secondary to alterations in the normal bacterial flora) in the females at all doses. Further erosion of additional mucosal surfaces, including the esophagus, stomach (correlating with dark areas seen grossly), rectum, and vagina was reported in the 18 mg/kg/day group females. These findings were reversible.

Minimal to moderate inflammatory and degenerative changes to muscle at the injection sites were seen in mid- and high dose animals (corresponding to test article concentrations of 0.8 and 3.6 mg/mL, respectively), correlating with clinical observations, and associated in some instances with impaired use of the hind limb(s). These findings appeared to be reversible at the mid-dose, but persisted somewhat in high dose females.

The Sponsor considered the no-observed-adverse-effect level (NOAEL) to be 4 mg/kg/day. However, based on findings at the mid-dose that appeared to be on a continuum with effects at the high dose, including mucosal atrophy, inflammatory changes, erosion of the mucosal surface of the tongue with the presence of an opportunistic yeast infection, and local injection site microscopic observations, although reversible at that dose, that dose might be considered a LOAEL.

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Toxicokinetic monitoring was performed on Study Days 0 and 13 to evaluate parameters following single and repeat daily intravenous dosing. The mean steady state C_{max} values (males and females combined) for the three analytes evaluated in this study (eravacycline, TP-498, TP-6208) following administration of eravacycline at 4 mg/kg/day for 14 days in cynomolgus monkeys were 30.7, 0.614, and 0.0452 µg/mL, respectively. $AUC_{0\text{-}24\ h}$ values at that dose and time were 47.4, 2.13, and 0.680 µg*hr/mL for eravacycline, TP-498, and TP-6208, respectively.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: TP-434: Bacterial mutation test (Study no. 962272)

Key Study Findings:

- Only low concentrations could be tested due to toxicity to the tester bacterial strains
- Negative for mutagenicity at lowest concentrations

GLP compliance: Yes

Test system: *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and *E.coli* strain WP2 *uvr*A; main test up to 5.0 µg/plate, confirmatory test up to 2.56 µg/plate; +/-S9

Study is valid: The conduct of the study was valid, but antibacterial activity against the test system make it uninformative.

In Vitro Assays in Mammalian Cells

Study title/ number: TP-434: Mammalian cell mutation test (Study no. 962602)

Key Study Findings:

- TP-434 was negative for genetic toxicity in the mouse lymphoma assay.

GLP compliance: Yes

Test system: Mouse lymphoma L5178Y $TK^{+/-}$ cells; +/-S9. For the 3 hour incubation without metabolic activation, final concentrations were 28.1-450 µg/mL. For the 3 hour incubation with metabolic activation, final concentrations were 5.50-75.0 µg/mL. For the 24 hour incubation without metabolic activation, final concentrations were 0.686-9.50 µg/mL.

Study is valid: Yes

Study title/ number: TP-434: Chromosome aberration test (Study no. 962273)

Key Study Findings:

- TP-434 was negative for induction of chromosome damage in the chromosome aberration assay.

GLP compliance: Yes

Test system: Human peripheral blood lymphocytes (HPBL); up to 640 ug/mL; +/-S9

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: TP-434: Rat micronucleus test (Study no. 962274)

Key Study Findings:

- TP-434 was negative for genetic toxicity in the rat bone marrow micronucleus test.

GLP compliance: Yes

Reference ID: 4312284

Test system: Sprague-Dawley rats, bone marrow immature erythrocytes examined for presence of micronuclei; single IV doses of vehicle (0.9% sodium chloride for injection, USP), 15, 30, or 60 mg/kg TP-434
Study is valid: Yes

Other Genetic Toxicity Studies

Bacterial mutation tests were performed for TP-034 and TP-630. Both studies were negative for mutagenicity, however, TP-034 was toxic to the bacteria test strains, so only low doses could be evaluated.

5.5.3 Carcinogenicity

Not applicable

5.5.4 Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

The following studies have been reviewed under IND 104839.

Study no. 20013503: A GLP-compliant intravenous (bolus) fertility and general reproduction toxicity study of eravacycline (TP-434) in male rats

Twenty-five male rats per dose group were administered 0, 1, 4, 12, or 16 mg/kg/day eravacycline intravenously once daily for 70 days prior to cohabitation with untreated female rats, during up to 12 days cohabitation, and through Study Day 101/102. Ten males per dose group were euthanized and evaluated on Study Day 102/103; remaining males in the 0, 12, and 16 mg/kg/day groups underwent two recovery periods, each followed by a 4 day cohabitation period.

The 12 and 16 mg/kg/day dosages were associated with mortality, clinical signs (including swollen snout, excessive salivation, chromorhinorrhea, chromodacryorrhea, and urine-stained abdominal fur at 12 and 16 mg/kg/day, as well as transient signs during the first 4 days of dose administration of swollen limbs and/or paws, decreased motor activity, red ears, ptosis, swollen ears, and tachypnea in the 16 mg/kg/day male rats), reduced body weights and body weight gains and initial reductions in food consumption. The no-observable-adverse-effect level (NOAEL) for general toxicity in male rats was 4 mg/kg/day eravacycline

Fertility and mating parameters in the control, 1, and 4 mg/kg/day eravacycline groups were comparable. Although all male rats in the 12 and 16 mg/kg/day dose groups mated with the cohort females during all three cohabitation periods, 1 of 24 and 0 of 24 female rats were pregnant in these two respective groups in the first cohabitation period (at end of treatment period), and 3 of 13 and 0 of 12 female rats were pregnant in these two respective groups after the second cohabitation period (after 5 weeks of recovery). Epididymal weights and sperm motility and count were reduced at 12 and 16 mg/kg/day and histopathologic changes occurred in the testes and epididymides of male rats in these dose groups at the end of the dose period (Study Day 102/103), including impaired spermiation in the testis and sperm maturation in the

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epididymis, resulting in sperm with abnormal morphology and poor motility. After approximately 10 weeks (70 days) of recovery (start of the third cohabitation period), male rats in the 12 and 16 mg/kg/day dose group demonstrated improved fertility. Pregnancy occurred in 15 of 15 (100%), 12 of 13 (92.3%) and 11 of 12 (91.7%) mated female rats in the 0, 12 and 16 mg/kg/day dose groups, respectively. At termination on Study Day 192/193, male reproductive organ weights and sperm parameters in the 12 and 16 mg/kg/day dose groups were comparable to control group values. Reversal of eravacycline-related histopathological lesions in the testis occurred in all males in the 12 mg/kg/day group, and in 83.3% of the 16 mg/kg/day male rats by 90 days after the end of dosing, but persisted in two high dose males. The reproductive NOAEL in male rats was also 4 mg/kg/day eravacycline.

Study no. 20039198: A GLP-compliant intravenous (bolus) fertility and general reproduction toxicity study of eravacycline (TP-434) in female rats

Female Crl:CD(SD) rats were administered eravacycline (TP-434) intravenously at doses of 0 (saline), 4, 8, or 20 mg/kg/day via the lateral tail vein once daily beginning 15 days before cohabitation, during the cohabitation period (up to 14 days) and continuing through Gestation Day (GD) 7. Rats were euthanized on GD 13 and evaluated.

Clinical signs were mostly considered to be related to a histaminergic response. Swollen snout, limbs and/or paws and decreased motor activity were reported in the 20 mg/kg/day dose group during the pre-cohabitation period and the gestation dosing periods. Additionally, excess salivation was noted in the 20 mg/kg/day group on isolated days during gestation. Chromorhinorrhea was noted in rats in the 8 and 20 mg/kg/day groups primarily on the first day of dosing, as well as in two 4 mg/kg/day animals on Study Day 1; these were considered to be “histamine-like symptoms.”

There were no test article-related deaths. All rats appeared normal at necropsy. Body weight gains were significantly reduced in all three treatment groups for the first week of study (SD 1 to 8) and continued to be reduced (42% below control) in the 20 mg/kg/day group for the second week of study (SD 8 to 15), resulting in significantly lower body weight gain for the entire pre-cohabitation period (SD 1 to 15) in that group. Body weight gain for the gestation dosing period (DG 0 to 8) was statistically significantly reduced (17% below control) in the 20 mg/kg/day dose group. Food consumption was statistically significantly decreased in all three treatment groups during the first week of the study, correlating with the decreases in body weight gains over that interval.

The number of estrous stages per 14 days was comparable among the four dose groups before the start of test article administration and during the pre-cohabitation period. No effect of treatment on mating and fertility parameters, on Caesarean-sectioning findings, or on litter parameters were reported.

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The Sponsor considered the maternal NOAEL for eravacycline to be 8 mg/kg/day, although there was some evidence of histaminergic reaction. The 20 mg/kg/day dose was associated with reduced body weight gain during the first two weeks of dosing and during the gestation dosing period (GD 0 to 8). There were no reported adverse effects on mating or fertility of the female rats and no adverse findings were reported for Caesarean-sectioning and litter parameters evaluated at GD 13. The NOAEL for female fertility and early embryonic development was considered to be 20 mg/kg/day eravacycline.

Embryo-Fetal Development
The following studies have been reviewed under IND 104839.

Study no. 20013499: A dosage range-finding embryo-fetal development study of TP-434 by intravenous injection in rats

Female rats were administered eravacycline at doses of 0 (vehicle, 0.9% sodium chloride for injection, USP, pH adjusted to 6.5), 1, 10, 20 or 40 mg/kg/day once daily via intravenous injection (1 to 2 minute infusion) on Days 7 through 17 of presumed gestation. Female rats assigned to the main study were euthanized on Day 21 of presumed gestation, and necropsy and Caesarean section were performed. Rats assigned to the toxicokinetic phase of the study were euthanized after blood collection on Day 18 of presumed gestation.

Two deaths in the 40 mg/kg/day group (rats 7039 and 7067) were considered to be test article-related. One main study animal was found dead on Gestation Day (GD) 17 and one toxicokinetics animal was euthanized on GD 17 due to adverse clinical observations.

Clinical signs consistent with a histaminergic response (red/purple paws and/or ears, swollen snout or paws, ptosis, changes in respiration, e.g. dyspnea or bradypnea) occurred in the 10, 20 and 40 mg/kg/day dose groups. Other findings at those doses included decreased motor activity, while at 20 and 40 mg/kg/day, ataxia, low carriage, red/brown perivaginal substance, urine-stained abdominal fur, piloerection, and chromorhinorrhea were reported. In the 40 mg/kg/day dose group, increased numbers of rats had excess salivation, hunched posture, and chromodacryorrhea. Orange or red urine, prostrate position and tip toe walking each occurred in two rats at 40 mg/kg/day, and individual rats at that dose were observed with tachypnea, vocalization to touch, excessive grooming, swollen ears, mild dehydration, red perioral substance and hyperpnea. With the exception of red/brown perivaginal substance, these findings were limited to the dosing period.

Body weight gain for GD 7 through 18 was reduced in a dose-dependent manner in the 10, 20 and 40 mg/kg/day dose groups (85%, 47%, and 4% of concurrent control, respectively). Mean body weight loss was reported in the 40 mg/kg/day dose group over GD 7 to 10, 12 to 15 and 15 to 18. In the post-dosing period, mean bodyweight gain continued to be reduced at 20 and 40 mg/kg/day. Food consumption was decreased in a dose –related manner by 26-14% of

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control at 20 and 40 mg/kg/day continued to be reduced in those groups during the post-dose period.

There were no necropsy findings at any dose level.

Pregnancy occurred in 8 (100%), 7 (87.5%), 6 (75.0%), 8 (100%) and 7 (87.5%) rats in the control, 1, 10, 20, and 40 mg/kg/day groups, respectively. All pregnant dams in the 40 mg/kg/day dose group had litters consisting entirely of early resorptions (100% post-implantation loss). Post-implantation loss also was increased in the 20 mg/kg/day group; two of eight (25%) litters in this group were completely resorbed.

Mean fetal body weights (male, female and combined) were decreased in the 20 mg/kg/day (48% to 50% below control) and 10 mg/kg/day (16% to 17% below control) dose groups. No test article-related gross external fetal alterations were reported. Visceral and skeletal evaluations were not performed.

Based on the results of this study, doses of 0 (Control), 1, 3 and 10 mg/kg/day of eravacycline were recommended for the definitive rat embryo-fetal developmental toxicology study.

Study no. 20013500: A GLP embryo-fetal developmental toxicity study in rats with eravacycline (TP-434) co-administered with a metabolite (TP-6208) by intravenous injection

Female Crl:CD(SD) rats were administered intravenous doses of 0, 3, 5, or 10 mg/kg/day eravacycline (TP-434) with 3.5 mg/kg/day of the test article metabolite TP-6208 once daily on Days 7 through 17 of presumed gestation. Additional groups were administered vehicle control or 5 mg/kg/day eravacycline without TP-6209. Female rats assigned to main study groups were euthanized on Gestation Day (GD) 21. Female rats assigned to the toxicokinetics groups were euthanized after blood collection on GD 18.

There were no test article-related deaths reported. Test article-related clinical observations in the two higher combination groups (3.5/5 and/or 3.5/10 mg/kg/day TP-6208/eravacycline) included swollen snout, swollen limbs and/or paws, and chromorhinorrhea. These may have been indicative of a histaminergic reaction.

Body weight gains were significantly reduced in the 3.5/5 and 3.5/10 mg/kg/day TP-6208/eravacycline groups during the dosing period by as much as 51% relative to control, but appeared to improve later in the dosing period. Body weight gains were significantly reduced in the 3.5/10 mg/kg/day TP-6208/eravacycline dose group for the entire gestation period after the initiation of dosing (GD 7 to 21). Nevertheless, average body weights were comparable among the five dose groups throughout the study. Absolute and relative food consumption values were reduced in all treated groups early in the treatment period, but were comparable among the groups after GD 10.

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No test article-related necropsy observations were reported.

Fetal body weights were significantly reduced (89% of the control group value) in the 3.5/10 mg/kg/day TP-6208/eravacycline group and were below the historical control range for the laboratory. No other Caesarean-sectioning or litter parameters were reported.

Delays in skeletal ossification were reported at 3.5/10 mg/kg/day TP-6208/eravacycline, and were associated with reduced fetal body weights in this group. The average number of ossified caudal vertebrae, forelimb phalanges, metatarsals and hind limb phalanges were significantly reduced in the 3.5/10 mg/kg/day dose group, and values were below the historical control ranges for the testing laboratory. No test article-related gross external or soft tissue fetal alterations were reported.

In conclusion, the reported maternal and developmental NOAEL in this study was 5 mg/kg/day eravacycline, either in the presence or absence of 3.5 mg/kg/day TP-6208 ($AUC_{(0\text{-}24h)}$ = 21.5-27.4 µg*hr/mL for eravacycline, and 10.7-14.7 µg*hr/mL for TP-6208). The report attributed reduced fetal body weights and delayed ossification to maternal body weight effects. However, there was no body weight loss in dams at the higher dose that would constitute maternal toxicity, and it seems more likely that the decreased maternal body weight gain may have reflected the lower fetal body weights. Known effects of tetracycline class antibiotics on calcium may have contributed to reduced ossification.

Study no. 20013501: A dose range-finding embryo-fetal development study of TP-434 by intravenous injection in rabbits

Timed-mated female rabbits were administered doses of 0 (vehicle, 0.9% sodium chloride, USP, for injection), 1, 3, 6, or 12, mg/kg/day eravacycline once daily by intravenous injection (1 to 2 minute infusion) on Days 7 through 19 of presumed gestation. Rabbits assigned to the main study were euthanized on Day 29 of presumed gestation, and rabbits assigned to the toxicokinetic phase of the study were euthanized after blood collection on Day 20 of presumed gestation.

One rabbit in the 12 mg/kg/day main study dose group (3323) was euthanized due to adverse signs on GD 16 and one rabbit in the 12 mg/kg/day dose group assigned to toxicokinetic sample collection (3338) aborted and was euthanized on GD 19. Both were considered to be test article-related.

Clinical observations that were considered to be related to reduced body weight gain or loss occurred at increased incidence at doses of 3, 6 and 12 mg/kg/day (scant, soft or liquid or no feces; ungroomed coat; thin body condition) and clinical observations related to litter resorption (red substance in the cage pan or peri-vaginally) were observed at increased

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incidence in does at 12 mg/kg/day. Purple discoloration at the injection site occurred in 1 and 2 does in the 6 and 12 mg/kg/day dose groups, respectively. Decreased motor activity, pale ears and cold to touch occurred only in the main study doe that was euthanized in the 12 mg/kg/day dose group.

Rabbits in the 6 and 12 mg/kg/day dose groups lost weight in a dose-dependent manner over GD 7 through 20. Over the same interval, body weight gain was reduced (73% below control) in the 3 mg/kg/day dose group. Absolute and relative food consumption values were reduced in a dose-dependent manner over GD 7 through 20 in all test article-treated groups relative to control. Food consumption did not fully recover during GD 20 to 24.

There were no test article-related necropsy observations. All litters in the 12 mg/kg/day dose group consisted of only early resorptions. Average female fetal body weights were reduced (16% below control) in the 6 mg/kg/day dose group. All fetuses appeared normal at gross external examination. No visceral or skeletal examination was performed.

Doses of 0 (Control), 1, 2 and 4 mg/kg/day of eravacycline were recommended for the definitive GLP-compliant developmental toxicity study in rabbits.

Study no. 20013502: An embryo-fetal development study of eravacycline (TP-434) by intravenous injection in rabbits

Female Hra:(NZW)SPF timed-mated rabbits were administered the IV doses of 0 (vehicle,), 1, 2, or 4 mg/kg/day eravacycline) once daily on Days 7 through 19 of presumed gestation (GD 7-19). All surviving rabbits were euthanized on GD 29, and a Caesarean section was performed.

One high dose female rabbit aborted on GD 26 and was euthanized. The report attributed this abortion to test article-related reductions in food consumption and body weight loss. All other does survived to scheduled euthanasia.

Clinical observations in the 4 mg/kg/day dose group (ungroomed coat, changes in fecal output, and thin body condition) were attributed to test article-related changes in body weight. Body weight gain was significantly reduced (79% below control) in the 4 mg/kg/day dose group for the entire dosing period (GD 7 to 20) and statistically significant body weight loss occurred in this group on GD 16 to 20. These changes corresponded to significant reductions in absolute and relative food consumption in the 4 mg/kg/day dose group for the entire dosing period. Absolute and relative food consumption values continued to be reduced or significantly reduced in the 4 mg/kg/day dose group on GD 20 to 24 but were comparable to controls on GD 24 to 29.

At necropsy, one doe in the 4 mg/kg/day dose group had a pale heart and liver. Findings on Caesarean section included significantly increased average number of late resorptions in the 4

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mg/kg/day dose group, which contribute to increases in the percent post-implantation loss, the percentage of does with any resorptions, and the percent dead or resorbed conceptuses per litter. There was one dead fetus in a 4 mg/kg/day litter. Average fetal body weights were reduced by 6-8% below control in the 4 mg/kg/day dose group, and the reduction was statistically significant for female fetuses relative to controls and outside of the historical control range for the laboratory.

External and visceral examinations revealed no findings that were considered to be treatment-related. On skeletal examination, the average number of ossified forepaw phalanges was significantly reduced in the 4 mg/kg/day dose group. The average numbers of ossified metacarpals, tarsals and hind paw phalanges were reduced below the historical control ranges in the same group. The report attributed this finding to reductions in fetal body weight observed in this dose group, but the tendency for tetracyclines to bind calcium may have contributed.

The maternal and the developmental no-observable-effect level (NOAEL) for eravacycline in this study was considered to be 2 mg/kg/day. (HED = 0.67 mg/kg/day). Toxicokinetic data for pregnant rabbits at this dose were not generated in the dose range-finding study.

Prenatal and Postnatal Development

The following study was reviewed under IND 104839.

Study no. 20047549: A GLP-Compliant Developmental and Perinatal/Postnatal Reproduction Study of Eravacycline (TP-434) by Intravenous Injection in Rats, Including a Postnatal Behavioral/Functional Evaluation

Mated F0 generation female Crl:CD(SD) Sprague Dawley rats were administered the test article, eravacycline, at intravenous doses of 0, 3, 5, or 10 mg/kg/day once daily via the lateral tail vein on Gestation Day (GD) 7 through Lactation Day (LD) 20. End points evaluated for the F0 generation dams in this study included: clinical signs, body weights, body weight changes, food consumption, maternal behavior observations, natural delivery and litter observations, ovarian and uterine examinations, gross necropsy findings, and concentrations of eravacycline, TP-498, and TP-6208 in milk.

There were no deaths in the F0 generation female rats that were considered to be eravacycline-related. The finding of swollen snout was significantly increased in the 10 mg/kg/day dose group during the gestation period. The report states that this finding was "related to the pharmacologic action of eravacycline and not considered to be toxicologically important," but was probably indicative of a histaminergic reaction to the test article.

In the 10 mg/kg/day F0 generation dose group, body weight gain for the gestation dosing period (GD 7 to 20) was significantly reduced (18% below control) and average body weights on

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GD 20 were up to 6% lower than controls in treated groups. While there seemed to be an effect at the high dose, it did not meet the criterion of 10% body weight loss to support this dose as maternally toxic. There did not appear to be an effect of treatment on body weight during lactation, or on food consumption during gestation or lactation in F0 animals.

All natural delivery and litter observations in the F0 generation rats were reported to be comparable between control and treated groups. No test article-related gross necropsy or uterine observations in the F0 generation dams were reported. Concentrations of eravacycline, TP-498 and TP-6208 in the milk from F0 generation rats on LD 15 increased in a generally dose proportional manner from 3 to 10 mg/kg/day. Concentrations of eravacycline were approximately 14- to 19-fold greater than that observed for TP-498. Concentrations of TP-6208 were very low in comparison to eravacycline.

Pre-weaning assessment of F1 pups revealed no test article-related clinical observations and decreased pup body weight on Post-natal Day (PND) 1 only. A trend toward increased stillborn or found dead pups was seen in treated groups, but the report indicates that most were found to appear normal at necropsy. Surviving pups euthanized and necropsied on PND 21 were also reported to appear normal at necropsy.

Post-weaning assessment of randomly selected (25/sex/dose group, 1/sex/litter if possible) F1 pups included viability, clinical signs, body weights, body weight changes, food consumption during the post-weaning, pre-cohabitation and gestation periods, sexual maturation, behavioral testing (passive avoidance and water maze testing), mating and fertility parameters (reproductive capacity after PND 90), gross necropsy findings, testicular and epididymal organ weights (male rats), ovarian and uterine examinations (female rats), and Caesarean-sectioning and litter parameters.

There were no eravacycline-related deaths in the F1 generation male and female rats. No remarkable findings were reported for most of the observations listed, although absolute testis and epididymis weights in high dose male pups were decreased relative to control. No external findings of the F2 generation fetuses were considered to be treatment-related.

The report concluded that the maternal (F0 generation) toxicological no-observable-adverse effect level (NOAEL) for eravacycline was 5 mg/kg/day. The 10 mg/kg/day dose was associated with reduced body weights and body weight gain during the gestation dosing interval, but was not of sufficient magnitude to constitute maternal toxicity. This dose also was associated with an increased incidence of swollen snouts, which the report stated was “a non-adverse clinical observation secondary to the pharmacology of eravacycline,” but was more likely a histaminergic reaction. If the latter was not adverse, as the report indicates, then the high dose, 10 mg/kg/day, is a more reasonable estimate of the maternal (F0 generation) NOAEL.

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The report also concludes that the NOAEL for reproduction in the F0 generation dams, and for viability, growth, and reproduction in the F1 generation rats was 10 mg/kg/day (highest dose level tested).

5.5.5 Other Toxicology Studies

Local tolerance was evaluated in two studies in the rabbit. In **Study no. 20007331**, concentrations up to 5 mg/mL were administered by IV infusion over 30 minutes for three days. The highest concentration (5 mg/mL) resulted in gross and microscopic inflammatory changes that were greater in incidence and severity than in animals administered vehicle control. In **Study no 20009082**, eravacycline was administered by IV infusion, BID, over 60 and 30 minutes, at least 2 hours apart. Concentrations tested were 5, 10, and 20 mg/mL. The study was intended to include three full days of dosing, but the study was terminated after two days due to mortality. Microscopically, an increase in the incidence and severity of vascular/perivascular inflammation was present at ≥ 5 mg/mL that was similar in all eravacycline-treated groups; the report concluded that there were no differences in inflammatory changes that were related to the concentration or rate of infusion of TP-434. However, the early termination of this study and the use of alternating infusion sites may have attenuated effects somewhat. In contrast, in general toxicology studies in which test article was directly injected without a catheter or vascular access port, irritation/inflammation appeared to be dose-dependent.

Findings related to immunotoxicity included lymphoid depletion or atrophy in lymphoid organs, as well as decreased white blood cell parameters correlating with apparent bone marrow suppression. Additionally, in the 13-week toxicology study in cynomolgus monkeys, a T-cell dependent antibody response assay was performed to assess immune function. A statistically significant decrease in IgG antibody directed against the test antigen, KLH, was observed in the high dose group, 8 mg/kg/day. This effect was not recorded at the next lowest dose, 4 mg/kg/day (AUC_{0-24} = 44.8 and 50.6 µg*hr/mL in males and females, respectively, on Day 90).

Two in vitro studies were conducted to evaluate potential for phototoxicity. In the first, the phototoxic potential of eravacycline was measured by the relative reduction in viability of BALB/c 3T3 mouse fibroblasts exposed to the test article and ultraviolet A light (+UVA) compared with the viability of fibroblasts exposed to the test article only (-UVA) using the neutral red assay (**Report 2504/0007**). The results of this test predicted no phototoxic potential for eravacycline, but no certificate of analysis was available for the test material, so the study was repeated. In the second, GLP-compliant study, the phototoxic potential of eravacycline again was measured by the relative reduction in viability of BALB/c 3T3 mouse fibroblasts exposed to eravacycline and ultraviolet radiation (+UVR; UVA and ultraviolet B light (UVB)) compared with the viability of fibroblasts exposed to eravacycline in the absence of ultraviolet radiation (-UVA) (**Report 20080946**). This study did demonstrate potential for phototoxicity of eravacycline.

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A GLP-compliant in vivo study was performed to determine the potential phototoxic effects of eravacycline on the eyes and skin of Long-Evans pigmented rats (**Report 20082951**). Female Long-Evans rats (5/control group and 7/treated group) were administered slow bolus IV injections over 1 to 2 minutes of 0, 10, 20, and 40 mg/kg/day eravacycline daily for 3 days, followed immediately by exposure to ultraviolet B, ultraviolet A, and visible light from a xenon lamp. Sham and positive controls were included. No cutaneous responses or eravacycline-related ocular findings were reported that were considered to be indicative of phototoxicity. The report concluded that eravacycline was not phototoxic.

The three major human metabolites of eravacycline identified by the Applicant were TP-498 (b) (4) TP-6208, and TP-034 (b) (4) These were qualified through their presence in the eravacycline batches used for toxicology studies, by their co-administration in toxicology studies and/or in separate evaluations.

The Applicant's summary indicates that clinical exposure to TP-498 following administration of 1 mg/kg BID results in a mean AUC_{0-24h} of approximately 1.70 µg*hr/mL. Mean AUC_{0-24h} values at the NOAEL or LOAEL doses in the 13-week rat study (4.62 and 26.0 µg*hr/mL in males and females, respectively, 14-day (2.19 and 2.06 µg*hr/mL in males and females, respectively) and 13-week (3.38 and 3.86 µg*hr/mL in males and females, respectively) monkey studies, rat (4.00 µg*hr/mL) and rabbit (3.26 µg*hr/mL) embryo-fetal toxicology studies were greater than that value.

Exposure to TP-6208 in clinical patients following administration of 1 mg/kg eravacycline BID resulted in a mean AUC_{0-24h} of approximately 4.06 µg*hr/mL. The rat apparently does not produce sufficient levels of TP-6208 to qualify that metabolite in toxicology studies; in the 13-week rat study, plasma concentrations were below the limit of quantitation. In the cynomolgus monkey, TP-6208 exposures in the 2 and 13-week studies were below the clinical exposure at the NOAEL/LOAEL dose, but the Applicant indicates that exposure at the maximum tolerated dose, 18 mg/kg/day, in the 2-week study (AUC_{0-24h} = 12.9 and 13.6 µg*hr/mL in males and females, respectively) was approximately three times the clinical exposure. Computational assessment for genetic toxicity and a rat micronucleus assay of IV-administered TP-6208 were negative for genetic toxicity (**Report 2012-1660** and **Report 8310326**, respectively). In embryo-fetal development (EFD) studies, neither the rat nor the rabbit produce sufficient levels of TP-6208 to qualify it in the eravacycline studies. Instead, TP-6208 was administered in addition to eravacycline in the definitive rat EFD study. At the NOAEL, 5 mg/kg/day eravacycline co-administered with 3.5 mg/kg/day TP-6208, the AUC_{0-24h} on GD 17 for TP-6208 was 14.7 µg*hr/mL.

(b) (4) In two clinical drug interaction studies, after a single 1 mg/kg dose of eravacycline, administered as a 60-minute infusion, mean AUC_{0-24h} values were 0.659 and 0.734 µg*hr/mL. In a 14-day toxicology study of that metabolite in rats (**Report 20080455**), the

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NOAEL was the highest dose tested, 1.25 mg/kg/day IV. The mean $AUC_{0\text{-}24h}$ values at that dose were 6.04 and 6.22 µg*hr/mL in males and females, respectively. In genetic toxicity testing, TP-034 was toxic to bacteria used in the reverse mutation assay, was negative in the mouse lymphoma assay for mutation in mammalian cells (**Report 83092580**), and was negative in the rat bone marrow micronucleus assay (**Report 8320847**). In an EFD study in rats (**Report 20073144**), the NOAEL dose was again the highest dose tested, 1.25 mg/kg/day IV (mean maternal $AUC_{0\text{-}24h}$ = 9.54 µg*hr/mL on GD 17), with TP-034 detected in fetal plasma in 1 of 3 litters at that dose.

A large number of impurities (process impurities, degradation products, intermediates, or starting materials) were evaluated by computational assessment methods. For those impurities that had a positive signal in the computational assessment, additional genetic toxicology evaluation was performed. Other impurities were assessed either in separate toxicology studies or in general toxicology studies in which the impurity was added to the eravacycline test article. Extractables and leachables were evaluated in a literature-based assessment. Studies performed to qualify impurities are shown in the Applicant's table below:

Table 18 Toxicology Studies with (b) (4)

Test Article	Study Type	Method of Admin.	Test System	Dose or Conc.	GLP	Report No.
(b) (4)						

The following table from the Applicant's nonclinical overview describes impurity qualification and specifications:

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Table 19 Qualification of Impurities in Eravacycline Drug Substance

(b) (4)

Overall, the safety evaluation of the identified impurities and metabolites appears to support the proposed use of the drug product.

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6 Clinical Pharmacology

6.1 Executive Summary

The Office of Clinical Pharmacology (Division of Clinical Pharmacology IV and Division of Pharmacometrics) reviewed the information contained in NDA 211,109. The clinical pharmacology information submitted in the application supports the approval of XERAVA (eravacycline, ERV) for injection (for intravenous use) for the treatment of cIAI in patients 18 years of age and older. See Table 5 for a summary of clinical pharmacology-related recommendations and comments on key review issues.

Table 5: Summary of OCP Recommendations & Comments on Key Review Issues.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The evidence of effectiveness of eravacycline in patients with cIAI was provided by 2 Phase 3 studies: TP-434-08 and TP-434-25. Supportive evidence of effectiveness was provided by a Phase 2 dose-ranging study (TP-434-P2-cIAI-1) and an exposure-response analysis for efficacy.
General dosing instructions	The recommended dosing regimen is 1 mg/kg every 12 hours (q12h) administered intravenously (IV) over 60 minutes for 4 to 14 days.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Severe hepatic impairment (Child-Pugh C): 1 mg/kg q12h on the first day followed by 1 mg/kg every 24 hours (q24h) for a total duration of 4 to 14 days. Concomittant use of a strong CYP 3A Inducer: 1.5 mg/kg q12h for a total duration of 4 to 14 days.
Labeling	The Applicant's proposed labeling requires major edits. The review team has specific content and formatting change recommendations that will be communicated to the Applicant during labeling negotiations.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Table 6 provides a summary of the clinical pharmacology characteristics of eravacycline.

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Table 6: Summary of Clinical Pharmacology Characteristics of Eravacycline.

<table>
<tr><td>Distribution</td><td>Eravacycline has variable plasma protein binding ranging from 40% to 99% at concentrations from 0.1 µg/mL to 100 µg/mL. The fraction unbound decreases as the concentration increases.

The apparent volume of distribution is approximately 312 L.

Whole blood and plasma concentrations were similar at concentrations ranging from 0.5 to 10 µM.</td></tr>
<tr><td rowspan="3">Elimination</td><td>The mean terminal half-life is approximately 20 hours.

The clearance is approximately 10 L/h.</td></tr>
<tr><td>Metabolism

There are 3 major metabolites found in plasma after intravenous administration of eravacycline: TP-498, TP-034, and TP-6208. The formation of TP-6208 is mediated by CYP 3A4 and Flavin monooxygenase (FMO).</td></tr>
<tr><td>Excretion

Eravacycline is excreted in urine and feces in the form of the unchanged drug and metabolites as shown in the table below.
<table>
<tr><td colspan="4">Percent of Dose, Mean (CV%)</td></tr>
<tr><td></td><td>Eravacycline</td><td>TP-6208/TP-498</td><td>TP-034</td></tr>
<tr><td>Urine</td><td>20% (3.6%)</td><td>4.77% (0.39%)</td><td>1.84% (0.96%)</td></tr>
<tr><td>Feces</td><td>17.2% (2.5%)</td><td>7.57% (0.49%)</td><td>1.06% (2.9%)</td></tr>
</table>
Source: Study TP-434-12</td></tr>
</table>

6.2.2 General Dosing and Therapeutic Individualization

General Dosing

The Applicant's proposed dosage regimen of XERAVA is 1.0 mg/kg IV q12h for 4 to 14 days.

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The Applicant's proposed dosing regimen is supported by the efficacy, safety, and exposure-efficacy analyses from the clinical trials submitted in the NDA.

Therapeutic Individualization

Severe Hepatic Impairment (Child-Pugh Class C)

(b) (4)

Results from the dedicated hepatic impairment study showed the AUC of eravacycline in patients with severe hepatic impairment is over 2-fold higher than the AUC of eravacycline in patients with normal hepatic function following a single dose of 1.5 mg/kg eravacycline. No patients with severe hepatic impairment were enrolled in the Phase 2 and 3 studies. The predicted eravacycline AUC in patients with severe hepatic impairment exceeds the range of exposures observed in Phase 2/3 trials. Given the observed trend of increasing incidence of nausea/vomiting and laboratory values with increasing eravacycline exposure, the 2-fold increase in eravacycline AUC in severe hepatic impairment without dose adjustment poses a safety concern. Based on the reviewer's simulations using the population PK model, the Clinical Pharmacology review team recommends the following dosage regimen in patients with severe hepatic impairment: XERAVA 1.0 mg/kg IV q12h on the first day followed by 1.0 mg/kg IV q24h for a total duration of 4 to 14 days (See Section 6.3.2 Clinical Pharmacology Question 3 for details).

Concomitant Use of a Strong CYP3A Inducer

(b) (4)

results from the drug-drug interaction study of rifampin, a strong CYP3A inducer, and eravacycline, a CYP3A4 substrate, showed that concomitant use of rifampin caused a 35% decrease in eravacycline exposure. The Clinical Pharmacology review team is concerned that the 35% decrease in exposure may decrease eravacycline efficacy because it would lead to eravacycline exposure below the exposure shown to be effective in Phase 2 and 3 studies. (b) (4) which was conveyed to the Applicant in the late-cycle meeting document.

At the late-cycle meeting, the Applicant proposed a dose adjustment in patients with concomitant use of a strong CYP3A inducer. Based on the reviewer's simulations using new data submitted by the Applicant, the Clinical Pharmacology review team agrees with the Applicant's proposal and recommends the following dosage regimen in patients with concomitant use of a strong CYP3A inducer: XERAVA 1.5 mg/kg IV q12h for 4 to 14 days (See Section 6.3.2 Clinical Pharmacology Question 4 for details).

Outstanding Issues

None.

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6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Information of general pharmacology and pharmacokinetic characteristics is shown in Table 7.

Table 7: General Pharmacology and Pharmacokinetic Characteristics.

<table>
<tr><th colspan="2">Pharmacology</th></tr>
<tr><td>Mechanism of Action</td><td>Eravacycline, like other members of the structurally related tetracycline class, inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit and blocking the entry of aminoacyl-tRNA molecules, which prevents the incorporation of amino acid residues into peptide chains.</td></tr>
<tr><td>Active Moieties</td><td>Eravacycline</td></tr>
<tr><td>QT Prolongation</td><td>At a single intravenous dose of 1.5 mg/kg (1.5 times the recommended dose), eravacycline does not prolong the QT interval to any clinically relevant extent. (Study TP-434-004)</td></tr>
<tr><th colspan="2">General Information</th></tr>
<tr><td>Bioanalysis</td><td>Validated LC/MS/MS methods were used to determine eravacycline, TP-498, TP-6208, and TP-034 concentrations in human plasma and urine. (See APPENDIX 15.4)</td></tr>
<tr><td>Healthy vs. Patients</td><td>Eravacycline AUC is approximately 21% lower in patients with cIAI relative to healthy volunteers based on population PK (PPK) analysis. (See APPENDIX 15.4)</td></tr>
<tr><td>Drug exposure at steady state following the therapeutic dosing regimen</td><td>The steady state exposure of eravacycline following 10 days of 1.0 mg/kg q12h IV eravacycline is shown below:
<table><tr><th></th><th>Mean (CV%) N=4</th></tr><tr><td>$AUC_{0\text{-}12h}$ (µg*h/mL)</td><td>6.31 (15.0%)</td></tr><tr><td>C_{max} (µg/mL)</td><td>1.83 (15.5%)</td></tr></table>Source: Study TP-434-P1-MAD-1</td></tr>
<tr><td>Range of effective dose or exposure</td><td>1 mg/kg q12h and 1.5 mg/kg q24h IV eravacycline were shown to be effective in Phase 2 and 3 studies.</td></tr>
<tr><td>Maximally tolerated dose (MTD) or exposure</td><td>1.5 mg/kg IV eravacycline is the maximally tolerated single dose. 1 mg/kg q12h IV eravacycline is the maximally tolerated daily dose, but it is also the highest tested dose in the MAD study. (Study TP-434-P1-SAD-1, Study TP-434-P1-MAD-1)</td></tr>
</table>

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<table>
<tr><td>Dose Proportionality</td><td>The AUC and C_{max} increase in a roughly dose-proportional manner from 1 mg/kg to 3 mg/kg. (Study TP-434-P1-SAD-1)</td></tr>
<tr><td>Accumulation</td><td>The accumulation ratio for the dosing regimen of 1 mg/kg IV q12h at steady state (Day 10) was approximately 1.39. (Study TP-434-P1-MAD-1)</td></tr>
<tr><td>Variability</td><td>The inter-subject variability (%CV) in C_{max} and AUCt values for eravacycline ranged from 15%-28% and 14%-22% in healthy subjects administered eravacycline 1 mg/kg IV, respectively. (Studies TP-434-P1-SAD-1 and TP-434-P1-MAD-1)</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td>Bioavailability</td><td>N/A</td></tr>
<tr><td>T_{max}</td><td>1 h</td></tr>
<tr><td>Food effect
(Fed/fasted)
Geometric Mean % [90% CI]</td><td>N/A</td></tr>
<tr><td>Volume of Distribution</td><td>The steady state volume of distribution in healthy volunteers administered 1 mg/kg q12h for 10 days is 312 L (16.9%). (TP-434-P1-MAD-1)</td></tr>
<tr><td>Plasma Protein Binding</td><td>Eravacycline shows concentration-dependent binding to plasma proteins. The fraction unbound decreases with increasing concentration.

Multiple studies yielded conflicting results on the magnitude of protein binding at different concentrations as shown in the table below.
<table>
<tr><td>Study</td><td>Method</td><td colspan="8">Mean % free Eravacycline at Various Concentrations (µg/mL)</td></tr>
<tr><td></td><td></td><td>0.1</td><td>0.25</td><td>0.50</td><td>1.0</td><td>2.5</td><td>5.0</td><td>10</td><td>100</td></tr>
<tr><td>AD15-4</td><td>ED</td><td>61.7</td><td>43.9</td><td>ND</td><td>40.6</td><td>34.5</td><td>ND</td><td>ND</td><td>ND</td></tr>
<tr><td>AD09-06</td><td>UF</td><td>ND</td><td>ND</td><td>11.5</td><td>ND</td><td>ND</td><td>ND</td><td>ND</td><td>ND</td></tr>
<tr><td>(b) (4)</td><td>MD(UF)</td><td>20.7</td><td>ND</td><td>ND</td><td>14.0</td><td>ND</td><td>ND</td><td>10.5</td><td>2.4</td></tr>
<tr><td>001</td><td></td><td>12.8</td><td>4.3*</td><td>ND</td><td>5.2</td><td>1.0**</td><td>ND</td><td>ND</td><td>ND</td></tr>
<tr><td>TET-R4384</td><td>ED</td><td>31.6</td><td>ND</td><td>ND</td><td>24.6</td><td>ND</td><td>23</td><td>13.1</td><td>ND</td></tr>
</table>
Source: Summary of Clinical Pharmacology.
*actual concentration 0.3, ** actual concentration 3.0, ED = Equilibrium dialysis, MD = microdialysis, UF = Ultrafiltration, ND = Not Determined</td></tr>
<tr><td>Substrate transporter systems
[in vitro]</td><td>Eravacycline and its metabolites TP-498, TP-6208, and TP-034 were not substrates for major human drug transporters.</td></tr>
</table>

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<table>
<tr><th colspan="2">Elimination</th></tr>
<tr><td>Half-life</td><td>In a single-ascending dose study, the mean half-life of eravacycline was 20.2 (28%) hours. (Study TP-434-P1-SAD-1) Based on the population pharmacokinetic (PPK) model, the predicted half-life for an average patient of 70 kg and 45 years with cIAI is 13.3 hours. (See Appendix 15.4)</td></tr>
<tr><td colspan="2">Metabolism</td></tr>
<tr><td>Fraction metabolized (% dose)</td><td>No active metabolites have been identified.

After IV administration of 60 mg [14C]-eravacycline, unchanged eravacycline was excreted in both urine and feces and accounted for approximately 20% and 17% of the dose, respectively. The distribution of eravacycline and the major metabolites is shown below:
<table>
<tr><td colspan="4">Percent of Dose, Mean (CV%)</td></tr>
<tr><td></td><td>Eravacycline</td><td>TP-6208/TP-498</td><td>TP-034</td></tr>
<tr><td>Urine</td><td>20% (3.6%)</td><td>4.77% (0.39%)</td><td>1.84% (0.96%)</td></tr>
<tr><td>Feces</td><td>17.2% (2.5%)</td><td>7.57% (0.49%)</td><td>1.06% (2.9%)</td></tr>
</table>
Source: Study TP-434-12

Within 24 hours of IV administration of 60 mg [14C]-eravacycline, eravacycline as the unchanged parent drug accounted for 59.3% of the radioactivity in plasma with TP-6208/TP-498 and TP-034 accounting for 29.7% and 2.4%, respectively, of the radioactivity in plasma. (Study TP-434-12)</td></tr>
<tr><td>Primary metabolic pathway(s) [in vitro]</td><td>Eravacycline is metabolized primarily by CYP3A4- and FMO-mediated oxidation of the pyrolidine ring to TP-6208, and by chemical epimerization at C-4 to TP-498. (Study TET-R2645)

TP-034 is produced by oxidative cleavage of the ethylamido side chain and TP-034 could also be formed by CYP3A4, an oxidative amide cleavage reaction not typically associated with CYP metabolism. Additional minor metabolites are formed by glucuronidation, oxidation and hydrolysis. (Study TET-R4680)

TP-498, TP-6208 and TP-034 are not considered to be pharmacologically active.</td></tr>
<tr><td colspan="2">Excretion</td></tr>
<tr><td>Primary excretion pathways (% dose) ±SD</td><td>Following a single intravenous dose of 60 mg [14C]-eravacycline, 35% and 47.7% of the dose was recovered as unchanged eravacycline and metabolites in urine and feces, respectively (Study TP-434-012).</td></tr>
</table>

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In vitro interaction liability (Drug as perpetrator)	
Inhibition/Induction of metabolism	Results from in vitro studies suggest eravacycline and its metabolites TP-498, TP-6208, and TP-034 do not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 at clinically relevant concentrations. (Studies (b) (4)085084, (b) (4)145065, (b) (4) 35050, (b) (4) 55034) Results from in vitro studies suggest eravacycline and its metabolites TP-498, TP-6208, and TP-034 do not induce CYP1A2, 2B6, or 3A4 at clinically relevant concentrations. (Studies 10TETPP2, (b) (4)153026, (b) (4)133065, (b) (4) 43046)
Inhibition/Induction of transporter systems	Eravacycline and its metabolites TP-6208, TP-498, and TP-034 were not inhibitors of the following transporters at clinically relevant concentrations: MDR1, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, and MATE2-K transporters. (Studies Tetraphase-02-12Jun2013, Tetraphase-03-14Jul2014 and (b) (4)158063)

Pharmacokinetic parameters are presented as mean (CV%), mean ±standard deviation (SD), or median (minimum, maximum) unless otherwise noted.

6.3.2 Clinical Pharmacology Questions

1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The primary evidence of effectiveness of eravacycline for the treatment of adult patients with cIAI was provided by two Phase 3 studies, TP-434-08 and TP-434-25. Supportive evidence of effectiveness was provided by one Phase 2 study, TP-434-P2-cIAI-1.

The exposure-response (E-R) analysis based on pharmacokinetic (PK) and efficacy data from the Phase 2 and 3 studies provided additional supportive evidence of effectiveness of eravacycline. (See Clinical Pharmacology Question 2 for details)

2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen of eravacycline, 1 mg/kg IV q12h for 4 to 14 days, is appropriate for adult patients with cIAI.

The primary efficacy endpoint for cIAI was the clinical response at the Test-of-Cure (TOC) visit. Phase 2 study TP-434-P2-cIAI-1 evaluated the efficacy of eravacycline at 1 mg/kg q12h and 1.5 mg/kg q24h IV doses. The clinical response at the TOC visit was 92.9% in the 1.5 mg/kg q24h group (n=42) and 100% in the 1.0 mg/kg q12h group (n=41). The 1 mg/kg IV q12h dose was

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then selected for Phase 3 studies. Pooled analysis using data from the Phase 3 studies showed that clinical response of eravacycline at the TOC visit was 88.7% compared to 89.3% for the active comparators. (See Section 15.3.3: Exposure-Response Analysis**Error! Reference source not found.** for a thorough review of the results of Phase 2/3 trials)

Exposure-Response Analysis for Efficacy

The review team conducted an independent exposure-response (E-R) analysis using data from Phase 2 and 3 trials. Efficacy was measured as microbiological response, Sponsor-assessed clinical response, and Investigator-assessed clinical response each at the end-of-treatment (EOT), the TOC visit, and the follow-up (FU) visit with the exception of microbiological response, which was not analyzed at the FU visit. All 8 measures of efficacy were highly correlated. Figure 2 shows the results of a logistic regression analysis between exposure (Day 1 free AUC:MIC and Day 1 free AUC) and microbiological response at the TOC visit. These results demonstrate that there does not appear to be a significant relationship between eravacycline exposure and clinical response at the 1 mg/kg q12h and the 1.5 mg/kg q24h doses.

This observed flat exposure-response relationship may be due to the high clinical response rates (>88%) observed from eravacycline treatment and the limited range of exposures resulting from 1.5 mg/kg q24h and 1.0 mg/kg q12h doses used in the Phase 2/3 studies. Thus, the exposures achieved with the doses administered in these trials appear to be on the plateau of the exposure-response curve.

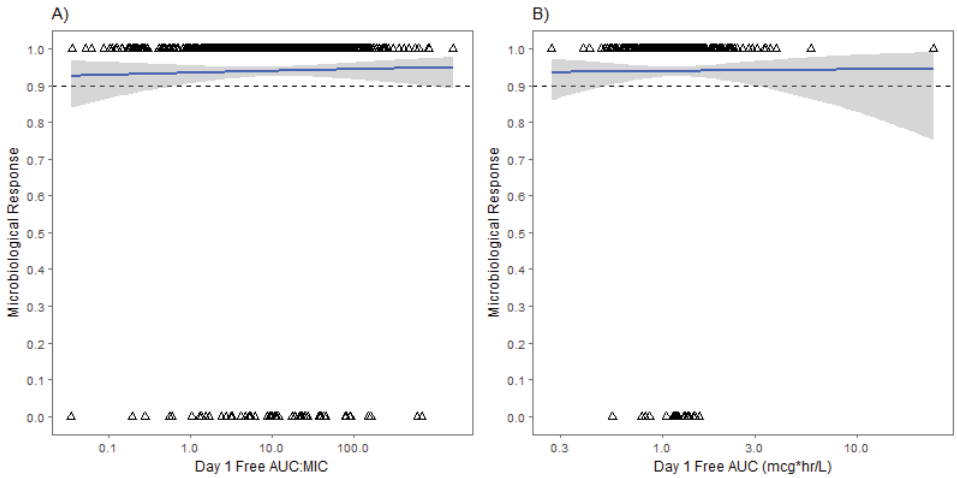

Figure 2: Relationship Between Exposure Measured as A) Day 1 Free AUC:MIC and B) Day 1 Free AUC and Microbiological Response at the Test-of-Cure Visit in the Phase 2 and 3 Studies.

Exposure-Response Analysis for Safety

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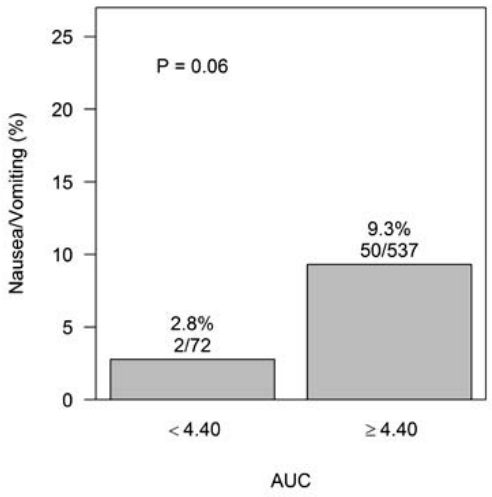
Nausea and vomiting are the most common side effects of eravacycline. In the single-ascending dose study, TP-434-P1-SAD-1, nausea and vomiting were most prevalent at eravacycline doses ≥2 mg/kg. Nausea and vomiting was also assessed in Phase 2/3 trials. In patients experiencing nausea or vomiting, the mean (standard deviation) time of onset was 3 (6.24) days, and the mean (standard deviation) duration was 2.9 (3.6) days. Overall, only 6 of 385 patients administered eravacycline 1.0 mg/kg q12h withdrew from a study due to adverse events. Based on an exposure-response analysis conducted by the Applicant, there was a trend towards increasing incidence of nausea/vomiting with increasing AUC of eravacycline as shown in Figure 3 .



Source: Applicant's report ICPD 0381
Figure 3: Relationship Between Nausea/Vomiting and AUC.

The Applicant also conducted an exposure-response relationship to analyze the effect of eravacycline exposure on changes in laboratory values. Eravacycline exposure as AUC, C_{min}, and C_{max} were significant predictors of changes in the following laboratory values: amylase, lipase, aPTT, and INR. However, the changes in laboratory values were not considered to be clinically significant in majority of patients receiving the 1 mg/kg q12h dose.

Conclusion

Considering both the efficacy and safety results of eravacycline at the 1 mg/kg q12h dose and the exposure-response analysis for efficacy and safety, the proposed dose of 1 mg/kg q12h for 4 to 14 days for the general patient population is acceptable from a Clinical Pharmacology perspective.

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3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Hepatic Impairment

We agree with the Applicant that no dose adjustment is needed for patients with mild and moderate hepatic impairment. (b) (4) we recommend eravacycline dose be adjusted to 1 mg/kg q12h on Day 1 followed by 1 mg/kg q24h for a total treatment duration of 4 to 14 days in patients with severe hepatic impairment.

In a dedicated hepatic impairment study (TP-434-013) of subjects receiving 1.5 mg/kg IV (1.5 times the recommended dose), patients with severe hepatic impairment had a 2.2-fold higher $AUC_{0-\infty}$ relative to healthy volunteers as shown in Table 8.

Table 8: PK Results of the Dedicated Hepatic Impairment Study, TP-434-013.

	Healthy Subjects	Mild Hepatic Impairment		Moderate Hepatic Impairment		Severe Hepatic Impairment	
PK Parameter	Mean (CV%)	Mean (CV%)	Fold Change vs. Healthy Subjects	Mean (CV%)	Fold Change vs. Healthy Subjects	Mean (CV%)	Fold Change vs. Healthy Subjects
$AUC_{0-\infty}$ (ng*hr/mL)	3810 (15.3%)	4730 (21.5%)	1.2	5680 (50.1%)	1.5	8330 (32.2%)	2.2
C_{max} (ng/mL)	1160 (28.1%)	1330 (26.9%)	1.2	1340 (23.2%)	1.2	1360 (17.5%)	1.2
$t_{1/2}$ (hr)	16.3 (38%)	21.4 (46.7%)	1.3	21.6 (36.8%)	1.3	25.6 (16.9%)	1.6

Source: Study TP-434-013

Reviewer Comment: Eravacycline AUC and Cmax in healthy subjects in the hepatic and renal impairment studies were significantly lower compared to healthy subjects in other Phase 1 trials as shown in Table 9. An Information Request was issued to the Applicant on March 14, 2018 in which the Division requested a rationale for the difference in eravacycline exposure across studies. The Applicant responded to the Information Request on March 19, 2018 and notified the Division that a different anticoagulant was used in the hepatic and renal impairment studies (EDTA) than in other studies (heparin). The blood:plasma partitioning ratio of eravacycline is approximately twice as high when EDTA is used as the anticoagulant as it is when heparin is used as the anticoagulant. Therefore, it is plausible that the use of EDTA as an anticoagulant would cause eravacycline to shift into blood cells resulting in lower concentrations of eravacycline in plasma. Thus, absolute values of AUC and C_{max} are not comparable among the dedicated hepatic and renal impairment studies and other studies. However, the fold changes of eravacycline exposure in patients with hepatic/renal impairment relative to the control group within each study are considered to be accurate.

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Table 9: PK Parameters of a Single 1.5 mg/kg IV Dose of Eravacycline.

Study	C_{max} (ng/mL)[a]	AUC_{0-inf} (ng·hr/mL)[a]	CL (L/hr)[b]	Anticoagulant
TP-434-013 (HIP)	1126.4 (25.6)	3775.3 (15.3)	35.6 (27.7)	EDTA
TP-434-014 (RIP)	1334.3 (15.7)	4887.2 (12.8)	28.3 (19.0)	EDTA
TP-434-P1-SAD-1 (IV SAD)	3158 (24.8)	8730.1 (18.9)	13.4 (14.4)	Heparin
TP-434-P1-MAD-1 (IV MAD)	2729 (22.4)	8286.4 (17.5)	14.3 (18.9)	Heparin
TP-434-004 (TQT)	2299.4 (18.9)	8490.9 (18.2)	14.6 (23.4)	Heparin

AUC_{0-inf} = area under concentration-time curve extrapolated to infinity; CL = clearance; C_{max} = maximum observed concentration; CV = coefficient of variation; EDTA = ethylenediamine tetra-acetic acid; HIP = hepatic impairment; IV = intravenous; MAD = multiple ascending dose; RIP = renal impairment; SAD = single ascending dose; TQT = thorough QT.
[a] = Geometric mean (CV%).
[b] = Arithmetic mean (CV%).

Source: Applicant's Response to Clinical Pharmacology Information Request Submitted on March 19, 2018.

Patients with mild and moderate hepatic impairment were included in the Phase 2 and 3 studies, as shown in Table 10. These patients did not have significantly higher rates of adverse events compared to patients with normal hepatic function. Thus, the review team agrees with the Applicant's proposal of no dose adjustment in patients with mild or moderate hepatic impairment.

Table 10: Patients with Hepatic Impairment in the Phase 2 and 3 Studies.

Parameter	Eravacycline 1.0 mg/kg q12h IV N=576	Eravacycline 1.5 mg/kg q24h IV N=53	Comparators[a] N=547
Hepatic Impairment, n (%)			
Child-Pugh Class A	418 (72.6)	33 (62.3)	382 (69.8)
Child-Pugh Class B	77 (13.4)	12 (22.6)	84 (15.4)
Child-Pugh Class C	0	0	0
Missing	81 (14.1)	8 (15.1)	81 (14.8)
AST and/or ALT > 2xULN	56 (9.7)	3 (5.7)	55 (10.1)
AST and ALT ≤ 2xULN	483 (83.9)	42 (79.2)	457 (83.5)
Missing	37 (6.4)	8 (15.1)	35 (6.4)

Source: Pooled analysis tables – Integrated safety, *Table 1.2.4.*

However, no patients with severe hepatic impairment were enrolled in the Phase 2 and 3 studies. The predicted eravacycline AUC in patients with severe hepatic impairment exceeds the range of exposures observed in Phase 2/3 trials. In addition, exposure-response analysis for safety showed that there was a trend towards increasing incidence of nausea/vomiting and laboratory values with increasing eravacycline exposure. Therefore, the 2-fold increase in eravacycline AUC in patients severe hepatic impairment without dose adjustment poses a safety concern.

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Simulations based on the reviewer's population PK model were used to evaluate the predicted exposure of eravacycline in patients with severe hepatic impairment under various dose adjustment scenarios where the dosing interval was extended or the dose was halved with or without a loading dose:

- Dosing scenario #1: 0.5 mg/kg q12h
- Dosing scenario #2: 1 mg/kg loading dose followed by 0.5 mg/kg q12h
- Dosing scenario #3: 1 mg/kg q24h
- Dosing scenario #4: 1 mg/kg q12h on Day 1 followed by 1 mg/kg q24h

The results of the simulation are shown in Table 11.

Table 11: Simulated Median AUC at Selected Doses of Eravacycline in Patients with Different Degrees of Hepatic Function.

Degree of Hepatic Impairment	None/ Normal	Mild		Moderate		Severe									
Dose Regimen	1 mg/kg q12h					1 mg/kg q12h		0.5 mg/kg q12h		1 mg/kg load, then 0.5 mg/kg q12h		1 mg/kg q24h		1 mg/kg q12h on Day 1, then 1 mg/kg q24h	
Day	AUC	AUC	RD (%)	AUC	RD (%)	AUC	RD (%)	AUC	RD (%)	AUC	RD (%)	AUC	RD (%)	AUC	RD (%)
1	7.3	8.3	12.8	8.2	11.8	9.5	30.2	4.8	-34.7	7.6	4.4	5.7	-22.2	9.5	30.0
4	12.2	15.4	26.7	15.1	23.8	21.1	73.2	10.5	-13.7	11.0	-9.4	10.7	-11.9	11.9	-2.3
9	12.6	16.5	30.7	16.1	27.5	24.2	92.2	12.1	-4.0	12.3	-2.9	12.2	-3.3	12.3	-2.7
14	12.6	16.5	30.8	16.1	27.7	24.6	94.8	12.3	-2.5	12.4	-2.0	12.4	-2.3	12.3	-2.4

Source: Reviewer's Analysis.
RD: Relative Difference is defined as the percent change in eravacycline AUC in patients with various degrees of hepatic impairment relative to eravacycline AUC in patients with normal hepatic function on each day.
AUC: $AUC_{0\text{-}24}$ (µg*hr/mL)

The simulation confirms that the 1 mg/kg q12h dose produces a 95% higher exposure in patients with severe hepatic impairment relative to the reference (patients with normal hepatic function administered 1 mg/kg q12h) by Day 14. All 4 dose adjustment scenarios for patients with severe hepatic impairment produce median values of AUC within 5% of the reference by Day 9. However, the dosing scenarios that lacked a loading dose, i.e., #1 and #3 (0.5 mg/kg q12h and 1 mg/kg q24h), produce median values of AUC over 20% lower than the reference on Day 1. Both dosing scenarios with a loading dose, i.e., #2 and #4 (1 mg/kg load followed by 0.5 mg/kg q12h and 1 mg/kg q12h on Day 1 followed by 1 mg/kg q24h), are predicted to produce median AUC values similar to or slightly higher than the reference over the course of treatment.

While the median predicted AUC of dosing scenario #4 (1 mg/kg q12h on Day 1 followed by 1 mg/kg q24h) in patients with severe hepatic impairment is 30% higher than the reference on Day 1, it is well within the range of predicted exposure in patients with normal hepatic function as shown in Figure 4. In addition, dosing scenario #4 (1 mg/kg q12h on Day 1 followed by 1

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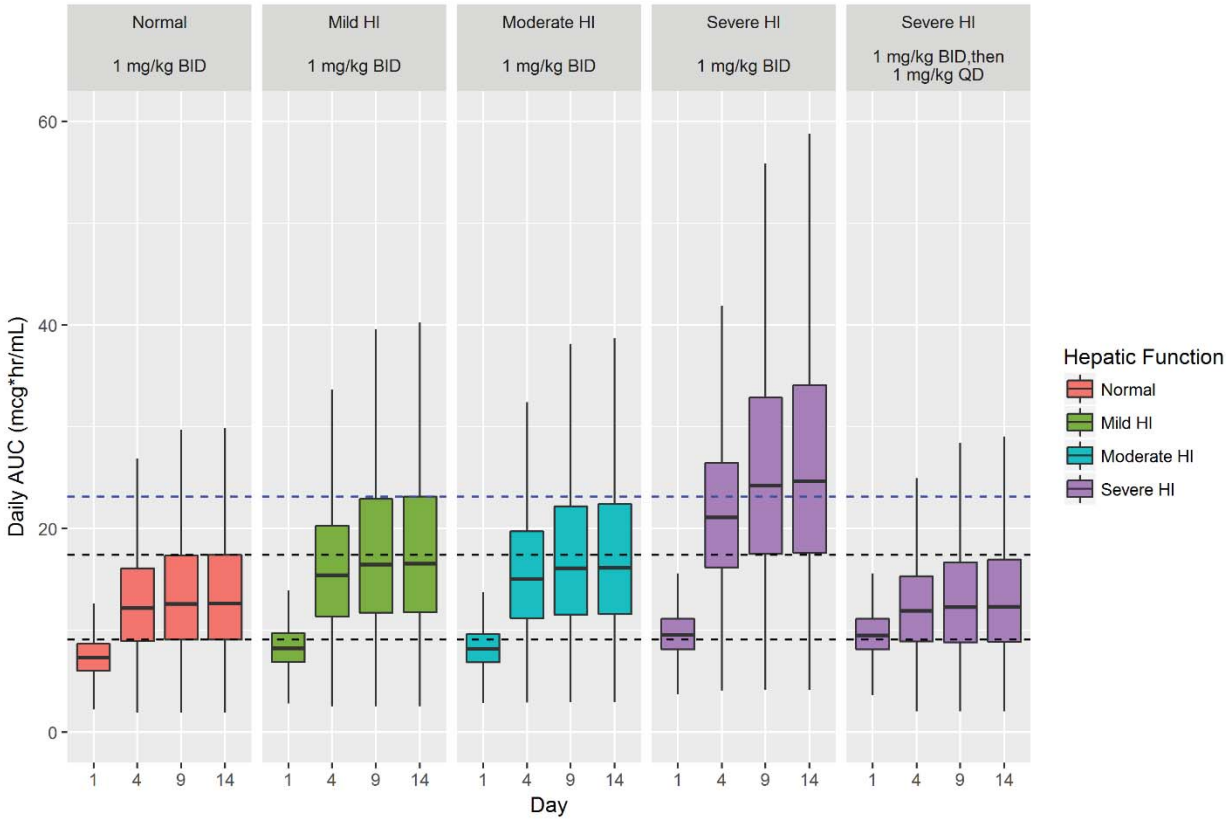
mg/kg q24h) appears more convenient in terms of dose administration than dosing scenario #2 (1 mg/kg loading dose followed by 0.5 mg/kg q12h) by maintaining the same dose (1 mg/kg) while reducing the dosing frequency from q12h to q24h from Day 2 onwards.



The black dashed lines represent the 25th and 75th percentile of predicted AUC_{0-24h} in patients with normal hepatic function administered 1 mg/kg q12h at steady state: 9.01 and 17.5 µg*hr/mL, respectively. The blue dashed line represents the 75th percentile of 11 predicted AUC_{0-24h} in patients with mild hepatic impairment administered 1 mg/kg q12h at steady state: 23.1 µg*hr/mL.
HI: Hepatic Impairment, BID: Twice Daily (q12h), QD: Once Daily (q24h)

Figure 4: Simulated Total AUC of Eravacycline by Hepatic Function and Dose.

As such, the Clinical Pharmacology review team recommends eravacycline dose be adjusted to 1 mg/kg q12h on Day 1, followed by 1 mg/kg q24h in patients with severe hepatic impairment. This dose regimen is predicted to achieve comparable exposure of eravacycline (with slightly higher AUC on Day 1) in patients with severe hepatic impairment to the efficacious exposure demonstrated in patients with normal hepatic function in the Phase 2 and 3 trials.

Renal Impairment

The review team concurs with the Applicant's proposal that no dose adjustment of eravacycline is needed in patients with renal impairment.

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In the mass balance study, TP-434-012, following IV administration of 60 mg [14C]-eravacycline, approximately 20% of total radioactivity was recovered in urine as unchanged eravacycline. These results suggest that renal excretion is not a major route of elimination for eravacycline.

In the dedicated renal impairment study with a reduced design (TP-434-014), subjects with normal renal function and subjects with end-stage renal disease (ESRD) requiring dialysis received 1.5 mg/kg IV eravacycline. Subjects with ESRD received eravacycline only on non-dialysis days such that the administration of eravacycline occurred on the day after dialysis. There are no significant changes in eravacycline AUC and C_{max} relative to healthy volunteers as shown in Table 12.

Table 12: Eravacycline PK Results of the Dedicated Renal Impairment Study, TP-434-012.

	Healthy Subjects (n=6)	Patients with ESRD (n=6)	
PK Parameter	**Mean (CV%)**	**Mean (CV%)**	**Fold Change vs. Healthy Subjects**
$AUC_{0-\infty}$ (ng*hr/mL)	4920 (13%)	4750 (17.5%)	0.97
C_{max} (ng/mL)	1350 (16.4%)	1540 (42.9%)	1.14
$t_{1/2}$ (hr)	20.5 (34.8%)	22.2 (40.2%)	1.09

Source: TP-434-012

Other Intrinsic Factors (Age, Sex, Ethnicity)
Based on the population PK analysis, eravacycline PK are not significantly affected by age, sex, or ethnicity to the extent that a dose adjustment is needed.

4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The potential for eravacycline and the metabolites TP-6208, TP-498 and TP-034 to cause or be subject to drug-drug interactions via CYP enzyme inhibition, or by interaction with major human uptake and efflux transporters is low. However, dose adjustment is recommended with concomitant use of CYP3A4 inducer (e.g., rifampin) due to clinically observed 35% decrease in eravacycline AUC_{0-inf} when coadministered with rifampin.

The food-drug interation is not relevant to eravacycline as the drug is given intravenously.

Approximately half of the administered dose of eravacycline is metabolized following intravenous administration. There are three major metabolites (TP-6208, TP-034 and TP-498); none of which are pharmacologically active. Oxidation of the pyrrolidine ring to TP-6208 is mediated by cytochrome P450 isoenzymes (CYP), specifically CYP3A4/5, as well as by Flavin

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monoxygenases (FMO). Hydrolysis of the amide side chain to TP-034 appears to an important pathway *in vivo.* Increased C-4 epimerisation to TP-498, (b) (4) was also observed. Glucuronidation of TP-434 is a minor pathway and the transferase enzyme responsible for this reaction has not been identified (Studies TET-R2645 and TET-R680).

CYP Enzyme Related Drug-Drug Interactions (DDIs)

Eravacycline as a substrate of CYP isoenzymes: Clinical DDI studies were conducted to evaluate the effect of rifampin (Strong inducer of CYP3A) and itraconazole (strong inhibitor of CYP3A) on the PK of eravacycline.

Effect of Strong CYP3A Inducer on Eravacycline PK
Concomitant administration of eravacycline and rifampin to healthy subjects resulted in a decrease in eravacycline AUC0-inf by 35%, an increase in CL 54% and a decrease in half-life of 27%, with negligible effects on Vss (13% decrease) and C_{max} (8% increase) (Table 13) (Study TP-434-020). There are no data to ensure the efficacy with a 35% decrease in eravacycline AUC. The Applicant proposed increasing the dose (i.e., 1.5 mg/kg q12h) in patients with concomitant use of strong CYP3A inducer.

Table 13. PK Parameters of Eravacycline and Metabolites Following 1.0 mg/kg Intravenous Infusion of Eravacycline With and Without Rifampin

Study TP-434-020: A Phase 1, Open-Label Clinical Study to Assess the Impact of Rifampin on Eravacycline Pharmacokinetics in Healthy Subjects			
	C_{max} (ng/mL)	AUC0-inf (h*ng/mL)	T1/2 (h)
Eravacycline	1170	5380	15
Eravacycline+Rifampin	1260	3520	11

Simulations based on the reviewer's population PK model were used to evaluate the predicted exposure of eravacycline in patients with or without concomitant administration of a strong CYP3A inducer under various dose adjustment scenarios:

- Dosing Scenario 1: 1 mg/kg q12h
- Dosing Scenario 2: 1.5 mg/kg q24h
- Dosing Scenario 3: 1.5 mg/kg q12h
- Dosing Scenario 4: 2 mg/kg q12h

Dosing Scenarios 1, 3, and 4 were simulated with and without concomitant administration of a strong CYP3A inducer, but Dosing Scenario 2 was only simulated without concomitant administration of a strong CYP3A inducer. Dosing Scenario 2 was included to represent minimum acceptable exposure as the dose was tested in the Phase 2 study and shown to be effective. The results of the simulations are shown in Table 14.

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Table 14. Simulated Median AUC at Selected Doses of Eravacycline in Patients with and Without Concomitant Administration of a Strong CYP3A Inducer.

	Without Inducer			With Inducer					
	1 mg/kg q12h	1.5 mg/kg q24h		1 mg/kg q12h		1.5 mg/kg q12h		2 mg/kg q12h	
Day	AUC	AUC	RD (%)	AUC	RD (%)	AUC	RD (%)	AUC	RD (%)
1	7.0	6.0	-13.7	5.0	-27.7	7.6	**8.5**	10.1	44.6
4	11.4	8.6	-24.4	6.7	-40.9	10.1	**-11.4**	13.5	18.1
9	11.8	8.9	-24.9	6.8	-42.4	10.2	**-13.8**	13.6	14.9
14	11.9	8.9	-24.9	6.8	-42.5	10.2	**-14.0**	13.6	14.7

Source: Reviewer's Analysis.
RD: Difference relative to AUC in patients administered 1 mg/kg q12h without a strong CYP3A inducer
AUC: $AUC_{0\text{-}24h}$ (µg*hr/mL)

The simulations demonstrate that the 1 mg/kg q12h dose produces a 42.5% lower exposure ($AUC_{0\text{-}24h}$) in patients with concomitant administration of a strong CYP3A inducer relative to the reference (patients administered 1 mg/kg q12h without inducer) by Day 14. Only the 1.5 mg/kg q12h dose produces median values of AUC within 15% of the reference throughout the course of the treatment in patients with concomitant use of a strong CYP3A inducer.

The results of the simulation are alo presented graphically in Figure 5.

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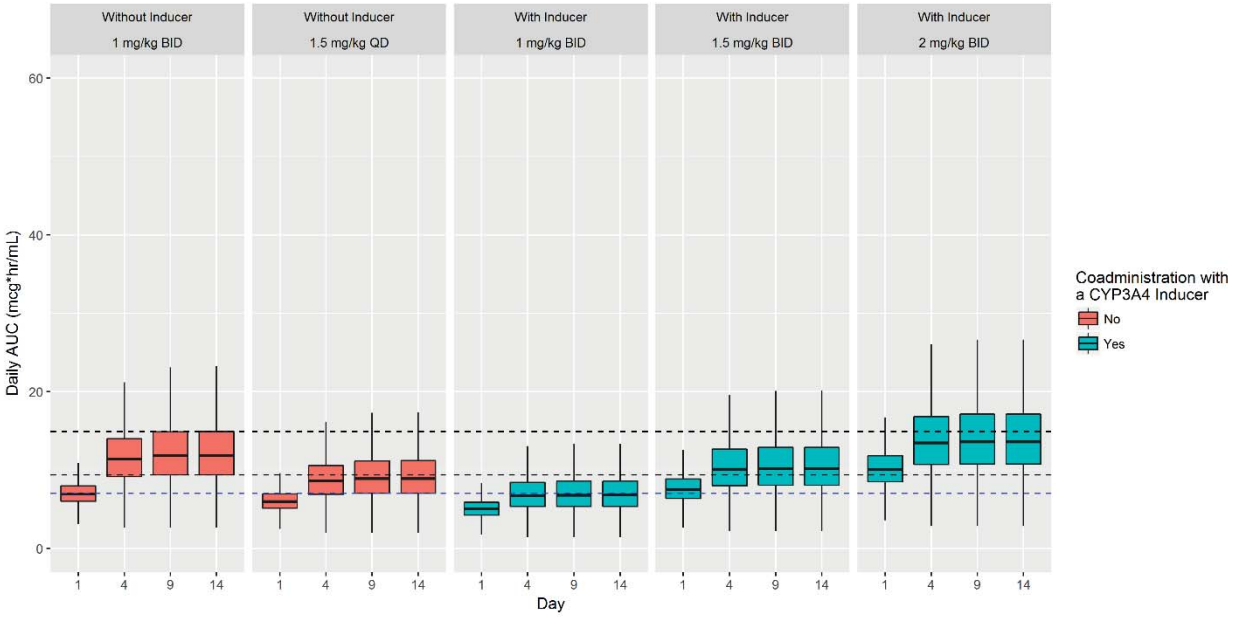

The black dashed lines represent the 25th and 75th percentile of predicted $AUC_{0\text{-}24h}$ in patients administered 1 mg/kg q12h alone at steady state: 9.40 and 14.9 µg*hr/mL, respectively. The blue dashed line represents the 25th percentile of predicted $AUC_{0\text{-}24h}$ in patients administered 1.5 mg/kg q24h alone at steady state: 7.05 µg*hr/mL.
BID: Twice Daily (q12h), QD: Once Daily (q24h)

Figure 5. Simulated AUC of Eravacycline with and without Concomitant Administration of a Strong CYP 3A4 Inducer.

The review team also analyzed the Cmax and Cmin of eravacycline at various dosing adjustment scenarios. The median values of Cmin and Cmax at 1.5 mg/kg q12h with a strong CYP3A inducer fall in the range of Cmin/Cmax values at doses studied in Phase 2 and 3 trials (1 mg/kg q12h and 1.5 mg/kg q24h) without a strong CYP3A inducer.

Taken together, the Applicant's proposed dosage regimen of 1.5 mg/kg q12h produces values of AUC, Cmin, and Cmax in patients co-administered a strong CYP3A inducer that are in the range of those at doses studied in Phase 2 and 3 trials found to be generally safe and effective. As such, the Clinical Pharmacology review team recommends eravacycline dosage be adjusted to 1.5 mg/kg q12h in patients with concomitant administration of a strong CYP3A inducer.

Effect of Strong CYP3A Inhibitor on Eravacycline PK

Concomitant administration of eravacycline and itraconazole to healthy subjects resulted in an increase in eravacycline AUC0-t of approximately 32% (Table 15). Similarly, there was a reduction in mean eravacycline clearance of approximately 32% and in mean AUC of its metabolites, TP-6208 and TP-034, of approximately 65% (Study TP-434-016). The extent of increase in eravacycline AUC by itraconazole is not considered clinically significant because no safety issues were observed in patients with mild/moderate hepatic impairment with a predicted ~30% increase in eravacycline AUC.

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Table 15. PK Parameters of Eravacycline and Metabolites Following 1.0 mg/kg Intravenous Infusion of Eravacycline With and Without Probe Substrate Itraconazole

Study TP-434-016: A Phase 1, Open-Label Clinical Study to Assess the Impact of Itraconazole on Eravacycline Pharmacokinetics in Healthy Subjects			
	C_{max} (ng/mL)	AUC0-t (h*ng/mL)	T1/2 (h)
Eravacycline	1100	4320	14
Eravacycline+Itraconazole	1160	5700	19

Eravacycline and metabolites as inhibitors of CYP isoenzymes: In vitro, eravacycline demonstrated negligible direct inhibition of CYP1A2, 2B6, 2C9, 2C19, 2D6 or 3A4/5. High concentrations of eravacycline produced slight direct inhibition of CYP2C8 (45% at 85.6 µM), but is unlikely to be clinically relevant at C_{max} concentrations of eravacycline produced by a 1.0 mg/kg i.v. dose given every 12 h (1.29 µM) (Study (b) (4) 085084).

Based on in vitro results, the potential for TP-498, TP-6208, and TP-034 to inhibit major human CYP isoenzymes directly, or in a time- or metabolism-dependent fashion is negligible (Study (b) (4) 145065).

TP-6208 did not inhibit CYP isoenzymes at concentrations up to 100 uM (Study (b) (4) 35050).

Based on estimates for R1 and R2 values <1.1, TP-034 is not predicted to cause clinically relevant reversible ot irreversible inhibition of either hepatic or intestinal CYP enzymes (Study (b) (4) 155034).

Eravacycline and metabolites as inducers of CYP isoenzymes: The *in vitro* induction effects of eravacycline (0.1, 1, and 10 µM) on CYP1A2, 2B6, and 3A4 enzyme activities were evaluated using fresh human hepatocytes from three donors. Eravacycline did not show any inductive effects on CYP1A2, 2B6, or 3A4 (Study 10TETPP2).

Treatment of human hepatocytes with up to 30 µM of the metabolite TP-6208 produced little or no increase (< 2-fold) in CYP1A2, CYP2B6, or CYP3A4 mRNA and enzyme activity levels (Study (b) (4) 133065).

CYP1A2, CYP2B6 and CYP3A4 were not induced by the metabolite TP-498 at concentrations of up to 4 to 10 µM or with eravacycline at concentrations of up to 3 µM. (Study (b) (4) 143046).

In human liver microsomes incubated with the metabolite TP-034, there was no evidence of time- or metabolism-dependent inhibition of CYP1A2. The *R*3 values for CYP 3A4 and CYP2B6 fell slightly below the FDA's cutoff of 0.9 in two and three cultures of human hepatocytes, respectively using the total concentration of TP-034. These results may suggest TP-034 has the

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potential to cause clinically relevant induction of CYP2B6 and CYP3A4; however, the results particularly associate with CYP3A4 should be interpreted with caution given that mRNA increases were less than 20% of positive controls (Study (b) (4) 53026).

Transporter Related Drug-Drug Interactions

The potential for eravacycline, TP-498, TP-6208 and TP-034 to be substrates or inhibitors for major human uptake and efflux transporters was studied with cell culture and vector expression systems (Studies Tetraphase-02-12Jun2013, Tetraphase-03-14Jul2014 and (b) (4) 158063).

Eravacycline as a substrate of human transporters (OATP1B1,mOATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 and MATE2-K): Eravacycline is not a substrate (defined as >2- fold accumulation) for MDR1, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1 and OCT2. It was not tested as a substrate for MATE1 or MATE2-K (Tetraphase-02-12Jun2013. substrate for MATE1 or MATE2-K (Tetraphase-02-12Jun2013).

Eravacycline and its metabolites as inhibitors of human transporters (OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 and MATE2-K): Eravacycline did not inhibit transport mediated by BCRP, BSEP, OATP1B1, OAT1, OCT1, OCT2, MATE1 or MATE2-K. Eravacycline inhibited P-gp (26.1% to 29.3%), OATP1B3 (35.7%) and OAT3 transporter activity (53.4%) at 36 µM. However, in vivo DDIs are not anticipated at clinically relevant concentrations following IV administration of 1 mg/kg q12h eravacycline (Study Tetraphase-02-12Jun2013).

TP-498 did not inhibit (<20%) the MDR1, BCRP, BSEP, OATP1B1, OCT1, OCT2, OAT1, MATE1 and MATE2-K mediated transport. The OATP1B3 mediated transport of CCK-8 was inhibited slightly with a maximum inhibition of 24%; however, no IC50 could be determined (Tetraphase-03-14Jul2014). TP-034 did not inhibit any of the transporters examined, and caused less than 50% inhibition of at the highest concentration tested. IC50 values could not be determined experimentally (Study (b) (4) 158063). TP-6208 did not inhibit any transporter in vitro (Study Tetraphase-02-12June2013).

5. Does the clinical pharmacology information support the proposed breakpoint?

(b) (4)

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(b) (4)

Therefore, given the variability of PK/PD target observed in animal models and the uncertainty in the plasma protein binding of eravacycline in mice and humans, the PTA analysis is considered inadequate to support the breakpoint determination for Enterobacteriaceae.

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7 Statistical and Clinical Evaluation

7.1 Sources of Clinical Data and Review Strategy

7.1.1 Table of Clinical Trials

To support the efficacy and safety of eravacycline, the applicant's developmental program included one Phase 2 clinical study (Study TP-434-P2-cIAI-1) and two confirmatory Phase 3 clinical studies (Studies TP-434-008 and TP-434-025). Study TP-434-P2-cIAI-1 is a proof-of-concept study comparing two IV regimens of eravacycline to ertapenem; Study TP-434-008 is a non-inferiority study comparing eravacycline to ertapenem; and Study TP-434-025 is a non-inferiority study comparing eravacycline to meropenem. Table 19 provides an overview of these studies.

Table 19: Overview of Clinical Studies Relevant to this NDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
TP-434-P2-cIAI-1	Phase 2, randomized, double-blind, double-dummy, comparative study of 2 dose regimens of TP-434	Regimen A: Eravacyline IV 1.5 mg/kg q24h Regimen B: Eravacyline IV 1.0 mg/kg q12h Regimen C: Ertapenem IV 1.0 g q24h	Primary: Clinical response at TOC in the micro-evaluable population	Treatment duration: 4-14 days (4-7 days for Indian sites) TOC Visit: 10-14 days after last dose of study drug Follow-up Visit: 28-42 days after last dose of study drug	Regimen A: 56 Regimen B: 57 Regimen C: 30	Subjects with cIAI 18-75 years (18-65 years in Indian sites) , male and female	40 sites in 6 countries: Bulgaria, Lithuania, Latvia, Romania, US, India

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TP-434-008	Phase 3, randomized, double-blind, double-dummy, comparative, noninferiority	Regimen A: Eravacyline IV 1.0 mg/kg q12h Regimen B: Ertapenem IV 1 g q24h	Primary: Clinical response at TOC in the micro-ITT population	Treatment duration: 4-14 days TOC Visit: Day 25-31 Follow-up Visit: Day 38-50	Eravacycline arm: 270 patients Ertapenem arm: 271 patients	Subjects with cIAI 18-75 years, male and female	66 sites in 11 countries: Bulgaria, Estonia, Lithuania, Latvia, Romania, Ukraine Russia, US Czech Republic, Germany, South Africa
TP-434-025	Phase 3, randomized, double-blind, double-dummy, comparative, noninferiority	Regimen A: Eravacyline IV 1.0 mg/kg q12h Regimen B: Meropenem IV 1.0 g q8h	Primary: Clinical response at TOC (Day 25-31) in the micro-ITT population	Treatment duration: 4-14 days TOC Visit: Day 25-31 Follow-up Visit: Day 38-50	Eravacycline arm: 250 patients Ertapenem arm: 250 patients	Subjects with cIAI 18-75 years, male and female	65 sites in 11 countries: Bulgaria, Czech Republic, Estonia, Hungary, Latvia Lithuania, Romania Gerogia, Russia, Ukraine, US

Source: Reviewer Table

Reviewer Comments: *There were 33 of 66 (50%) of sites from Trial 008 that were also used in Trial 025. This is considered to be*

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acceptable. Note that the FDA guidance for cIAI (2015) does not place a specific restriction on the percentage of sites which can be shared between studies.

APPEARS THIS WAY ON ORIGINAL

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7.1.2 Review Strategy

Data Sources

This application was submitted in eCTD format. The sources of data used for the evaluation of efficacy and safety for eravacycline included applicant study reports, data sets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)] and literature references which can be found at the following link: \\cdsesub1\evsprod\NDA211109\0001

Data and Analysis Quality

The statistical and clinical review teams evaluated the data and analysis quality with assistance from the Office of Computational Science (OCS). This included an assessment of the compatibility of the data with the review tools and data quality metrics such as the availability of appropriate variables, variables populated by expected data points and the appropriate use of standard terminology. In general, the data submitted by the applicant was acceptable.

7.2 Review of Relevant Individual Trials Used to Support Efficacy

7.2.1 Pivotal Phase 3 Trials, Trials 008 & 025

7.2.1.1 Study Design and Endpoints

Study Design

The applicant conducted two Phase 3, randomized, double-blind, double-dummy, multicenter NI studies in hospitalized subjects with cIAIs requiring surgery or percutaneous drainage. The design of these studies followed the FDA guidance for cIAI (2018).[1] The primary objective of these trials was to assess the efficacy and safety of eravacycline (1.0 mg/kg q12h). In Trial 008, the comparator regimen was ertapenem (1.0 g q24h) and in Trial 025, the comparator regimen was meropenem (1.0 g q8h). In both trials, patients were randomized with a 1:1 allocation to either eravacycline or comparator therapy. The randomization was stratified by primary site of infection (complicated appendicitis versus all other cIAI diagnoses).

Eligible patients in these trials were adults with abdominal pain (or flank pain or pain caused by cIAI) who were diagnosed with a cIAI that required surgery or percutaneous drainage and hospitalization. This included patients diagnosed with appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, intra-abdominal abscess, perforation of intestine, and peritonitis. Patients with complicated appendicitis were limited to 30% (Trial 008) or 50% (Trial 025) of enrolled patients and patients with renal failure or hepatic disease were excluded from these

[1] https://www.fda.gov/downloads/drugs/guidances/ucm321390.pdf

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trials. Eligible patients also could not receive effective antibacterial therapy for their current infection for more than 24 hours during the 72 hours preceding enrollment, unless they were prior treatment failures with documented cIAI.

In both trials, patients received between 4 to 14 dosing cycles which usually corresponded to 4 to 14 days of therapy. Clinical response was evaluated at the end-of-therapy (EOT) visit occurring 24 hours of the last dose of study drug, the test-of-cure (TOC) visit on Day 25-31, and the follow-up (FU) visit on Day 38-50. Clinical response included three categories: 'Clinical Cure', 'Clinical Failure' and 'Missing/Indeterminate'. 'Clinical cure' was defined as complete resolution or signficant improvement in signs and symptoms of the infection such that no additional therapy is required; 'Clinical Failure' was defined as death related to cIAI, persistence of symptoms of cIAI, unplanned surgical procedure or radiological intervention, need for systemic antibacterial drugs or rescue medication; and 'Missing/Indeterminate' was defined as incomplete study visit/assessment or death unrelated to cIAI. A double-dummy design was used for evaluating clinical response in order to minimize potential study biases. This design accounted for differences between eravacycline and comparator infusion volumes, time of drug administration and the length of the infusion time.

Reviewer Comments: *The FDA guidance defines clinical success (or cure) as resolution of the baseline signs and symptoms of cIAI based on objective assessments of events from randomization until approximately Day 28. The guidance does not specifically state that complete resolution is required. The clinical team considers the Sponsor's definition of clinical cure to be adequate. In Trials 008 and 025, the signs/symptoms which most often did not have complete resolution among clinical cures were tenderness, tenderness to palpation, induration and skin erythema.*

The analysis populations defined for these trials included the ITT defined as all randomized patients, the modified ITT (MITT) defined as all ITT patients receiving study drug and the micro-ITT defined as all randomized patients with a valid baseline pathogen against which eravacycline has antibacterial activity. Clinically evaluable (CE) and microbiologically evaluable (ME) populations were also defined at the EOT and TOC visits using the 'CE-EOT', 'ME-EOT', 'CE-TOC' and 'ME-TOC' analysis populations. CE patients included MITT patients meeting additional requirements relating to minimal disease criteria, prior and concomitant antibiotic use, source control, study drug therapy, clinical outcome assessment and baseline or intercurrent medical events. ME patients included micro-ITT patients meeting the same requirements.

Reviewer Comments: *The definition of the micro-ITT population is concerning because it is silent on the activity of the control drug to the baseline pathogen. It is problematic in a non-inferiority trial to include patients with pathogens resistant to the comparator, because assessment of efficacy of the test drug hinges on the known effectiveness of the comparator. However, Trials 008 and 025 had as an exclusion criterion "was known at study entry to have cIAI caused by a pathogen(s) resistant to one of the study drugs." The Reviewer verified that*

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there were no subjects in the comparator arm with baseline pathogens that were resistant to comparator drug.

The primary endpoint was defined as clinical response at TOC in the micro-ITT population. The pre-specified NI margin was 10% in Trial 008 and 12.5% in Trial 025. Secondary endpoints included clinical response at the EOT, TOC, and FU visits in both ITT-based and evaluable analysis populations (excluding the micro-ITT at TOC). Primary and secondary comparisons for clinical response endpoints were based on clinical cure rates (i.e. clinical cures vs. non-cures) where non-cures included patients classified as either a 'Clinical Failure' or as 'Missing/Indeterminate'. Additional secondary endpoints included microbiological response at EOT and TOC in the micro-ITT and ME populations.

Adequate surgical source control was evaluated by an independent surgical assessment committee (SAC) composed of a single experienced surgeon. The SAC assessed only patients who were clinical failures at the TOC visit or clinical cures who underwent a second surgical procedure which may have been related to the original cIAI. All other patients were assumed to have adequate source control. For those subjects reviewed by the SAC, the committee assessment of clinical response was used in the analysis of the primary and secondary efficacy endpoints.

Reviewer Comments*: The Reviewer agrees with the design and endpoints of these studies which follow the current FDA Guidance for cIAI. The use of a blinded committee (i.e. the SAC) to make the assessment of clinical response is appropriate since this may reduce investigator biases. The pre-specified non-inferiority margins of 10% (Trial 008) and 12.5% (Trial 025) are also appropriate since both margins are smaller than the estimated effect size of antibacterial therapy in the treatment of cIAI based on historical data. Note that due to favorable findings observed from Trial 008, the Division agreed to a wider NI margin in Trial 025.*

Key Inclusion and Exclusion Criteria

The following are the key criteria for inclusion in Studies 008 and 025.

- Subjects aged at least 18 years
- Were hospitalized for cIAI with a diagnosis of intra-abdominal abscess, gastric or intestinal perforation associated with diffuse peritonitis, peritonitis due to perforated viscus or other focus of infection, appendicitis, cholecystitis, intra-abdominal abscess (single or multiple; including hepatic and splenic abscesses), or peritonitis (local or diffuse)
- Had evidence of a systemic inflammatory response of fever, elevated white blood cell (WBC) count, increased pulse (heart rate), or increased respiratory rate

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- Had abdominal pain or flank pain (with or without rebound tenderness), or pain caused by cIAI that was referred to another anatomic area such as back or hip, or localized or diffuse abdominal wall rigidity, or mass, or ileus

- And either
  - Met the criteria for preoperative enrollment:
    - Had sonogram or radiographic imaging results congruent with the diagnosis of cIAI, and
    - Acute surgical or percutaneous intervention (open laparotomy, laparoscopic surgery, or percutaneous drainage of an abscess) was foreseen within 48 hours
  - Or met intraoperative/postoperative criteria for enrollment:
    - Had visual confirmation of cIAI (presence of pus within the abdominal cavity), and
    - Surgical intervention included open laparotomy, laparoscopic surgery, or percutaneous draining of an abscess, and
    - Intervention was adequate (i.e., a procedure in which all communications between the GI tract and the peritoneal cavity were closed, no necrotic intestine was left, and all infected collections were drained at the procedure)

The following are the key criteria for exclusion in Studies 008 and 025.

- Considered unlikely to survive the 6- to 8-week study period.

- Had renal failure, possible signs of significant hepatic disease, an immunocompromised condition, known or suspected current central nervous system disorder or systemic malignancy

- Had a history of moderate or severe hypersensitivity reactions to tetracyclines, carbapenems, β-lactam antibiotics, or any of the excipients contained in the study drug formulations

- Had antibiotic-related exclusions
  - Receipt of effective antibacterial drug therapy for cIAI for a continuous duration of >24 hours during the 72 hours preceding enrollment (however, subjects with documented cIAI [i.e., known baseline pathogen] who had received at least 72 hours of antibiotic therapy and were considered treatment failures may have been enrolled.
  - Receipt of ertapenem or any other carbapenem or tigecycline for the current infection
  - Need for concomitant systemic antimicrobial agents other than the study drug

- Had known or suspected inflammatory bowel disease or associated visceral abscess

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- Was known at study entry to have cIAI caused by a pathogen(s) resistant to one of the study drugs

Protocol Amendments

Amendments made to the current versions of the protocols, Version 3.0 (31 October 2013) for Trial 008 and Version 2.0 (20 March 2017) for Trial 025 are summarized below. These amemdments took place after the start (first enrollment) of Trial 008 on 28 August 2013 and Trial 025 on 13 October 2016. These amendments were considered to be minor and unlikely to affect the integrity of the trials or the interpretation of the results.

Trial 008

1. Terminology: "Day" is distinguished from "Dosing Cycle" since "dosing cycle" can span more than one day. The expected duration of treatment for a study subject is specified to be between four and fourteen 24-h dosing cycles.
2. Exclusion Criteria: Subjects with a creatine clearance below 50 mL/min and subjects at increased risk of inadequate clinical response to study drug will be excluded.
3. Microbiology: Both blood cultures and cIAI specimens (i.e. tissue cultures) will be sent to a central laboratory as opposed to just blood cultures.
4. Concomitant medications: Concomitant use of valproic acid and divalproex sodium is not permitted.
5. Clinical cures: Patients receving routine imaging procuedures are considered as having a radiological intervention and therefore could potentially satisfy the criteria for a clinical cure.
6. Blinding: A blinded study site member will be responsible for the randomization of study subjects rather than the site pharmacist. The study blind may also be broken when it is considered to be in the best interest of the patient.
7. Dosing: The 12-h interval between doses can be reduced by up to 2 hours in each of the 3 initial 24-h dosing cycles. No infusion should skipped or missed.

Trial 025

8. Sample size assumptions: The planned blinded interim analysis to assess evaluability following completion of the 250th subject showed an evaluability rate of 68.75% which was lower the the 80% used to estimate the sample size required for the study. This resulted in an increase in the target study enrollment from 400 to 466 subjects.

Statistical Methodologies

Both studies were designed to demonstrate the non-inferiority of eravacyline 1.0 mg/kg q12h to comparator therapy (ertapenem 1.0 g q24h in Trial 008 and meropenem 1.0 g q8h in Trial

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025) in the micro-ITT population using a pre-specified NI margin of 10% (Trial 008) or 12.5% (Trial 025). Primary analyses considered unadjusted two-sided 95% confidence intervals based on the method of Miettinen and Nurminen to evaluate the difference in the proportions of clinical cures among micro-ITT subjects at TOC. If the lower limit of this confidence interval exceeded -10% (Trial 008) or -12.5% (Trial 025) then non-inferiority was demonstrated.

In the primary analysis, clinical cure rates at TOC were estimated using both the SAC and investigator assessments. The SAC made the final decision in evaluating the patient's clinical response for patients who were clinical failures or patients who were clinical cures who underwent a second surgical procedure which may be related to the cIAI. Patients with missing data at the TOC visit were classified as indeterminate/missing and counted the same as failures in estimating the clinical cure rate. All micro-ITT patients were included in the denominator of the clinical cure rate and only clinical cures were included in the numerator (i.e. no micro-ITT patients were excluded). If non-inferiority was demonstrated in the primary analysis then superiority testing would be performed.

Several secondary endpoints were also tested however this testing was not statistically controlled since no methodology for controlling the type I error rate associated with testing multiple secondary endpoints had been pre-specified.

The Reviewer followed the same general approach for the primary and secondary analyses of Trials 008 and 025. The Reviewer also considered additional sensitivity analyses to evaluate the robustness of the findings such as stratified analyses (e.g. stratification by primary site of infection, complicated appendicitis versus all other cIAI diagnoses), analyses requiring clinical cures to have complete resolution of all signs and symptoms, analyses with different assumptions for missing data (e.g. counting patients with missing/indeterminate outcomes as cures in both arms or as failures in the eravacycline arm and as cures in the comparator arm) and analyses using an alternative approach for the assessment at TOC (e.g. using the investigator assessment only).

7.2.1.2 Patient Disposition, Demographics and Baseline Characteristics

Patient disposition for Trials 008 and 025 is shown in **Table 20**.

In Trial 008, 270 and 271 subjects were randomized to the eravacycline and ertapenem arms, respectively, with 220 (81%) and 226 (83%) included in the micro-ITT (primary analysis population) and 246 (91%) and 255 (94%) completing the study. The slightly lower study completion rate in the eravacycline arm was related to an imbalance in the number of subjects who were lost to follow-up which was 15 (6%) in the eravacycline arm vs. 3 (1%) in the ertapenem arm. Premature discontinuations due to treatment were similar between the study arms at 15 (6%) vs. 16 (6%).

In Trial 025, 250 subjects were randomized to each of the eravacycline and meropenem arms with 195 (78%) and 205 (82%) included in the micro-ITT and 237 (95%) and 241 (96%)

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completing the study. Premature discontinuations due to treatment were similar between treatment arms at 10 (4%) vs. 8 (3%).

Table 20: Patient Disposition-ITT population

	Trial 008		Trial 025	
Population	**Eravacycline** n (%)	**Ertapenem** n (%)	**Eravacycline** n (%)	**Meropenem** n (%)
Randomized ITT	**270 (100)**	**271 (100)**	**250 (100)**	**250 (100)**
Not treated	0	3 (1)	0	1 (0)
MITT	270 (100)	268 (99)	250 (100)	249 (100)
Safety	270 (100)	268 (99)	250 (100)	249 (100)
Micro-ITT	220 (81)	226 (83)	195 (78)	205 (82)
CE-TOC	239 (89)	238 (88)	225 (90)	231 (92)
ME-TOC	198 (73)	199 (73)	174 (70)	194 (78)
Completed Study	**246 (91)**	**255 (94)**	**237 (95)**	**241 (96)**
Did not complete study	**24 (9)**	**16 (6)**	**13 (5)**	**9 (4)**
Lost to follow-up	15 (6)	3 (1)	6 (2)	4 (2)
Adverse Event	3 (1)	6 (2)	4 (2)	2 (1)
Withdrawal of consent	3 (1)	2 (1)	1 (0)	3 (1)
Subject noncompliance	2 (1)	3 (1)	2 (1)	0
Other	1 (0)	2 (1)	0	0
Discontinued treatment prematurely	**15(6)**	**16 (6)**	**10 (4)**	**8 (3)**
Adverse event	7 (3)	6 (2)	3 (1)	5 (2)
Lack of efficacy	4 (1)	3 (1)	1 (0)	0
Withdrawal of consent	2 (1)	2 (1)	2 (1)	3 (1)
Subject noncompliance	0	1 (0)	1 (0)	0
Other	2 (1)	4 (1)	3(1)	0

Source: Reviewer Table

Protocol Violations/Deviations

Table 21 provides a summary of protocol violations/deviations for Trials 008 and 025. In both trials, the number of subjects with minor protocol violation/deviations was higher in the eravacycline arm while the number of subjects with major protocol violations/deviations was higher in the comparator arm. The most common reason for major protocol deviations/violations was 'subject visit completion or timing'. In Trial 008, there were fewer eravacycline patients with this reason at 5 (2%) vs. 14 (5%) for ertapenem.

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Table 21: Subjects with Protocol Violation/Deviations

	Trial 008		Trial 025	
Measure	**Eravacycline** (N=270) n (%)	**Ertapenem** (N=271) n (%)	**Eravacycline** (N=250) n (%)	**Meropenem** (N=250) n (%)
Subjects with any protocol violation/deviation	197 (73)	179 (66)	161 (64)	143 (57)
Minor	197 (73)	176 (65)	157 (63)	137 (55)
Major	13 (5)	22 (8)	19 (8)	23 (9)
Type of major protocol deviation/violation				
SAE Reporting	0	0	4 (2)	4 (2)
Informed Consent	0	0	0	3 (1)
Inclusion/Exclusion	10 (4)	11 (4)	2 (1)	2 (1)
Subject visit completion or timing	5 (2)	14 (5)	11 (4)	10 (4)
Study medication	0	0	2 (1)	4 (2)
Other	1 (0)	1 (0)	1 (0)	2 (1)

Source: Reviewer Table
Note: Subjects can have multiple protocol violations/deviations.

Demographic Characteristics

Table 22 shows the demographic characteristics of patients in the primary analysis population (i.e. micro-ITT). In both trials, patients were well balanced across both treatment arms with respect to sex, age, age group, race, ethnicity and region. Demographic characteristics were also similar in cross-study comparisons of Trial 008 vs. Trial 025 with the exception that Trial 008 included more patients who were non-white (16 vs. 1) or from U.S. sites (32 vs. 8), though numbers for these subgroups were low in both trials.

Table 22: Demographic of the (micro-ITT population)

	Trial 008		Trial 025	
Demographic Parameters	**Eravacycline** (N=220) n (%)	**Ertapenem** (N=226) n (%)	**Eravacycline** (N=195) n (%)	**Meropenem** (N=205) n (%)
Sex				
Male	126 (57)	132 (58)	109 (56)	105 (51)
Female	94 (43)	94 (42)	86 (44)	100 (49)
Age				
Mean years (SD)	54.9 (17.1)	55.4 (16.2)	50.3 (17.7)	52.3 (18.3)
Median (years)	57	57	53	54
Min, max (years)	19, 86	20, 87	18, 84	19, 87
Age Group				
< 65 years	149 (68)	159 (70)	148 (76)	145 (71)

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≥ 65 years	71 (32)	67 (30)	47 (24)	60 (29)
Race				
White	214 (97)	215 (95)	194 (99)	205 (100)
Non-white	5 (2)	11 (5)	1 (1)	0
Missing/Unknown	1 (0)	0	0	0
Ethnicity				
Hispanic or Latino	6 (3)	8 (4)	3 (2)	0
Not Hispanic or Latino	213 (97)	218 (96)	186 (95)	195 (95)
Missing/Unknown	1 (0)	0	6 (3)	10 (5)
Region/Country				
United States	15 (7)	17 (8)	6 (3)	2 (1)
Russia/Ukraine/Georgia	55 (25)	48 (21)	58 (30)	60 (29)
Rest of Europe (including South Africa)	150 (68)	161 (71)	131 (67)	143 (70)

Source: Reviewer Table

Other Baseline Characteristics

Table 23 shows other baseline characteristics of patients in the micro-ITT population. In both trials, patients were well balanced across the treatment arms by primary diagnosis, procedure type, prior antibacterial use within 72 hours and APACHE II scores. Cross-study comparisons of Trial 008 vs. Trial 025 showed trials to be generally similar with the exception that Trial 008 was designed to include fewer patients with complicated appendicitis at baseline.

Table 23: Other Baseline Characteristics of the Primary Efficacy Analysis (micro-ITT Population)

	Trial 008		**Trial 025**	
Demographic Parameters	**Eravacycline** (N=220) n (%)	**Ertapenem** (N=226) n (%)	**Eravacycline** (N=195) n (%)	**Meropenem** (N=205) n (%)
Primary Diagnosis				
Complicated appendicitis	65 (30)	66 (29)	95 (49)	90 (44)
Other cIAI	155 (70)	160 (71)	100 (51)	115 (56)
Procedure Type				
Open	134 (61)	145 (64)	117 (60)	130 (63)
Laparoscopic	68 (31)	71 (31)	69 (35)	67 (33)
Percutaneous	25 (11)	19 (8)	12 (6)	15 (7)
Other	1 (0)	2 (1)	0	1 (0)
Prior systemic antibacterial use within 72 hours				
Yes	107 (49)	110 (48)	106 (54)	101 (49)

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No	113 (51)	116 (51)	89 (46)	104 (51)
APACHE II Score				
0-10	189 (86)	183 (81)	171 (88)	173 (84)
11-15	25 (11)	34 (15)	21 (11)	27 (13)
16-20	4 (2)	5 (2)	3 (2)	5 (2)
> 20	1 (0)	1 (0)	0	0
Misssing	1 (0)	3 (0)	0	0

Source: Reviewer Table

Reviewer Comments: *Nearly 50% of enrolled patients had received prior antibacterial drugs (24 hours or less) within 72 hours of the start of treatment. The cIAI guidance does not place a specific restriction on the percentage of patients who may receive up to 24 hours of prior antibiotic therapy. However, the guidance states that enrollment of these patients should be limited as much as possible as it is currently unclear as to how such patients may affect the primary outcome. We consider this in the subgroup analysis below.*

Treatment Compliance, Concomitant Medication Use and Rescue Therapy

Treatment differences in compliance, concomitant medication use and rescue therapy were observed to be relatively minor and unlikely to meaningfully impact primary analysis findings. In the micro-ITT population (eravacycline vs. comparator), the mean duration of treatment was 7.3 vs. 7.5 days in Trial 008 and 7.8 vs. 7.6 days in Trial 025. Nearly all subjects receiving study drug had an 80% or higher compliance to study drug administration in both studies. The number of patients using concomitant systemic antibacterial medications from the first dose of study drug through the TOC visit were similar between the eravacycline arm and the control arm in Trial 008 at 28 (13%) vs. 18 (8%) and in Trial 025 at 18 (9%) vs. 18 (9%). In both trials, the most common antibacterials for concomitant use were imidazole derivatives which were used in 11 (5%) vs. 8 (4%) subjects in Trial 008 and 10 (5%) vs. 5 (2%) subjects in Trial 025. Concomitant antibacterial medications were primarily administered to patients who were treatment failures. The number of patients using rescue medications for cIAI was also similar among treatments at 6 (3%) vs. 4 (2%) in Trial 008 and 6 (3%) vs. 6 (3%) in Trial 025.

7.2.1.3 Results for Primary Efficacy Endpoints

Table 24 shows the results for primary efficacy endpoints in Trials 008 and 025. In Trial 008, non-inferiority of Eravacycline IV therapy to comparator therapy (ertapenem IV) was demonstrated for the primary endpoint. The number of clinical cures at TOC was 191 (86.8%) in the eravacycline arm vs. 198 (87.6%) in the control arm, a difference of -0.8%. Since the lower confidence limit of the treatment difference was -7.1% which exceeded the pre-specified non-inferiority margin of -10%, non-inferiority was demonstrated. The number of clinical failures was slightly larger in the eravacycline arm at 19 (8.6%) vs. 11 (4.9%); however, this difference was not significant using Fisher's exact test (p-value=0.13).

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In Trial 025, non-inferiority of eravacycline IV therapy to meropenem IV was also demonstrated for the primary endpoint. The number of clinical cures was 177 (90.8%) in the eravacycline arm vs. 187 (91.2%) in the control arm, a difference of -0.5% (95% CI: -6.3%, 5.3%). Since the lower confidence limit was -6.3% which exceeded the pre-specified non-inferiority margin of -12.5%, non-inferiority was demonstrated. The percentage of clinical failures was observed to be similar in both treatment arms at 7 (3.6%) vs. 7 (3.4%).

Table 24: Clinical Cure Rates at TOC in the micro-ITT (Primary Analysis)

	Trial 008		Trial 025	
Classification	**Eravacycline (N=220) n (%)**	**Ertapenem (N=226) n (%)**	**Eravacycline (N=195) n (%)**	**Meropenem (N=205) n (%)**
Clinical Cure	191 (86.8)	198 (87.6)	177 (90.8)	187 (91.2)
Difference (95% CI)	-0.8 (-7.1, 5.5)		-0.5 (-6.3, 5.3)	
Clinical Failure	19 (8.6)	11 (4.9)	7 (3.6)	7 (3.4)
Indeterminate/Missing	10 (4.5)	17 (7.5)	11 (5.6)	11 (5.4)

Source: Reviewer Table

Table 25 provides the reasons for clinical failure and missing/indeterminate classifications in the primary analysis. In general, the distributions of patients across the possible reasons for clinical failure and missing/indeterminate classifications were similar between eravacycline vs. the comparator in both trials. The most common reasons for clinical failure in the trials included 'unplanned surgery or percutaneous drainage' and 'rescue antibacterial therapy for cIAI'. In cross-study comparisons, patients in Trial 008 showed higher clinical failure rates compared to patients in Trial 025 at 30/446 (6.7%) vs. 14/400 (3.5%).

Table 25: Reasons for Patients with Clinical Failure and Missing/Indeterminate Assessments at TOC (Primary Analysis, micro-ITT)

	Trial 008		Trial 025	
Classification	**Eravacycline (N=220)**	**Ertapenem (N=226)**	**Eravacycline (N=195)**	**Meropem (N=205)**
Clinical Failure, n (%)	**19 (8.6%)**	**11 (4.9%)**	**7 (3.6%)**	**7 (3.4%)**
Reason, number of patients (patients may have more than one reason)				
Unplanned surgery or percutaneous drainage	10	9	5	5

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Rescue antibacterial therapy for cIAI	6	4	6	6
Persistence of clinical symptoms of cIAI	5	4	1	3
Post-surgical wound infections requiring systemic antibiotics	5	2	2	0
Other	3	2	0	0
Surgical Adjudication Committere	0	1	0	1
Death due to cIAI	0	0	0	0
Missing/Indeterminate, n (%)	**10 (4.5%)**	**17 (7.5%)**	**11 (5.6%)**	**11(5.4%)**
Reason, number of patients				
Failure to meet eligibility criteria	0	1	1	1
Withdrawal of consent	1	2	1	3
Non-compliance with follow-up visits	2	2	1	0
Lost-to-follow-up	2	2	1	0
AEs	2	5	2	3
Inadequate source control determined by SAC	3	5	2	1
Other	0	0	3	3

Source: Reviewer Table

Table 26 shows findings from Reviewer sensitivity analyses which considered alternative assumptions to evaluate the robustness of primary analysis findings. These analyses included stratification in the primary analysis (e.g. stratification by primary site of infection), analyses requiring clinical cures to have complete resolution, different imputation methods (e.g. counting indeterminate/missing as successes rather than failures or a worst case analysis in which indeterminate/missing were counted as successes in the comparator arm and failures in the eravacycine arm) and different approaches for assessment (e.g. investigator only assessments).

Overall, sensitivity analyses were generally consistent with primary analysis findings with lower limits mostly near the pre-specified NI margin of -10% and -12.5% used in Trials 008 and 025, respectively. In analyses requiring cures to have complete resolution, clinical cure rates favored the comparator in both trials with differences that were slightly more pronounced than in the primary analyses, resulting in lower limits for the treatment difference of -11.7% in Trial 008 and -8.9% in Trial 025. A worst case analysis of missing data (assuming missing as failures for eravacycline and cures for the comparator) showed even more pronounced treatment

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differences favoring the comparator as would be expected with lower limits of -13.9% for Trial 008 and -11.1% for 025. However, since this is an analysis to assess the extreme, but unlikely, impact of missing data, it is notable that Trials 025 would still have met its pre-specified non-inferiroity margin. In Trial 025, all sensivity analyses showed lower confidence limits above the -12.5% limit which indicates that primary analyses in Trial 025 were highly robust.

Table 26: Reviewer Sensitivity Analyses of Primary Endpoint: Clinical Cure Rates at TOC in the micro-ITT

	Trial 008		Trial 025	
Classification	**Eravacycline (N=220) n (%)**	**Ertapenem (N=226) n (%)**	**Eravacycline (N=195) n (%)**	**Meropem (N=205) n (%)**
Clinical Cures must have complete resolution of all signs and symptoms[1]				
Clinical Cure	163 (74.1)	176 (77.9)	160 (82.1)	171 (83.4)
Difference (95% CI)	-3.8 (-11.7, 4.2)		-1.4 (-8.9, 6.1)	
Improved[2]	28 (12.7)	22 (9.7)	17 (8.7)	16 (7.8)
Clinical Failure	19 (8.6)	11 (4.9)	7 (3.6)	7 (3.4)
Indeterminate/Missing	10 (4.5)	17 (4.5)	11 (5.6)	11 (5.4)
Indeterminate/missing counted as clinical cures				
Clinical Cure	201 (91.4)	215 (95.1)	188 (96.4)	198 (96.6)
Difference (95% CI)	-3.8 (-8.8, 0.9)		-0.2 (-4.2, 3.8)	
Clinical Failure	19 (8.6)	11 (4.9)	7 (3.6)	7 (3.4)
Indeterminate/missing counted as clinical cures for the comparator and as failures for eravacycline				
Clinical Cure	191 (86.8)	215 (95.1)	177 (90.8)	198 (96.6)
Difference (95% CI)	-8.3 (-13.9, -3.1)		-5.8 (-11.1, -1.1)	
Clinical Failure	29 (13.2)	11 (4.9)	18 (9.2)	7 (3.4)
Investigator assessment used for clinical response (No SAC assessment)				
Clinical Cure	192 (87.3)	200 (88.5)	177 (90.8)	188 (91.7)
Difference (95% CI)	-1.2 (-7.4, 4.9)		-0.9 (-6.7, 4.7)	
Clinical Failure	21 (9.5)	14 (6.2)	9 (4.6)	7 (3.4)
Indeterminate/Missing	7 (3.2)	12 (5.3)	9 (4.6)	10 (4.9)

Source: Reviewer Table

1- Signs and symptoms included abdominal pain, fluctuance, ileus, induration, nasogastric tube present, discharge (non-purulent, purulent, serous,mucoid), mass, organ/space wound infection, rebound tenderness, skin erythema, stitch fistula, superficial wound pain, tenderness and tenderness to palpation.

2- Patient was not a clinical cure due to lack of complete resolution of all signs and symptoms.

Note: Analyses adjusting for type of infection were also performed and showed findings which were similar to findings in the primary analysis.

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7.2.1.4 Results for Secondary Efficacy Endpoints

The Sponsor's pre-specified secondary endpoints evaluated clinical response using alternative time points (EOT, TOC and FU) and/or analysis populations (CE-EOT, CE-TOC, CE-FU, ME-EOT, ME-TOC and ME-FU). **Table 27** and **Table 28** present secondary analysis findings for the ITT-based and evaluable analysis populations, respectively. In general, clinical cure rates decreased over time mostly due to increases in indeterminate/missing data. Although there were comparisons in Trial 008 at the follow-up visit where the lower confidence limits fell as low as -11.9%, overall findings were still considered to be generally consistent with the conclusion of non-inferiority.

Among ITT patients in Trial 008, there were 3 deaths (1.1%) in the eravacycline arm vs. 6 deaths (2.2%) for the ertapenem arm. In Trial 025 there were 4 deaths (2.1%) in the eravacycline arm vs. 1 death (0.4%) for the meropenem. All of these deaths were considered by the Sponsor to be unrelated to the treatment. In Trial 008, 7 of 9 patients with deaths were excluded from the clinically evaluable population at TOC while in Trial 025, 4 of 5 patients with deaths were excluded.

Reviewer Comments*: Analyses of these secondary endpoints are descriptive (not statistically controlled) and were not intended for making inferences of non-inferiority. In addition, it is unclear what an appropriate NI margin would be at different time points and using these alternative analysis populations.*

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Table 27: Clinical Cure Rates- ITT and Micro-ITT Populations

	Trial 008			Trial 025		
Population Visit	**Eravacycline n (%)**	**Ertapenem n (%)**	**Difference (95% CI)**	**Eravacycline n (%)**	**Meropenem n (%)**	**Difference (95% CI)**
	Intent to Treat Based Populations					
ITT	N=270	N=271		N=250	N=250	
EOT						
Clinical Cure	248 (91.9)	253 (93.4)	-1.5 (-6.1, 3.0)	235 (94.0)	234 (93.6)	0.4 (-4.0, 4.8)
Clinical Failure	15 (5.6)	7 (2.6)		7 (2.8)	3 (1.2)	
Indet./Missing	7 (2.6)	11 (4.1)		8 (3.2)	13 (5.2)	
TOC						
Clinical Cure	235 (87.0)	238 (87.8)	-0.8 (-6.5, 4.9)	231 (92.4)	228 (91.2)	1.2 (-3.7, 6.2)
Clinical Failure	19 (7.0)	15 (5.5)		7 (2.8)	9 (3.6)	
Indet./Missing	16 (5.9)	18 (6.6)		12 (4.8)	13 (5.2)	
FU						
Clinical Cure	222 (82.2)	236 (87.1)	-4.9 (-11.0, 1.2)	224 (89.6)	226 (90.4)	-0.8 (-6.2, 4.6)
Clinical Failure	20 (7.4)	15 (5.5)		9 (3.6)	10 (4.0)	
Indet./Missing	28 (10.4)	20 (7.4)		17 (6.8)	14 (5.6)	
Micro-ITT	N=220	N=226		N=195	N=205	
EOT						
Clinical Cure	201 (91.4)	211 (93.4)	-2.0 (-7.2, 3.0)	181 (92.8)	193 (94.1)	-1.3 (-6.5, 3.7)
Clinical Failure	15 (6.8)	5 (2.2)		7 (3.6)	3 (1.5)	
Indet./Missing	4 (1.8)	10 (4.4)		7 (3.6)	9 (4.4)	
TOC [1]						
Clinical Cure	*191 (86.8)*	*198 (87.6)*	*-0.8 (-7.1, 5.5)*	*177 (90.8)*	*187 (91.2)*	*-0.5 (-6.3, 5.3)*
Clinical Failure	*19 (8.6)*	*11 (4.9)*		*7 (3.6)*	*7 (3.4)*	
Indet./Missing	*10 (4.5)*	*17 (7.5)*		*11 (5.6)*	*11 (5.4)*	
FU						

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Clinical Cure	181 (82.3)	196 (86.7)	-4.5 (-11.3, 2.3)	170 (87.2)	185 (90.2)	-3.1 (-9.5, 3.2)
Clinical Failure	20 (9.1)	11 (4.9)		9 (4.6)	8 (3.9)	
Indet./Missing	19 (8.6)	19 (8.4)		16 (8.2)	12 (5.9)	

Source: Reviewer Table
1- Primary analysis

Table 28: Clinical Cure Rates- Evaluable Populations

	Trial 008			**Trial 025**		
Population Visit	**Eravacycline n (%)**	**Ertapenem n (%)**	**Difference (95% CI)**	**Eravacycline n (%)**	**Meropenem n (%)**	**Difference (95% CI)**
	Clinically Evaluable					
CE-EOT EOT	N=252	N=255		N=239	N=237	
Clinical Cure	238 (94.4)	250 (98.0)	-3.6 (-7.4,-0.3)	232 (97.1)	234 (98.7)	-1.7 (-4.8, 1.1)
Clinical Failure	14 (5.6)	5 (2.0)		7 (2.9)	3 (1.3)	
CE-TOC TOC	N=239	N=238		N=225	N=231	
Clinical Cure	222 (92.9)	225 (94.5)	-1.7 (-6.3, 2.8)	218 (96.9)	222 (96.1)	0.8 (-2.9, 4.5)
Clinical Failure	17 (7.1)	13 (5.5)		7 (3.1)	9 (3.9)	
CE-FU FU	N=208	N=212		N=229	N=231	
Clinical Cure	211 (91.7)	228 (94.6)	-2.9 (-7.8, 1.8)	220 (96.1)	221 (95.7)	0.4 (-3.5, 4.3)
Clinical Failure	19 (8.3)	13 (5.4)		9 (3.9)	10 (4.3)	
	Microbiologically Evaluable					
ME-EOT EOT	N=239	N=238		N=187	N=196	
Clinical Cure	194 (93.3)	208 (98.1)	-4.8 (-9.3,-1.1)	180 (96.3)	193 (98.5)	-2.2 (6.2, 1.2)
Clinical Failure	14 (6.7)	4 (1.9)		7 (3.7)	3 (1.5)	
ME-TOC TOC	N=198	N=199		N=174	N=194	
Clinical Cure	181 (91.4)	189 (95.0)	-3.6 (-8.9, 1.5)	167 (96.0)	187 (96.4)	-0.4 (-4.9, 3.8)
Clinical Failure	17 (8.6)	10 (5.0)		7 (4.0)	7 (3.6)	
ME-FU FU	N=190	N=200		N=177	N=192	

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Clinical Cure	171 (90.0)	190 (95.0)	-5.0 (-10.7, 0.2)	168 (94.9)	184 (95.8)	-0.9 (-5.7, 3.6)
Clinical Failure	19 (10.0)	10 (5.0)		9 (5.1)	8 (4.2)	

Source: Reviewer Table

Reviewer Comments: *Analyses in ITT-based populations are generally recommended over analyses in evaluable populations which can involve post-randomization exclusions affected by the treatment received and this can lead to potential biases. However, they are helpful in the assessment of a non-inferiority trial and are therefore presented in this Review.*

7.2.1.5 Findings in Special/Subgroup Populations

7.2.1.5.1 Gender, Race, Age, Geographic Region

Table 29 shows subgroup analyses of the primary endpoint by gender, race, age and geographic region. Overall, there were no major differences in findings among these subgroups that would affect primary inferences. Note that subgroup analyses by race (white vs. other) and by geographic region (U.S. vs. non-U.S) were limited due to the high percentage of white patients (96% in Trial 008 and > 99% in Trial 025) and non-US patients (93% in Trial 008 and 96% in Trial 025).

Table 29: Clinical Cure Rates by Gender, Race, Age and Geographic Region

	Trial 008			Trial 025		
Subgroup	**Eravacycline (N=220)**	**Ertapenem (N=226)**	**Difference (95% CI)**	**Eravacycline (N=195)**	**Meropenem (N=205)**	**Difference (95% CI)**
Gender						
Male	107/126 (84.9)	117/132 (88.6)	-3.7 (-12.3, 4.7)	98/109 (89.9)	95/105 (90.5)	-0.6 (-8.9, 7.9)
Female	84/94 (89.4)	81/94 (86.2)	3.2 (-6.5, 13.0)	79/86 (91.9)	92/100 (92.0)	-0.1 (-8.9, 8.1)
Race	N=219[1]	N=226				
White	186/214 (86.9)	190/215 (88.4)	-1.5 (-7.8, 4.9)	176/194 (90.7)	187/205 (91.2)	-0.5 (-6.4, 5.3)
Other	4/5 (80.0)	8/11 (72.7)	7.3 (-42.7, 45.2)	1/1 (100)	0	n.e.
Age						
< 65 yrs	132/149 (88.6)	142/159 (89.3)	-0.7 (-8.0, 6.4)	136/148 (91.9)	134/145 (92.4)	-0.5 (-7.0, 6.0)
≥ 65 yrs	59/71 (83.1)	56/67 (83.6)	-0.5 (-13.2, 12.4)	41/47 (87.2)	53/60 (88.3)	-1.1 (-15.1, 11.7)
Region	N=220	N=225[2]				
U.S.	11/15 (73.3)	10/17 (58.8)	14.5	4/6 (66.7)	1/2 (50.0)	16.7

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			(-19.0, 44.6)			(-47.9,72.9)
Europe (Non-EU):	49/55 (89.1)	43/48 (89.6)	-0.5 (-13.2, 12.8)	56 /58 (96.6)	53/60 (88.3)	8.2 (-1.7, 19.3)
Europe (EU)	131/150 (87.3)	144/160 (90.0)	-2.7 (-10.1, 4.5)	117/131 (89.3)	133/143 (93.0)	-3.7 (-11.0, 3.1)

Source: Reviewer Table
1 One eravacycline patient had missing race information and was not included.
2 One ertapenem patient from South Africa who was a cure is not included.
Note: n.e. denotes 'not estimable'

7.2.1.5.2 Other Baseline Variables

Table 30 presents subgroup analyses of the primary endpoint by other baseline variables. These analyses can assess treatment effects in certain subgroups which could be less susceptible to biases in a non-inferiority study (e.g. patients with no prior antibiotics and patients with more severe disease). Overall, there were no major differences in findings among subgroups of interest that would affect primary inferences. **Table 31** presents subgroup analyses by baseline pathogen.

Table 30: Clinical Cure Rates by Other Baseline Variables (Study 008)

	Trial 008			**Trial 025**		
	Eravacycline (N=220)	**Ertapenem (N=226)**	**Difference (95% CI)**	**Eravacycline (N=195)**	**Meropenem (N=205)**	**Difference (95% CI)**
Primary Diagnosis						
Complicated appendicitis	56/65 (86.2)	57/66 (86.4)	-0.4 (-12.8, 11.8)	86/95 (90.5)	81/90 (90.0)	0.5 (-8.4, 9.7)
Other cIAI	135/155 (87.1)	141/160 (88.1)	-1.0 (-8.5, 6.5)	91/100 (91.0)	106/115 (92.2)	-1.2 (-9.4, 6.5)
Procedure Type[1]						
Open	115/134 (85.8)	125/145 (86.2)	-0.4 (-8.8, 7.9)	104/117 (88.9)	118/130 (90.8)	-1.9 (-10.0, 5.8)
Laparoscopic	59/68 (86.8)	64/71 (90.1)	-3.4 (-14.8, 7.7)	64/69 (92.8)	62/67 (92.5)	0.2 (-9.5, 10.1)
Percutaneous	23/25 (92.0)	17/19 (89.5)	2.5 (-16.8, 25.0)	11/12 (91.7)	13/15 (86.7)	5.0 (-25.2, 32.1)
Other	1/1 (100)	1/2 (50.0)	50.0 (-64.2, 93.1)	0	1/1 (100)	n.e.
Prior Antibiotic Use						
Yes	89/107 (83.2)	92/110 (83.6)	-0.5 (-10.6, 9.6)	90/105 (85.7)	90/101 (89.1)	-3.4 (-12.8, 6.0)
No	102/113 (90.3)	106/116 (91.4)	-1.1 (-9.1, 6.7)	87/90 (96.7)	97/104 (93.3)	3.4 (-3.5, 10.4)

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APACHE II Score[2]						
0-10	165/189 (87.3)	164/183 (89.6)	-2.3 (-9.0, 4.3)	156/171 (91.2)	159/173 (91.9)	-0.7 (-6.8, 5.4)
> 10	25/30 (83.3)	33/40 (82.5)	0.8 (-18.7, 18.6)	21/24 (87.5)	28/32 (87.5)	0.0 (-20.6, 18.3)

Source: Reviewer Table
1 Some patients had more than one procedure type at baseline
2 In Trial 008, 1 patient in the eravacycline arm and 3 patients in the ertapenem arm had missing APACHE II Scores

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Table 31: Clinical Cure Rates by Baseline Pathogen (Micro-ITT)

	Trial 008		Trial 025	
Pathogen	**Eravacycline (N=220)**	**Ertapenem (N=226)**	**Eravacycline (N=195)**	**Meropenem (N=205)**
Enterobacteriaceae	142/168 (84.5)	147/171 (86.0)	129/146 (88.4)	142/154 (92.2)
Citrobacter freundii	14/15 (93.3)	7/9 (77.8)	5/7 (71.4)	1/1 (100.0)
Enterobacter cloacae complex	10/14 (71.4)	18/18 (100.0)	7/7 (100.0)	5/6 (83.3)
Escherichia coli	109/127 (85.8)	112/132 (84.8)	111/126 (88.1)	125/134 (93.3
Klebsiella oxytoca	7/7 (100.0)	12/13 (92.3)	7/8 (87.5)	4/6 (66.7)
Klebsiella pneumoniae	16/18 (88.9)	19/23 (82.6)	21/21 (100)	23/27 (85.2)
Acinetobacter baumanii	8/8 (100.0)	5/5 (100.0)	5/5 (100.0)	2/2 (100.0)
Enterococcus faecalis	16/23 (69.6)	21/26 (80.8)	29/31 (93.5)	26/28 (92.9)
Enterococcus faecium	13/16 (81.3)	26/30 (86.7)	25/29 (86.2)	22/23 (95.7)
Staphylococcus aureus (methicillin-susceptible)	8/8 (100.0)	5/6 (83.3)	16/16 (100)	7/8 (87.5)
Streptococcus anginosus group[a]	40/47 (85.1)	19/26 (73.1)	39/45 (86.7))	31/33 (93.9
Streptococcus mitis group[b]	6/7 (85.7)	16/17 (94.1)	0	0
Streptococcus salivarius group[c]	7/8 (87.5)	9/9 (100.0)	2/2 (100.0)	3/4 (75.0)
Anaerobes	88/106 (83.0)	92/105 (87.6)	98/109 (89.9)	102/109 (93.6)
Bacteroides caccae	8/11 (72.7)	2/2 (100.0)	5/6 (83.3)	5/5 (100.0)
Bacteroides fragilis	39/44 (88.6)	38/42 (90.5)	33/40 (82.5)	35/38 (92.1)
Bacteroides ovatus	13/19 (68.4)	15/17 (88.2)	19/24 (79.2)	28/28 (100.0)
Bacteroides thetaiotaomicron	23/26 (88.5)	17/20 (85.0)	27/30 (90.0)	30/33 (90.9)
Bacteroides uniformis	5/6 (83.3)	5/5 (100.0)	14/16 (87.5)	14/14 (100.0)
Bacteroides vulgatus	10/12 (83.3)	14/17 (82.4)	27/28 (96.4)	23/23 (100.0)
Clostridium perfringens	6/9 (66.7)	9/9 (100.0)	7/7 (100.0)	12/12 (100.0)
Parabacteroides distasonis	5/8 (62.5)	5/5 (100.0)	14/16 (87.5)	9/9 (100.0)

Source: Partially Adapted from Table 22 in SCE

[a] Includes *Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus intermedius*

[b] Includes *Streptococcus mitis*, *Streptococcus oralis*, *Streptococcus sanguinis*, *Streptococcus parasanguinis*, *Streptococcus gordonii*, and *Streptococcus cristatus*

[c] Includes *Streptococcus salivarius* and *Streptococcus vestibularis*

7.2.2 Additional Phase 2 Trial, Trial TP-434-P2-cIAI-1

7.2.2.1 Trial Design and Endpoints

Trial TP-434-P2-cIAI-1 was a Phase 2, randomized, double-blind, double-dummy, multicenter, prospective proof-of-concept study in hospitalized subjects with cIAIs requiring

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surgery or percutaneous drainage. Patients were randomized with a 2:2:1 allocation to either eravacycline 1.5 mg q24h, eravacycline 1.0 mg q12h, or ertapenem 1.0g q24h therapy. The randomization was stratified by primary site of infection (complicated appendicitis versus all other diagnoses).

Eligible patients were adults with abdominal pain who were diagnosed with a cIAI that required surgery or percutaneous drainage with hospitalization. Patients with complicated appendicitis were limited to 50% of enrolled patients. Eligible patients also could not receive prior administration of systemic antibacterial agents unless dosing of the antibiotic was less than 24 hours and would not be expected to eradicate the infection.

Patients included in this trial received 4 to 14 days of treatment (4 to 7 days for subjects in India). Clinical response was evaluated at the EOT visit occurring within 24 hours of the last dose of study drug, the TOC visit (10-14 Days after EOT) and the FU visit (28-42 days after EOT). The analysis populations included the ITT (all randomized patients), the MITT (ITT patients receiving study drug), the clinical MITT (c-MITT, MITT patients who met the minimal disease definition for IAI) and the micro-MITT (clinical MITT patients with a valid baseline pathogen identified, regardless of susceptibility to study drug). Other analysis populations included the CE (ME) populations in which MITT (micro-MITT) subjects were required to have sufficient information available to determine their outcome with no confounding factors present that interfered with the assessment of that outcome.

The primary endpoint was defined as clinical response at TOC in the ME population. The clinical response rate was determined as the number of subjects with clinical cure (complete or significant improvement of signs or symptoms such that no further systemic antibiotic treatment was required) at the TOC visit divided by the number of subjects in the analysis population. Secondary endpoints included clinical response at the EOT, TOC, and FU visits evaluated in the MITT, c-MITT, micro-MITT, CE, and ME populations (except for clinical response at TOC in the ME). Additional secondary endpoints included microbiological response at EOT and TOC in the micro-MITT and ME populations.

Reviewer Comments*: In contrast to Trials 008 and 025, Trial TP-434-P2-cIAI-1 was descriptive and not designed to show non-inferiority; its primary analysis population was the ME rather than the micro-ITT population; its timing of the TOC and FU visits depended on the duration of patient therapy; and it did not include an independent surgical assessment committee (SAC) to determine adequate surgical source control* in evaluating clinical response.

Note that we recommend ITT based populations to avoid post-baseline exclusions affected by the treatment which can lead to biases, fixed timing of endpoint assessment to control for effects due to differences in timing (such effects were limited in Trial TP-434-P2-cIAI-1 since mean *differences in visit timing were within 12 hours across treatments) and the use of an independent SAC.*

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7.2.2.1 Statistical Methodologies

For the primary and secondary endpoints related to clinical response, unadjusted response rates were computed for each treatment arm along with exact two-sided 95% CIs calculated using the Clopper-Pearson method. Treatment differences were also computed using an exact two-sided 95% CI based on the binomial Z1 statistic (Chan and Zhang). No adjustments were made for multiple test arms in this exploratory study. Note also that in secondary analyses, no adjustments were made for testing multiple endpoints against placebo in three study arms.

The planned sample size for this study was 150 randomized subjects (60 subjects in each eravacycline arm and 30 subjects in the ertapenem arm) which was expected to provide at least 115 ME subjects for the primary analysis. This sample size was chosen out of practical considerations.

Reviewer Comments: *This study is not designed to demonstrate non-inferiority (or superiority) since no formal testing of statistical hypotheses was planned. The primary goal of this proof-of-concept study was to determine the optimal dose of eravacycline and whether it may merit further study.*

7.2.2.2 Patient Disposition and Baseline and Demographics

Table 32 shows the patient disposition of randomized subjects in Trial *TP-434*-P2-cIAI-1. There were 56, 57 and 30 subjects randomized to the eravacycline 1.5 mg/kg q24h, eravacycline 1.0 mg/kg q12h and ertapenem 1.0 g q24h arms, respectively, with 44 (79%), 49 (86%) and 26 (87%) completing the study. Overall, there did not appear to be any notable differences between treatments related to subject disposition considering that a high degree of variability in point estimates would be expected given the small sample sizes, especially in the ertapenem arm.

Table 32: Patient Disposition-ITT population

Population	**Eravacycline 1.5 mg/kg q24h** n (%)	**Eravacycline 1.0 mg/kg q12h** n (%)	**Ertapenem 1.0 g q24h** n (%)
Randomized ITT	**56 (100)**	**57 (100)**	**30 (100)**
Not treated	2 (4)	1 (2)	1 (3)
MITT	54 (96)	56 (98)	29 (97)
Safety	54 (96)	56 (98)	29 (97)
c-MITT	54 (96)	56 (98)	29 (97)
micro-MITT	45 (80)	47 (82)	27 (90)
CE	49 (88)	48 (84)	28 (93)
ME	42 (75)	41 (72)	26 (87)
Completed Study	**44 (79)**	**49 (86)**	**26 (87)**

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Did not complete study	**12 (21)**	**8 (14)**	**4 (13)**
Lost to follow-up	5 (9)	3 (5)	2 (7)
Withdrawal of consent	0	4 (7)	0
Physician Decision	1 (2)	0	1 (3)
Not treated	2 (4)	1 (2)	1 (3)
Other	4 (7)	0	0
Discontinued treatment prematurely	**2 (4)**	**3 (5)**	**2 (7)**
Adverse event	2 (4)	0	2 (7)
Withdrawal of consent	0	3 (5)	0

Source: Reviewer Table

Demographic Characteristics

Table 33 shows the demographic characteristics of patients in the MITT population. Due to small numbers of patients in each classification with respect to sex, age group, race, ethnicity, country, primary diagnosis, prior systemic antibiotic use and APACHE II scores, some minor imbalances across the study arms were observed. However, these imbalances were not a major concern given the exploratory nature of this trial.

Table 33: Demographic Characteristics of the Primary Efficacy Analysis (MITT)

Demographic Parameters	**Eravacycline 1.5 mg/kg q24h** (N=54) n (%)	**Eravacycline 1.0 mg/kg q12h** (N=56) n (%)	**Ertapenem 1.0 g q24h** (N=29) n (%)
Sex			
Male	37 (69)	42 (75)	21 (72)
Female	17 (31)	14 (25)	8 (28)
Age			
Mean years (SD)	43.6 (17.9)	41.8 (17.2)	41.3 (17.7)
Median (years)	44	39	38
Min, max (years)	18, 74	18, 74	18, 74
Age Group			
< 65 years	45 (83)	51 (91)	25 (86)
≥ 65 years	9 (17)	5 (9)	4 (14)
Race			
White	38 (70)	36 (64)	21 (72)
Asian	16 (30)	20 (36)	8 (28)
Ethnicity			
Hispanic or Latino	1 (2)	1 (2)	0
Not Hispanic or Latino	53 (98)	55 (98)	29 (100)
Country			
United States	0	0	1 (3)

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India	16 (30)	20 (36)	8 (28)
Lithuania	17 (31)	13 (23)	7 (24)
Latvia	8 (15)	9 (16)	4 (14)
Bulgaria	7 (13)	5 (9)	3 (10)
Romania	6 (11)	9 (16)	6 (21)
Primary Diagnosis			
Complicated appendicitis	29 (54)	31 (55)	15 (52)
Other cIAI	25 (46)	25 (45)	14 (48)
Prior systemic antibacterial use			
Yes	18 (33)	26 (46)	11 (38)
No	36 (67)	30 (54)	18 (62)
APACHE II Score			
0-5	14 (26)	27 (48)	13 (45)
6-10	26 (48)	20 (36)	15 (52)
> 10	14 (26)	9 (16)	1 (3)

Source: Reviewer Table

7.2.2.3 Results for Primary and Secondary Efficacy Endpoints

Table 34 shows treatment comparisons of clinical cure rates at EOT, TOC and FU in the ME, micro-MITT and MITT populations. Although this trial was not designed as a non-inferiority trial, informal comparisons were considered assuming a 10% NI margin. In comparisons of eravacycline 1.0 mg/kg q12h vs. ertapenem 1.0 g q24h arm in the ME population, clinical cure rates at TOC and FU showed lower 95% confidence limits above -10% which was consistent with non-inferiority. However, this does not consider the multiple comparisons due to the two test arms and uses an analysis population that excludes subjects based on post-treatment information. Considering the TOC visit in the micro-MITT population, the clinical cure rate was 87.2% in the eravacycline 1.0 mg/kg q12h arm compared to 88.9% in the ertapenem 1.0 g q24h arm with a difference of -1.7 and a wide 95% confidence interval of (-25.9%, 20.8). Note that the lower limit is substantially below -10%. Due to the study's descriptive nature and limited power for detecting treatment differences or ruling out margins of interest for most of the comparisons, it is difficult to make reliable inferences regarding these findings.

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Table 34- Cure Rates in ME, Micro-MITT and MITT Populations

Classification	Eravacycline 1.5 mg/kg q24h n (%)	Eravacycline 1.0 mg/kg q12h n (%)	Ertapenem 1.0 g q24h n (%)
ME Population	N=42	N=41	N=26
EOT			
Cure	40 (95.2)	41 (100)	25 (96.2)
Difference (vs. Ertapenem)	-0.9 (-26.1, 22.0)	3.8 (-12.2, 36.2)	-
Failure	2 (4.8)	0	1 (3.8)
TOC (primary endpoint)			
Cure	39 (92.9)	41 (100)	24 (92.3)
Difference (vs. Ertapenem)	0.5 (-23.1, 25.2)	7.7 (-6.7, 40.9)	-
Failure	3 (7.1)	0	2 (7.7)
FU			
Cure	36 (85.7)	39 (95.1)	21 (80.8)
Difference (vs. Ertapenem)	4.9 (-17.8, 30.2)	14.4 (-4.8, 43.2)	-
Failure	4 (9.5)	0	2 (7.7)
Indeterminate	2 (4.8)	2 (4.9)	3 (11.5)
Micro-MITT Population	N=45	N=47	N=27
EOT			
Cure	41 (91.1)	44 (93.6)	26 (96.3)
Difference (vs. Ertapenem)	-5.2 (-34.1, 12.8)	-2.7 (-29.5, 17.2)	-
Failure	2 (4.4)	0	1 (3.7)
Indeterminate	2 (4.4)	3 (6.4)	0
TOC			
Cure	39 (86.7)	41 (87.2)	24 (88.9)
Difference (vs. Ertapenem)	-2.2 (-26.7, 20.3)	-1.7 (-25.9, 20.8)	-
Failure	3 (6.7)	0	2 (7.4)
Indeterminate	3 (6.7)	6 (12.8)	1 (3.7)
FU			
Cure	36 (80.0)	39 (83.0)	22 (81.5)
Difference (vs. Ertapenem)	-1.5 (-25.3, 21.7)	1.5 (-21.3, 25.4)	-
Failure	4 (8.9)	0	2 (7.4)
Indeterminate	5 (11.1)	8 (17.0)	3 (11.1)
MITT Population	N=54	N=56	N=29
EOT			
Cure	49 (90.7)	52 (92.9)	28 (96.6)
Difference (vs. Ertapenem)	-5.8 (-34.4, 9.7)	-3.7 (-30.1, 13.9)	-
Failure	2 (3.7)	1 (1.8)	1 (3.4)

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Indeterminate	3 (5.6)	3 (5.4)	0
TOC			
Cure	46 (85.2)	47 (83.9)	26 (89.7)
Difference (vs. Ertapenem)	-4.5 (-28.8, 15.7)	-5.7 (-30.1, 14.0)	-
Failure	3 (5.6)	1 (1.8)	2 (6.9)
Indeterminate	5 (9.3)	8 (14.3)	1 (3.4)
FU			
Cure	41 (75.9)	45 (80.4)	24 (82.9)
Difference (vs. Ertapenem)	-6.8 (-30.3, 14.2)	-2.4 (-24.9, 19.7)	-
Failure	4 (7.4)	1 (1.8)	2 (6.9)
Indeterminate	9 (16.7)	10 (17.9)	3 (10.3)

Source: Reviewer Table

Reviewer Comments: *Due to the descriptive nature of this trial and small sample sizes, especially for the ertapenem arm, subgroup analyses for variables such as gender, race, age were not conducted.*

7.3 Integrated Review of Effectiveness

Table 35 presents results for a pooled analysis of the primary endpoint in Trials 008 and 025 using the micro-ITT populations. Primary analysis findings from the individual studies are also shown for comparison. Pooling of Trials 008 and 025 was limited due to the different comparators that were used in these trials (i.e. ertapenem in Trial 008 and meropenem in Trial 025).

Primary analysis findings from the pooled and individual studies showed similar treatment differences ranging between 0.5% to 0.8% in favor of the comparator. However, due to the larger sample size (less variability) in the pooled analysis, its lower confidence limit of the treatment difference was more favorable. Pooled analysis finding showed clinical cure rates (eravacycline vs. comparators) of 88.7% vs. 89.3%, an adjusted difference of -0.6% (-4.8%, 3.6%) using trial as a stratification factor.

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Table 35: Clinical Cure Rates in Individual and Pooled Analyses (micro-ITT Population)

Micro-ITT Population	Trial 008		Trial 025		Pooled	
	Eravacycline (N=220) n (%)	Ertapenem (N=226) n (%)	Eravacycline (N=195) n (%)	Meropenem (N=205) n (%)	Eravacycline (N=415) n (%)	Comparators (N=431) n (%)
Clinical Cure	191 (86.8)	198 (87.6)	177 (90.8)	187 (91.2)	368 (88.7)	385 (89.3)
Difference, 95% CI	-0.8 (-7.1, 5.5)		-0.5 (-6.3, 5.3)		-0.6 (-4.8, 3.6)[1]	
Clinical Failure	19 (8.6)	11 (4.9)	7 (3.6)	7 (3.4)	26 (6.3)	18 (4.2)
Indet./Missing	10 (4.5)	17 (7.5)	11 (5.6)	11 (5.4)	21 (5.1)	28 (6.5)

Source: Reviewer Table
1-Adjusted difference with stratified Wald Confidence Interval using 'Trial' as a stratification factor

Table 36 presents results for a pooled analysis of the primary endpoint by baseline pathogen in Trials 008 and 025 using the micro-ITT populations. Cure rates by pathogen were generally similar between the eravacycline and comparator arms, however, a few comparisons were limited by small samples. The most notable treatment differences in cure rates were observed in patients with *Klebsiella pneumoniae* at baseline (difference favored eravacycline) and in patients with *Bacteroides ovatus at* baseline (difference favored the comparators).

Table 36: Clinical Cure Rates at TOC by Selected Baseline Pathogen in Pooled Phase 3 cIAI Trials, Micro-ITT Population

Pathogen/ MIC (mcg/mL)	Pooled Analysis	
	ERV 1 mg/kg, q12h IV (N=415) n/N1 (%)	All Comparators (ETP or MER) (N=431) n/N1 (%)
Enterobacteriaceae	271/314 (86.3)	289/325 (88.9)
Citrobacter freundii	19/22 (86.4)	8/10 (80.0)
Enterobacter cloacae complex	17/21 (81.0)	23/24 (95.8)
Escherichia coli	220/253 (87.0)	237/266 (89.1)
Klebsiella oxytoca	14/15 (93.3)	16/19 (84.2)
Klebsiella pneumoniae	37/39 (94.9)	42/50 (84.0)
Acinetobacter baumanii complex	13/13 (100.0)	7/7 (100.0)

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Pathogen/ MIC (mcg/mL)	Pooled Analysis	
	ERV 1 mg/kg, q12h IV (N=415) n/N1 (%)	All Comparators (ETP or MER) (N=431) n/N1 (%)
Enterococcus faecalis	45/54 (83.3)	47/54 (87.0)
Enterococcus faecium	38/45 (84.4)	48/53 (90.6)
Staphylococcus *aureus* (methicillin-susceptible)	23/23 (100.0)	12/14 (85.7)
Streptococcus anginosus group[a]	79/92 (85.9)	50/59 (84.7)
Streptococcus mitis group[b]	29/31 (93.5)	36/38 (94.7)
Streptococcus salivarius group[c]	9/10 (90.0)	12/13 (92.3)
Anaerobes	186/215 (86.5)	194/214 (90.7)
Bacteroides caccae	13/17 (76.5)	7/7 (100.0)
Bacteroides fragilis	72/84 (85.7)	73/80 (91.3)
Bacteroides ovatus	32/43 (74.4)	43/45 (95.6)
Bacteroides thetaiotaomicron	50/56 (89.3)	47/53 (88.7)
Bacteroides uniformis	19/22 (86.4)	19/19 (100.0)
Bacteroides vulgatus	37/40 (92.5)	37/40 (92.5)
Clostridium perfringens	13/16 (81.3)	21/21 (100.0)
Parabacteroides distasonis	19/24 (79.2)	14/14 (100.0)

[a] Includes *Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus intermedius*
[b] Includes *Streptococcus mitis*, *Streptococcus oralis*, *Streptococcus sanguinis*, *Streptococcus parasanguinis*, *Streptococcus gordonii*, and *Streptococcus cristatus*
[c] Includes *Streptococcus salivarius* and *Streptococcus vestibularis*

7.4 Summary and Conclusions

Overall evidence of efficacy and safety relied primarily upon findings of noninferiority from two Phase 3 trials, Trials 008 and 025, which evaluated the primary endpoint of clinical response at TOC in the micro-ITT population using NI margins of 10% and 12.5%, respectively. In both trials, non-inferiority of eravacycline to comparator therapy (eratapem in Trial 008 and meropenem in Trial 025) was clearly demonstrated. In Trial 008, the difference in clinical response rates between ervavacycline and comparator therapy was -0.8% (95% CI: -7.1%, 5.5%) and in Trial 025, the difference was -0.5% (95% CI: -6.3%, 5.3%). Since the lower 95% confidence limits were -7.1% and -6.3% which exceeded the allowable non-inferiority limits of -10% and -12.5%, respectively, non-inferiority was demonstrated in both trials.

In both trials, Reviewer sensitivity/secondary analyses were generally supportive of primary analysis findings. These analyses considered alternative assumptions regarding the definition of

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clinical cure (i.e. requirement for complete resolution), patient evaluation (SAC assessment vs. investigator assessment), stratification (e.g. by primary disease diagnosis), and missing data (imputing missing/indeterminates as successes rather failures or as failures in the eravacycline arm and successes only in the comparator arm). Secondary analyses which considered clinical response at different time points (EOT, TOC, FU) in different analysis populations (ITT-based and evaluable populations) showed a general consistency with primary analysis findings. Subgroup analyses did not raise concerns that non-inferiority inferences may not valid in selected groups of patients. However, it is noted there were small numbers of non-white subjects and US subjects represented in these studies which limits inferences in these subgroups. In both Phase 3 studies, the patients included in the micro-ITT population did not have pathogens resistant to either study treatment. Therefore, non-inferiority comparisons were not influenced by possible treatment differences in resistance among pathogens at baseline.

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8 Clinical Microbiology Review

8.1 Nonclinical Microbiology

8.1.1 Activity In Vitro

8.1.1.1 Antibacterial Activity

The tables below summarize the in vitro activity (b) (4) that were evaluated for relevance to the indications. This analysis included the MIC90 and Epidemiological Cut-off Value (ECOV). Information on pathogens was pooled from surveillance and the combined Phase 3 studies. The number of organisms, and the in vitro activity of eravacycline against isolates from the United States were also taken into consideration when determining whether eravacycline has activity against particular pathogens.

Table 37: In Vitro Activity of Eravacycline Against cIAI Pathogens (b) (4)

Pathogen	N	ECOV (mcg/mL)	MIC90 (mcg/mL)	MIC Range (mcg/mL)
Escherichia coli	2265	0.5	0.5	(b) (4)
Citrobacter freundii	540	1	1	
Enterobacter cloacae	1009	2	1	
Klebsiella oxytoca	829	0.5	0.5	
Klebsiella pneumoniae	1332	1	1	
Staphylococcus aureus (methicillin-susceptible)	1243	0.25	0.12	
Enterococcus faecalis (vancomycin-susceptible)	950	0.25	0.06	
Enterococcus faecium (vancomycin-susceptible)	453	0.12	0.06	
Streptococcus anginosus group	308	0.12	0.03	
Streptococcus mitis group	85	0.06	0.12	
Streptococcus salivarius group	27	0.06	0.03	
Bacteroides caccae	44	0.5	1	
Bacteroides fragilis	417	1	2	
Bacteroides ovatus	167	0.5	2	
Bacteroides thetaiotaomicron	231	1	1	
Bacteroides vulgatus	152	0.5	0.25	
Clostridium perfringens	135	0.125	0.5	

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				(b) (4)
Parabacteroides distasonis	94	2	1	
Acinetobacter baumannii	1178	4	1	

Source: Reviewer's table adapted from sources CANWARD 2014, (b) (4) Study 2300 (b) (4) Study 2636, (b) (4) 2530, TP-434-008 and TP-434-025.

The Applicant also provided *in vitro* activity data from the above studies on the following groups of combined bacterial species:
Enterobacteriaceae, 5975 isolates, MIC_{90} 0.5 mcg/mL, ECOV 1 mcg/mL
All *Enterococcus* spp., 1403 isolates, MIC_{90} 0.06 mcg/mL, ECOV 0.25 mcg/mL
All Viridans Group Streptococcus, 414 isolates, MIC_{90} 0.06 mcg/mL, ECOV 0.12 mcg/mL
Anaerobes, 1190 isolates, MIC_{90} 1 mcg/mL, ECOV 1 mcg/mL

Table 38: In Vitro Activity of Eravacycline Against cIAI Pathogens (b) (4)

Pathogen	**N**	**MIC90 (mcg/mL)**
Staphylococcus aureus USA	342	0.12
Enterococcus faecalis USA	353	0.06
Enterococcus faecium USA	308	0.06
Enterobacter aerogenes USA	216	0.5
Citrobacter koseri USA	69	0.25
Citrobacter koseri Europe	149	0.25
Serratia marcescens USA	347	2
Stenotrophomonas maltophilia USA	31	1
Stenotrophomonas maltophilia Europe	99	1
Proteus mirabilis USA	258	2
Proteus vulgaris USA	60	1
Proteus vulgaris Europe	149	1
Clostridium difficile USA	76	0.12
Clostridium difficile Europe	117	0.06

Source: Reviewer's table adapted from sources 05-12-2009-Tetraphase 8 and (b) (4) 038, (b) (4) 636, (b) (4) 2530, (b) (4) 15-16. Origin of isolates by region is indicated as United States of America (USA) or Europe.

Reviewer's Comment
The Applicant's in vitro data on the activity of eravacycline was evaluated for adequacy. *C. difficile* and *S. mitis* group were not considered relevant pathogens for cIAI. *S. salivarius* group was considered an opportunistic pathogen. The recommended number of isolates for in vitro testing of antibacterial drugs is described in the clinical microbiology guidance document, "Microbiology Data for Systemic Antibacterial Drugs-Development, Analysis, and Presentation;

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Guidance for Industry". Typically, 300 isolates are recommended for Enterobacteriaceae, and 100 isolates are recommended for most other organisms or organism groups. (b) (4) Relevant organisms listed above other than Enterobacteriaceae which did not have 100 isolates individually were *S. mitis* group, *S. salivarius*, and *B. caccae*, however, there was clinical experience on these organisms in the clinical studies. There were an adequate number of all Enterobacteriaceae, all *S. anginosus* group, and all *Bacteroides* spp. combined for analysis.

Table 39: In Vitro Activity of Eravacyline Against Carbapenem-resistant non-Proteae Enterobacteriaceae by Resistance Mechanism

Enzyme or Phenotype	N	MIC (µg/mL)		
		Range	MIC_{50}[a]	MIC_{90}
KPC	35	0.12 - 4	0.5	1
KPC + SHV	10	0.25 - 1	0.5	1
VIM	44	0.25 - 2	0.5	1
IMP	15	0.12 - 2	0.5	2
NDM	42	0.12 - 4	0.25	1
OXA-48	36	0.12 - 4	0.5	1
OXA-48 + ESBL	8	0.12 - 2	0.5	2
Porin loss + ESBL	30	0.12 - 4	0.5	2
Porin loss + AmpC	10	0.5 - 2	0.5	-
TOTAL	**230**	**0.12 - 4**	**0.5**	**2**

Source: Adapted from (b) (4) 5-10
MIC = minimum inhibitory concentration; MIC_{50} = minimum inhibitory concentration against 50% of the isolates; MIC_{90} = minimum inhibitory concentration against 90% of the isolates; KPC, SHV, VIM, IMP, NDM, OXA = carbapenemases; ESBL = extended-spectrum β-lactamase
a. MIC_{50} calculated based on the data in Table 1 and Appendix B and the SDLN database

Table 40: In Vitro Activity of Eravacycline Against Carbapenem-resistant *Klebsiella* spp. by Resistance Mechanism

Enzyme or Phenotype	N	MIC (µg/mL)		
		Range	MIC_{50}[a]	MIC_{90}
KPC	10	0.12 - 1	0.5	1
KPC + SHV	10	0.25 - 1	0.5	1
VIM	20	0.25 - 2	0.5	1
IMP	10	0.12 - 2	0.5	2
NDM	20	0.25 - 2	0.25	1
OXA-48	12	0.25 - 2	0.25	0.5
OXA-48 + ESBL	8	0.12 - 2	0.5	2
Porin loss + ESBL	20	0.25 - 4	1	4
TOTAL	**110**	**0.12 - 4**	**0.5**	**2**

Source: Adapted from (b) (4) 15-10
MIC = minimum inhibitory concentration; MIC_{50} = minimum inhibitory concentration against 50% of the isolates; MIC_{90} = minimum inhibitory concentration against 90% of the isolates; KPC, SHV, VIM, IMP, NDM, OXA = carbapenemases; ESBL = extended-spectrum β-lactamase
a. MIC_{50} calculated based on the data in Table 1 and Appendix B and the SDLN database

Reviewer's Comment
The Applicant included an analysis of eravacycline activity against certain resistance factors such as beta-lactamases as shown in the tables above, however, factors which are not directly

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relevant to the tetracycline class of antibacterial drugs are not expected to impact eravacycline activity.

Activity of TP-434 Metabolites and Impurities

(b) (4)

Table 41: Strain Background and Demographic Information

(b) (4)

Source: Study Report (b) (4) 15-4.

Reviewer's Comment

(b) (4)

Bactericidal Activity

The bactericidal activity of eravacycline was assessed by the Applicant using CLSI guidelines. The Minimum Bactericidal Concentration (MBC) was defined as the concentration at which a decrease of viable bacteria of 99.9% or greater (≥3-log) was observed relative to the viable count initial inoculum. Eravacycline was considered to be bactericidal if the observed MBCs were > 4-times higher than the observed MICs. MBCs for eravacycline against gram-positive and gram-negative aerobes were determined by the Applicant in two separate studies (b) (4) 10-07 and (b) (4) 500951). The results from these studies indicated that eravacycline and tigecycline are primarily bacteriostatic based on MBCs >4-times higher than the MIC observed for the

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majority of the evaluated isolates, though some strain-specific bactericidal activity was observed for eravacycline.

Time Kill

Time kill analysis was conducted by CLSI guidelines. Viable bacteria were quantified at baseline and at a given exposure to drug at multiples of the MIC. Eravacycline was considered bactericidal if the ≥3-log10 decrease described above was achieved at or before 24 hours of exposure, and was maintained without regrowth. The time-kill data for eravacycline at 4-times and 8-times the MIC were evaluated against gram-positive and -negative aerobes in multiple studies using tigecycline as a comparator (b) (4) 10-07 and (b) (4) 15-6). Based on MBC and time-kill analyses, eravacycline was bacteriostatic against *S. aureus*, *Enterococcus faecalis* and the majority of evaluated gram-negative pathogens (See tables below). There was evidence based on time-kill data that eravacycline was bactericidal against a subset of Enterobacteriaceae (e.g. *E. coli, K. pneumoniae* and *A. baumannii*) and that this bactericidal activity was isolate-specific. Eravacycline MBC data also suggested some strain-specific bactericidal activity against viridans streptococci, *A. baumannii*, and *A. lwoffii* (see table below). Overall, the results observed with eravacycline were generally comparable with those observed with tigecycline.

Table 42: Time-kill Studies for *S. aureus* and *E. faecalis*

Strain	Resistance Genotype	MIC (µg/mL)		Log $_{10}$ Change in CFU/mL Relative to Baseline at 24 h		
		Eravacycline	Tigecycline	Eravacycline		Tigecycline
				4X MIC	8X MIC	4X MIC
S. aureus SA418	*msrA*	0.125	0.125	-0.37	-0.72	-1.12
S. aureus SA540	*tet*(M)	0.25	0.25	-1.10	-2.45	-1.79
S. aureus SA558	*ermA*	0.25	0.5	-1.82	-2.02	-2.48
S. aureus SA191	HA-MRSA, *tet*(M)	1	0.5	-2.23	**-3.36**	-2.16
S. aureus SA192	CA-MRSA, *tet*(K)	0.5	0.25	-2.43	-2.37	-1.46
Enterococcus faecalis EF327	*tet*(M)	0.03	0.06	0.27	0.19	0.16
Enterococcus faecalis EF329	*tet*(M)	0.03	0.06	-0.02	-1.19	-1.07
Enterococcus faecalis EF331	*tet*(M)	0.03	0.06	0.06	-0.05	0.25

Source: adapted from (b) (4) 5-6; (b) (4) 10-07
CFU=colony-forming unit; MIC=minimum inhibitory concentration; HA-MRSA=hospital-acquired methicillin-resistant *S. aureus*, CA-MRSA=community-acquired methicillin-resistant *S. aureus*
A ≥3-log drop relative to baseline is indicated in bold font

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Table 43: Time Kill Studies for Enterobacteriaceae

Strain	Resistance Genotype	MIC (µg/mL)		Log 10 Change in CFU/mL Relative to Baseline at 24 h		
				ERV		TGC
		ERV	TGC	4X MIC	8X MIC	4X MIC
E. coli EC107		0.03	0.06	-1.43	-2.68	-2.72
E. coli EC806		0.125	0.125	**-3.25**	**-3.28**	-1.39
E. coli EC1024	*tet*(A), bla_{SHV-12}, bla_{CTX-M2}	0.5	0.5	**-4.48**	**-4.48**	**-4.48**
K. pneumoniae KP109	bla_{SHV}	0.25	0.25	**-3.04**	-2.13	**-3.28**
K. pneumoniae KP153	*tet*(A), $bla_{CTX-M1/3/15}$, bla_{OXA}	1	1	-1.54	**-3.00**	1.09
Proteus mirabilis PM700		4	8	**-3.19**	**-3.86**	**-3.56**
Proteus mirabilis PM716		8	16	-1.12	-1.92	-1.84
Proteus mirabilis PM723		2	4	-1.72	**-3.14**	-1.60
Enterobacter cloacae EC605		1	1	2.59	-0.65	3.53
Enterobacter cloacae EC732		0.5	0.5	-0.60	-1.26	-2.18
Enterobacter cloacae EC1016	bla_{CTX-M}	0.25	0.25	3.00	-2.75	-1.17
Serratia marcescens SM168		2	1	**-3.25**	**-4.51**	**-3.73**
Serratia marcescens SM502		4	2	-2.90	**-3.28**	-2.37
Serratia marcescens SM503		16	8	-1.60	-2.56	-0.25

Source: adapted from (b) (4)10-07, (b) (4)15-6
MIC = minimum inhibitory concentration; ERV = eravacycline; TGC = tigecycline
A ≥3-log reduction in cfu/mL relative to baseline is indicated in bold font

Table 44: Time-kill Studies for Non-fermenting Bacteria

Strain	Resistance Genotype	MIC (µg/mL)		Log 10 Change in CFU/mL Relative to Baseline at 24 h		
				ERV		TGC
		ERV	TGC	4X MIC	8X MIC	4X MIC
A. baumannii AB947	*tet*(B)	2	4	-0.64	**-3.83**	**-3.76**
A. baumannii AB959	*tet*(B)	1	4	**-4.23**	**-3.90**	-1.78
Stenotrophomonas maltophilia SM843		0.5	0.5	1.75	-1.52	2.34
Stenotrophomonas maltophilia SM870		0.125	0.25	0.94	-2.00	-2.00

Source: adapted from (b) (4)10-07
MIC = minimum inhibitory concentration; ERV = eravacycline; TGC = tigecycline
A ≥3-log reduction in cfu/mL relative to baseline is indicated in bold font

Post-antibiotic Effect

The post-antibiotic effect (PAE) is the ability of an antimicrobial agent to suppress growth of target pathogens after a brief *in vitro* exposure period to supra-inhibitory concentrations of the

agent followed by its subsequent removal. The PAE of eravacycline was evaluated against *S. aureus*, *S. pneumoniae*, *S. anginosus*, *E. faecium*, Enterobacteriaceae, and *A. baumannii*, by exposing a suspension of approximately 5 x 10^6 CFU/mL of bacteria to eravacycline at 2x, 4x, and 10x the MIC alongside an untreated growth control for 1 h under standard incubation conditions ([(b) (4)]10-27). The PAE was defined as the time required after exposure and removal of eravacycline for the organism to grow 1 $\log^{10}$ CFU/mL, minus the time for the untreated growth control to grow 1 $\log^{10}$ CFU/mL (Craig and Gudmundsson, 1996)[2].

The PAE results observed with eravacycline were reported by the Applicant from two independent experiments conducted on separate days. Overall, the observed PAE for eravacycline ranged from 1.0 to 3.2, 1.0 to 3.7, and 1.2 to 4.0 h following exposure to 2x, 4x, and 10x the MIC, respectively. With the exception of streptococci, where the PAE increased with increasing exposure, the PAE observed across exposures was similar. The PAE of eravacycline was typically longer with gram-positive cocci (2.3 to 4.0 h at 10x the MIC) relative to gram-negative bacilli (1.2 to 1.9 h at 10x the MIC).

8.1.1.2 Mechanism of Action

Eravacycline, is a novel, synthetic fluorocycline antibacterial drug that has structural similarities to other tetracyclines. The primary mode of action is the inhibition of bacterial protein synthesis by binding to the 30S ribosomal subunit and preventing the incorporation of amino acid residues into elongating peptide chains. Eravacycline differs from tigecycline by modifications to the D-ring structure, fluorine atom at position C-7 and a pyrrolidinoacetamido group at C-9. Both of these modifications are reported to contribute to its increased activity as assessed in the coupled transcription/ translation assay and activity against tetracycline-resistant strains due to tetracycline-specific efflux and/or ribosomal protection proteins (RPPs). See "Mechanism of Resistance" section of this review for a description of efflux and RPPs.

The mechanism of action of eravacycline was examined by the Applicant through testing of physiological effects of eravacycline on bacterial cells. Inhibition of macromolecular synthesis by eravacycline in comparison to tigecycline was evaluated in *Escherichia coli* strain ATCC® 25922 using radiolabeled biosynthetic precursors. The incorporation of precursors into DNA, RNA, protein, cell wall, and lipid was monitored over time following the addition of antibiotics (04-16-2015-Tetraphase 10). There was minimal inhibition of DNA and/or RNA synthesis at 10-40% for eravacycline or tigecycline in comparison to ciprofloxacin at near 100%. Neither eravacycline nor tigecycline inhibited cell wall or lipid synthesis in comparison to positive controls.

[2] Craig WA, Gudmundsson S. Post antibiotic effect. In *Antibiotics in Laboratory Medicine* 4th ed, (Lorian V, ed). 1996 p296-329.

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Eravacycline and tigecycline inhibited protein synthesis in a dose-dependent manner. Inhibition by eravacycline spanned from 0.12- to 4-times the Minimum Inhibitory Concentration (MIC) (0.12 mcg/mL). The 95% inhibition was at 4- to 8-times the MIC. The concentration inhibiting 50% inhibition of protein synthesis (IC_{50}) for eravacycline was 0.33-times the MIC, at approximately 0.04 mcg/mL. This was 9 times more than tigecycline (IC_{50} at 0.36 mcg/mL). There was limited inhibition of other macromolecules with eravacycline, and this was not dose-dependent.

The ability of eravacycline to inhibit translation was tested by the Sponsor in an *E. coli* cell-free coupled in vitro transcription/translation assay with a luminescent readout in the presence and absence of Tet(M) (Grossman et al., 2012)[3]. The IC_{50} in this assay in the presence of Tet(M) was 1.26+/- 0.48 mcg/mL for tetracycline, 0.08 +/-0.01 mcg/mL for tigecycline and 0.29 +/- 0.09 mcg/mL for TP-434. The results were similar in the absence of Tet(M) for tigecycline and TP-434 at 0.09 +/-0.04 mcg/mL and 0.27 +/-0.16 mcg/mL respectively. This was in contrast to tetracycline which had an increased inhibitory concentration without Tet(M) at 6.50 +/- 3.30 mcg/mL. These results showed that inhibition of protein synthesis by eravacycline was unaffected by Tet(M), and that the Tet(M) RPP mechanism was relevant for tetracycline.

In another experiment, the antibacterial properties of eravacycline, the effect of ribosome binding site mutations on eravacycline susceptibility was investigated. A ribosome competition assay with tritiated [^{3}H] tetracycline was performed. Briefly, eravacycline, tigecycline and erythromycin were tested at increasing concentrations for their ability to compete with labelled tetracycline for binding to purified ribosomes, and the IC_{50} were reported. Eravacycline competed with [^{3}H]tetracycline for ribosome binding, with an IC_{50} of 0.22±0.07 µM suggesting that it bound more strongly to the ribosome than tetracycline and at least partially in the tetracycline binding pocket (Grossman et al., 2012). Tigecycline had a similar IC_{50} values, and (0.22±0.08 µM) tetracycline was ~14-times less potent (IC_{50}=3.00±1.15 µM). These results suggested that eravacycline, tigecycline, and tetracycline bind to a similar site on the ribosome. Erythromycin failed to compete with [^{3}H] tetracycline which was consistent with the binding site for erythromycin being on the 50S ribosomal subunit rather than the 30S subunit, where the binding site is for tetracycline, eravacycline and tigecycline.

[3] Grossman TH, Starosta AL, Fyfe C, O'Brien W, Rothstein DM, Mikolajka A, Wilson DN, Sutcliffe JA. Target- and resistance-based mechanistic studies with TP-434, a novel fluorocycline antibiotic. *Antimicrob Agents Chemother*. 2012 May;56(5):2559-64. Erratum in: *Antimicrob Agents Chemother.* 2015 Sep;59(9):5870.

Reference ID: 4312284

8.1.1.3 Resistance

Eravacycline resistance in some bacteria is associated with upregulated, non-specific multidrug-resistant (MDR) efflux, and target-site modifications such as in the 16s rRNA or certain 30S ribosomal proteins (e.g., S10). The summary of this data and the conclusions which lead to this determination are in the studies below:

Multidrug Efflux

Eravacycline resistance in some bacteria is associated with upregulated, non-specific intrinsic multidrug-resistant (MDR) efflux. The Applicant reports that the C7 and C9 substitutions in eravacycline impart microbiological activities including retention of in vitro potency against gram-positive and gram-negative strains expressing tetracycline-specific resistance mechanism(s) [i.e., efflux mediated by *tet*(A), *tet*(B), and *tet*(K); ribosomal protection as encoded by *tet*(M) and *tet*(Q)].

Reviewer's Comment

Efflux pumps such as those described above are transport proteins involved in the extrusion of antibiotics from within cells to outside of the cell environment (Webber et al. 2003)[4]. In general, efflux pumps can be specific or transport multiple structurally dissimilar compounds and therefore they can be associated with multi-drug-resistance (Webber et al. 2003)[3]. Efflux pumps extrude tetracycline antibiotics from the inside of cells at the expense of a proton. Tet(A) and Tet(B) are the most frequently found tetracycline pumps in gram-negative clinical isolates and Tet(K) and Tet(L) are the most common tetracycline-specific efflux pumps in gram-positive clinical isolates (Chopra and Roberts, 2001)[5].

A description of the activity of eravacyline in the presence of resistance mechanisms, including tetracycline-specific resistance mechanisms (efflux and ribosomal protection) is below using recombinant and clinical bacterial isolates.

Table 45: Susceptibility of Eravacycline and Comparators to *E. coli* DH10B Expressing Recombinant Major Tetracycline Resistance Genes

Antibiotic	MIC (µg/mL)					
	EC971 *lacZ*	EC969 *tet*(M)	EC970 *tet*(K)	EC1082 *tet*(A)	EC1083 *tet*(B)	EC1153 *tet*(X)
Eravacycline	0.063	0.063	0.031	0.25	0.063	4
Tigecycline	0.063	0.13	0.063	1	0.063	2
Doxycycline	2	64	4	32	32	16
Minocycline	0.5	64	1	8	16	4
Tetracycline	2	128	128	>128	>128	128
Ceftriaxone	0.063	0.13	0.063	0.13	0.13	0.13

Source (b) (4) 5-5
MIC = minimum inhibitory concentration

[4] Webber MA, Piddock LJ. The importance of efflux pumps in bacterial antibiotic resistance. *J Antimicrob Chemother.* 2003 Jan;51(1):9-11.

[5] Chopra I, Roberts M. Tetracycline antibiotics: mode of action, applications, molecular biology and epidemiology of bacterial resistance. *Microbiol Mol Biol Rev*. 2001;65(2):232-60.

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Table 46: Activity of Eravacycline Against Clinical Isolates Expressing Tetracycline-specific Efflux Pumps

Efflux Pump	Organism	[N]	MIC Range (µg/mL)		
			Eravacycline	Tigecycline	Tetracycline
tet(A)	*E. coli*	42	0.06-1	0.06-1	>32
	K. pneumoniae	43	0.25-8	0.05-8	32->32
	A. baumannii	3	0.5-1	2	NT
tet(B)	*E. coli*	35	≤0.015-0.5	0.06-1	>32
	K. pneumoniae	2	0.125-1	0.25-0.5	>32
	A. baumannii	22	0.25-4	0.5-8	NT
tet(D)	*E. coli*	3	0.125-0.25	0.125-0.25	>32
	K. pneumoniae	9	0.06-0.5	0.125-1	>32
tet(K)	*S. aureus*	8	0.125-4	0.125-1	32->64

Adapted from (b) (4) 15-5
MIC = minimum inhibitory concentration; NT = not tested

The antibacterial activity of eravacycline was tested against panels of clinical isolates and engineered strains carrying resistance genes and chromosomal mutations known to impact the activity of tetracycline-class antibacterial drugs. The activity of eravacycline was minimally affected by the recombinant expression of major tetracycline-specific resistance genes [*tet*(A), *tet*(B), *tet*(K), *tet*(M)] in an isogenic *E. coli* background. The MIC of eravacycline increased from 0.06 to 4 mcg/mL in *E. coli* expressing *tet*(X).

Reviewer's Comment
The Applicant discussed resistance mechanisms that do not affect eravacycline activity in vitro. The Applicant did not list *tet*(X) and this reviewer agrees that it should not be listed, due to the increase in MIC for *E. coli* to beyond the Agency's proposed susceptible breakpoint for Enterobacteriaceae.

Eravacycline activity *in vitro* was more variable in panels of *E. coli, K. pneumoniae* and *A. baumannii* clinical isolates carrying *tet*(A) or *tet*(B); *E. coli* and *K. pneumoniae* containing *tet*(D); and *S. aureus* carrying *tet*(K) or *tet*(M). The Applicant suggested that differences in strain background and the existence of other resistance determinants likely impact susceptibility to eravacycline in these organisms. The Applicant reported that eravacycline activity against *B. fragilis* clinical isolates did not directly correlate with the presence of *tet*(Q) or *tet*(X), nor did it directly correlate with the tigecycline and minocycline activities against *B. fragilis*, suggesting that there may be other genes responsible for the differential activity against these three antibacterial drugs.
Similar to other antibacterial drugs of different classes, susceptibility to eravacycline was reduced by intrinsic MDR mechanisms regulated by *ramA* in *K. pneumoniae.* Eravacycline was postulated to be a substrate for the AdeAB pump in *A. baumannii,* several Mex pumps in *Pseudomonas aeruginosa,* and a poor substrate for MepA in *S. aureus*.

Reviewer's Comment
The activity of eravacycline in the presence of *tet*(Q) was further evaluated since the Applicant stated that eravacyline activity did not directly correlate with the presence of *tet*(Q). Study report 08-27-2015-Tetraphase 12 included the evaluation of a *tet*(Q) tetracycline-resistant

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isolate, *B. fragilis* 30272 for which eravacycline MIC increased from 0.015 to 0.5 mcg/mL from pass 13-15. This change was within the Agency's proposed susceptible breakpoint for anaerobes, and the broth confirmatory testing showed only a 2-fold increase in MIC from parental isolate. Tigecycline MICs also increased for this isolate from 0.25 mcg/mL to 2 mcg/mL from passage 13-15. Confirmatory broth testing suggested a 4-fold increase in tigecycline MIC. The eravacycline spontaneous mutation selection of *B. fragilis* 30272 tet(Q) was less than $1.2x10^{-9}$ (study report 06-10-2015-tetraphase 11).

(b) (4)

(b) (4) The MepA+ strain tested at 4-times the MIC of the parent strain, *S. aureus* SA981, at 0.016 mcg/mL versus 0.004 mcg/mL respectively. Only one *S. aureus* isolate was tested.

Ribosomal Protection Proteins

According to a review of ribosomal protection proteins and their mechanism in tetracycline resistance (Connell et al. 2003)[7], usually tetracyclines that are the subject of RPP-mediated resistance, bind to the ribosome and inhibit elongation of protein synthesis. This is accomplished through inhibition of the accommodation of aminoacyl-tRNA into the ribosomal A site. The new addition of amino acids to the growing peptide chain is subsequently prevented. Ribosomal protection proteins were described in the literature review as soluble cytoplasmic proteins of about 72 kDa that mediate tetracycline resistance. Tet(O) and Tet(M) are among those that have been well studied, both which are thought to dislodge tetracycline from the ribosome and therefore free the ribosome from inhibitory effects of the drug. (b) (4)

Target Site Modifications

Development of resistance by target modification was investigated by the Applicant. In addition to mutations of the 16S rRNA impacting the tetracycline binding pocket, mutations in *rpsJ*, encoding amino acid changes or deletions in a loop region extending towards the tetracycline binding site in the 30S ribosomal protein S10, have been linked to tetracycline

(b) (4)

[7] Connell SR, Tracz DM, Nierhaus KH, Taylor DE. Ribosomal protection proteins and their mechanism of tetracycline resistance. *Antimicrob Agents Chemother*. 2003 Dec;47(12):3675-81.

Reference ID: 4312284

resistance. For example, two *ramR* mutants of *K. pneumoniae* were found to have mutations in *rpsJ* and high MICs for eravacycline. During the analysis of *tet*(K)-positive *S. aureus* isolates, eravacycline activity was determined to not be impacted by *tet*(K) efflux with the exception of one isolate (SA181) which also contained a mutation in *rpsJ* (K57M) where the MICs of both eravacycline and tigecycline were elevated (4 and 1 mcg/mL, respectively) (MICRO15-5).
In another study, the in vitro susceptibility of eravacycline, tigecycline, tetracycline, doxycycline, erythromycin and penicillin were tested against *P. acne* rRNA mutants. One strain with mutations affecting tetracycline binding of the 16S rRNA [SW101T (23S rRNA A2058G; 16S rRNA G1058C; Ery^R Cli^R Tet^R)] region demonstrated increased MICs as follows: >62-times eravacycline MICs, 4-times tigecycline MICs, 128-times tetracycline MICs and a 64-times doxycycline MICs.

Reviewer's Comment
The identification of mutations such as those in the *rpsJ* gene and those described in *P. acnes* above are examples of target site modifications that affect eravacycline activity. (b) (4)

Reviewer's Comment
Taken together, these data appear to indicate that eravacycline retains activity against certain tetracycline-specific resistance mechanisms (ribosomal protection protein and efflux). However, eravacycline activity is negatively affected by expression of some MDR efflux pumps. Additionally, the activity of eravacyline is impacted by mutations in 30S ribosomal proteins near the tetracycline binding site (encoded by *rpsJ*) and mutations in 16S rRNA. (b) (4)

Laboratory selection of resistance
In bacteria, the main eravacycline resistant mechanisms include ribosomal modifications and the expression of efflux pumps. In the studies detailed below, eravacycline resistance development was evaluated *in vitro* using gram-negative and -positive organisms.
Against the gram-positive organisms tested, the frequency of resistance against *E. faecalis tet*(M) was low for eravacycline (3.82×10^{-9}) and moderate for tigecycline (2.07×10^{-8}) at 4 times the MIC. At 4 times the MIC, the frequencies of resistance against *tet*(M) and *tet*(K) *S. aureus* were about the same for eravacycline and tigecycline.

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Table 47: Spontaneous Mutation Frequency of Eravacycline and Comparators in Representative Gram-positive Pathogens

Isolate, strain Resistance	Antibiotic Selection	Inoculum (CFU)	Mutation Frequency		
			Eravacycline	Tigecycline	Vancomycin
S. aureus 100 ATCC 29213 MSSA	8 x MIC	2.46×10^9	$<4.07 \times 10^{-10}$	$<4.07 \times 10^{-10}$	$<4.07 \times 10^{-10}$
	4 x MIC	2.46×10^9	$<4.07 \times 10^{-10}$	$<4.07 \times 10^{-10}$	TNTC
S. aureus 0757 BAA-1556 (USA-300) CA-MRSA, *tet*(M)	8 x MIC	4.30×10^9	$<2.33 \times 10^{-10}$	$<2.33 \times 10^{-10}$	$<2.33 \times 10^{-10}$
	4 x MIC	4.30×10^9	$<2.33 \times 10^{-10}$	$<2.33 \times 10^{-10}$	TNTC
S. aureus 2053 HA-MRSA *tet*(M), *tet*(K)	8 x MIC	3.17×10^9	1.26×10^{-9}	$<3.15 \times 10^{-10}$	$<3.15 \times 10^{-10}$
	4 x MIC	3.17×10^9	9.46×10^{-9}	8.52×10^{-9}	$<3.15 \times 10^{-10}$
Streptococcus pyogenes 0404 ATCC 19615	8 x MIC	1.02×10^9	$<9.8 \times 10^{-10}$	9.35×10^{-10}	$<9.8 \times 10^{-10}$
	4 x MIC	1.02×10^9	1.96×10^{-9}	1.87×10^{-9}	$<9.8 \times 10^{-10}$
			Eravacycline	Tigecycline	Linezolid
Enterococcus faecalis 101 ATCC 29212 VSE	8 x MIC	1.51×10^9	$<6.62 \times 10^{-10}$	$<6.62 \times 10^{-10}$	$<6.62 \times 10^{-10}$
	4 x MIC	1.51×10^9	$<6.62 \times 10^{-10}$	1.99×10^{-8}	$<6.62 \times 10^{-10}$
Enterococcus faecalis 0850 VRE (VanA), *tet*(M)	8 x MIC	3.14×10^9	$<3.18 \times 10^{-10}$	5.73×10^{-9}	$<3.18 \times 10^{-10}$
	4 x MIC	3.14×10^9	3.82×10^{-9}	2.07×10^{-8}	$<3.18 \times 10^{-10}$

Source: (b) (4) *Study Report 05-20-2009-TetraPhase 7v3*
ATCC = American Type Culture Collection; CA-MRSA = community acquired methicillin-resistant *S. aureus*; CFU = colony forming unit; HA-MRSA = hospital acquired methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; VSE = vancomycin-susceptible enterococci; VRE = vancomycin-resistant enterococci; MIC = minimum inhibitory concentration; TNTC = too numerous to count

Table 48: In Vitro Activity of Eravacycline and Comparators Against Spontaneous Mutants of Gram-Positive Pathogens Selected on Eravacycline or Tigecycline

Compound	MIC (µg/mL)					
	S. aureus 2015			*Enterococcus faecalis* 850		
		Mutants selected on [N]			Mutants selected on [N]	
	Parent	ERV [11]	TGC [4]	Parent	ERV [2]	TGC [3]
Eravacycline	0.5	4-8	4-8	≤0.016	1	1
Eravacycline + EPI	≤0.016	0.03-0.25	≤0.016-0.125	≤0.016	0.5	0.25-0.5
Tigecycline	0.5	2-8	2-8	≤0.016	1	1
Tigecycline + EPI	≤0.016	≤0.016-0.25	0.06-0.25	≤0.016	0.5	0.5
Doxycycline	16	16-32	16-32	8	32	32
Tetracycline	>32	>32	>32	32	>32	>32
Linezolid	2	2	2	2	2	2
Meropenem	>32	>32	>32	8	8	8
Ethidium bromide	156.25	156.25	156.25	9.77	9.77	9.77-19.53

Adapted from: (b) (4) *10-02*; (b) (4) *0-04*
ERV = eravacycline, TGC = tigecycline; EPI = efflux pump inhibitor (25 µg/mL of reserpine); MIC = minimum inhibitory concentration

Reviewer's Comment

It was noted that there was a difference in MIC values when an efflux pump inhibitor (EPI) was used in combination with eravacycline in the table shown above. The MIC values of eravacycline and tigecycline decreased in the presence of inhibitor, further providing evidence that efflux pumps can affect the activity of those antibiotics.

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Table 49: Mutation Frequency of Eravacycline and Comparators in Gram-negative Pathogens

Isolate, strain Resistance	Antibiotic Selection	Inoculum (CFU)	Mutation Frequency		
			Eravacycline	Tigecycline	Ciprofloxacin
E. coli ATCC 25922	8 x MIC	1.15×10^{9}	$<8.70 \times 10^{-10}$	$<8.70 \times 10^{-10}$	$<8.70 \times 10^{-10}$
	4 x MIC	1.15×10^{9}	$<8.70 \times 10^{-10}$	$<8.70 \times 10^{-10}$	1.22×10^{-8}
E. coli 1246	8 x MIC	2.29×10^{9}	4.37×10^{-10}	$<4.37 \times 10^{-10}$	$<4.37 \times 10^{-10}$
	4 x MIC	2.29×10^{9}	3.49×10^{-9}	$<4.37 \times 10^{-10}$	4.37×10^{-10}
K. pneumoniae 0214 ATCC 13883	8 x MIC	1.57×10^{9}	$<6.37 \times 10^{-10}$	$<6.37 \times 10^{-10}$	$<6.37 \times 10^{-10}$
	4 x MIC	1.57×10^{9}	2.29×10^{-7}	$<6.37 \times 10^{-10}$	6.37×10^{-10}
K. pneumoniae 2551 ESBL, *tet*(B), *tet*(D), *acrR* frameshift mutation[a]	8 x MIC	4.90×10^{9}	6.12×10^{-10}	$<2.04 \times 10^{-10}$	$<2.04 \times 10^{-10}$
	4 x MIC	4.90×10^{9}	2.65×10^{-8}	1.22×10^{-9}	$<2.04 \times 10^{-10}$
C. freundii 4479	8 x MIC	3.57×10^{9}	3.36×10^{-9}	$<2.80 \times 10^{-10}$	$<2.80 \times 10^{-10}$
	4 x MIC	3.57×10^{9}	2.91×10^{-8}	2.75×10^{-8}	$<2.80 \times 10^{-10}$
A. baumannii 2594	8 x MIC	7.50×10^{9}	1.20×10^{-9}	7.20×10^{-9}	$<1.33 \times 10^{-10}$
	4 x MIC	7.50×10^{9}	1.07×10^{-9}	2.93×10^{-8}	5.33×10^{-10}
B. fragilis 0123 ATCC 25285	8 x MIC	2.2×10^{9}	$<4.5 \times 10^{-10}$	$<4.5 \times 10^{-10}$	NT
	4 x MIC	2.2×10^{9}	$<4.5 \times 10^{-10}$	$<4.5 \times 10^{-10}$	NT
B. thetaiotaomicron 5974 ATCC 29741	8 x MIC	1.7×10^{9}	$<5.9 \times 10^{-10}$	$<5.9 \times 10^{-10}$	NT
	4 x MIC	1.7×10^{9}	$<5.9 \times 10^{-10}$	$<5.9 \times 10^{-10}$	NT

Source: *05-20-2009-TetraPhase 7v3,* (b) (4) *15-15*
ATCC = American Type Culture Collection; CFU = colony forming unit; ESBL = expanded spectrum β-lactamase; MIC = minimum inhibitory concentration; NT = not tested
a. characterisation data detailed in (b) (4) *5-11*

Reviewer's Comment

(b) (4) the information from the study reports listed under the tables above. (b) (4)

Table 50: Spontaneous Mutation Frequency for Representative Additional Isolates of *K. pneumoniae* and *A. baumannii*

Organism	Strain	Known Genotype	Mutation frequency		MIC (µg/mL)	
			4x MIC	8x MIC	Parent	Mutant
K. pneumoniae	KP1664	bla_{SHV}, *tet*(D)	3.53×10^{-08}	3.75×10^{-08}	0.063	0.5 - 2
	KP1814		1.08×10^{-07}	3.28×10^{-08}	0.13	1 - 4
	KP1807	*tet*(D)	3.04×10^{-08}	6.62×10^{-10}	0.13	1 - 8
	KP1811	*tet*(D)	6.38×10^{-08}	1.61×10^{-08}	0.13	2 - 8
	KP1813	*tet*(A)	2.10×10^{-07}	ND	1	16 - 32
A. baumannii	AB932		2.29×10^{-06}	1.15×10^{-08}	≤0.016	0.13 - 0.5
	AB938		4.22×10^{-08}	4.46×10^{-09}	≤0.016	0.13 - 1
	AB1619	*tet*(B), bla_{ADC}	7.87×10^{-07}	9.78×10^{-07}	0.063	2 - 8
	AB951	*tet*(B)	3.10×10^{-07}	3.84×10^{-08}	0.25	2 - 4
	AB1620	bla_{ADC}	$<4.45 \times 10^{-10}$	$<4.45 \times 10^{-10}$	0.25	2

Adapted from: (b) (4) *5-9, Tables 11.1-2, 11.1-1*
MIC = minimum inhibitory concentration, ND = not determined

Multistep selection of gram-negative strains was reportedly a 16- to 32-fold increase in eravacycline MIC to 1 and 8 mcg/mL for 1 isolate of *Escherichia coli* and *Klebsiella pneumoniae*, respectively. The overall frequency of spontaneous mutants in gram-positive organisms was in the range of 10^{-9} to 10^{-10}/ gene-generation. *Klebsiella pneumoniae* and *Acinetobacter*

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baumannii mutants were obtained on plates containing eravacycline, but at a frequency of 10^{-6} to 10^{-7}/gene-generation.

Reviewer's Comment

(b) (4)

Table 51: In Vitro Activity of Eravacycline and Comparators Against Selected Spontaneous Mutants of Gram-negative Pathogens Selected on Eravacycline or Tigecycline

Compound	MIC (µg/mL)					
	K. pneumoniae 2551 *tet*(B)			*A. baumannii* 2594		
	Parent	Mutants selected on [N]		Parent	Mutants selected on [N]	
		ERV [8]	TGC [2]		ERV [2]	TGC [1]
Eravacycline	0.13	2-4	4	0.06	0.5-2	1-2
Eravacycline + EPI	0.13	0.25-0.5	0.25-0.5	0.25	0.25-0.5	0.25
Tigecycline	0.25	2-4	4-8	0.25	1-4	4
Tigecycline + EPI	0.25	0.5-1	0.5	0.5	0.5-1	0.5
Tetracycline	>32	>32	>32	8	16	16
Minocycline	>32	>32	>32	0.25	0.5-1	0.25-0.5
Imipenem	0.25	0.125-0.25	0.25	ND	ND	ND
Colistin	ND	ND	ND	0.5	0.5	0.5
Cefotaxime	16	16-32	32	16	8-32	4-8
Ciprofloxacin	1	4-8	4	0.25	0.5-2	0.5-1
Ethidium bromide	312.5	625-1250	625	312.5	156.3-625	156.3

Adapted from: (b) (4) *0-03*; (b) (4) *0-01*
ERV = eravacycline, N = number of mutants selected; TGC = tigecycline; EPI = efflux pump inhibitor (25 µg/mL of β-naphthylamide); ND = not done

Serial passage

The capacity for resistance to develop to eravacycline and comparator agents during repeated exposure to sub-inhibitory concentrations was evaluated by the Applicant for *S. aureus*, *E. faecalis*, *S. pyogenes*, *E. coli*, *K. pneumoniae* and *B. fragilis* (05-05-2009-TetraPhase 6; (b) (4) 15-14). In this experiment, 15 to 20 serial transfers in sub-inhibitory concentrations of each test agent were evaluated. No significant increase in MIC was reported for either eravacycline or tigecycline for the gram-positive organisms *S. aureus* (2 strains), *E. faecalis*, or *S. pyogenes*. Significant increases in eravacycline MICs were observed by the Applicant for the two gram-negative organisms evaluated. For *E. coli* (*lon* or *marA* mutations), the MIC of eravacycline increased 16-fold, while the MIC of tigecycline varied only 2-fold. For *K. pneumoniae*, MIC increases for both eravacycline and tigecycline were observed early during passage, with significant increases resulting for both agents by the end of the study (*ramR* mutations). For *B. fragilis*, eravacycline MICs increased during serial passage but the increase in MIC was not seen by broth microdilution MIC testing, indicating no reported emergence of resistance for eravacycline and *B. fragilis*.

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Reviewer's Comment

Lon protease controls expression of multidrug resistance response through proteolytic degradation of MarA, RamA, and SoxS, activators of MDR responses in gram-negative bacteria. The *lon* mutations have been shown to stabilize the transcriptional activators and promote constitutive expression, or precede duplication of *acrAB* and other resistance genes (Nicoloff et al. 2013)[8]. RamR is involved in the regulation of AcrAB multidrug efflux pump.

Table 52: Genetic Characterization of Resistant Mutants Selected on Eravacycline or Tigecycline

Organism	Strain	[N]	*rpsJ* Mutation	MIC (µg/mL)	
				ERV	TGC
S. aureus 2053	parent	1	WT	0.5	0.5
	ERV selected	1	K57M	4	2
		4	K57E	4-8	2-4
		5	Y58D	4-8	2-8
	TIG selected	2	WT	4-8	2-4
		1	K57E	4	4
		1	Y58D	8	8
Streptococcus pyogenes 0404	parent	1	WT	≤0.004	≤0.004
	ERV selected	3	K57Q	0.03	0.03
		2	K57E	0.016-0.06	0.008- 0.06
		1	Y58D	0.06	0.06
Enterococcus faecalis 0850	parent	1	WT	0.016	0.016
	ERV selected	2	ΔR53, A54,T55, H56	0.25	0.25
	TIG selected	2	ΔR53, A54,T55, H56	0.25-0.5	0.5
		1	K57E	0.5	0.5

Source: (b) (4) 5-11
ERV = eravacycline; TGC = tigecycline; WT = wildtype relative to amino acid sequence of parental strain; MIC = minimum inhibitory concentration

[8] Nicoloff H, Andersson DI. Lon protease inactivation, or translocation of the *lon* gene, potentiate bacterial evolution to antibiotic resistance. *Mol Microbiol*. 2013 Dec;90(6):1233-48. doi: 10.1111/mmi.12429. Epub 2013 Oct 30.

Reference ID: 4312284

Table 53: Genetic Characterization of *K. pneumoniae* Mutants Selected with Eravacycline or Tigecycline

Organism	Strain	[N]	*ramR*	*lon*	MIC (µg/mL)	
					ERV	TIG
K. pneumoniae 2551	parent	1	WT	WT	0.25	0.25
	ERV selected	2	Single point mutation	WT	4	4
		4	Insertion	WT	4	4
		1	Rearrangement	WT	4	4
			Frameshift	WT	4	4
				WT	4	4
	TGC selected	1	Frameshift	WT	4	4
		1	Insertion	WT	>32	>32
K. pneumoniae 0214	parent	1	WT	WT	0.25	0.25
	ERV selected	5	Single point mutation	WT	2-4	2
		1	Frameshift	WT	4	2
		1	WT	5 kb deletion	2	2

Source: adapted from (b) (4) 15-11
WT, wildtype relative to amino acid sequence of parental strain; kb, kilobase; ERV, eravacycline; TGC, tigecycline

Source: This submission.

In summary, all of the isolated mutants of *S. aureus*, *S. pyogenes*, and *E. faecalis* contained mutations in *rpsJ*, implicating mutation of the ribosomal target, specifically the 30S ribosomal protein S10 near the tetracycline binding pocket, as the likely mechanism of eravacycline resistance among these organisms. Similar mutations in *rpsJ* were identified in tigecycline-selected mutants. Genetic characterization of eravacycline-selected mutants of *K. pneumoniae* showed that the majority of mutants had mutations in *ramR*, which is involved in the regulation of the AcrAB multidrug efflux pump. Mutations in *ramR* were also identified in tigecycline-selected mutants. One eravacycline-selected mutant had a deletion in *lon* which is also involved in the control of AcrAB expression via degradation of *ramA*. For *A. baumannii*, eravacycline-selected mutants with the highest eravacycline and tigecycline MICs had an additional mutation in *adeS*, a gene involved in the regulation of the AdeABC multidrug efflux pump. (b) (4)

Reviewer's Comment

The Applicant states that overall genetic characterization data showed that the primary mechanism of resistance among evaluated eravacycline mutants was mutation of genes involved in the expression of multidrug efflux pumps in gram-negative bacteria and mutations in *rpsJ* in gram-positive bacteria. (b) (4) this reviewer recommends that the mechanism of resistance of target site mutations, should be included in the labeling. Mutations such as

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G1058C of the 16s rRNA from *Proprionibacterium acnes* were associated with increased MIC values for eravacycline, as these mutations are thought to change the primary binding site of tetracycline antibiotics (Grossman et al. 2012)[2].

8.1.1.4 Susceptibility Test Methods and Interpretive Criteria

Effect of Testing Conditions on Activity in Vitro

Effect of Comparative Laboratory Test Conditions

The ability to determine bacterial susceptibility to eravacycline using CLSI reference methods was evaluated in a series of studies. These studies included the determination of the appropriate eravacycline disk mass for disk diffusion assays, comparison of MICs determined by broth microdilution or agar dilution test methods, the effect of modification of test parameters on MICs, and the quality control ranges for reference strains used to control test methods. Among the conditions tested were the evaluation of effect on activity of the following: fresh and aged media, freezing reference panels, non-standard media, and variables in growth medium and inoculum size. Variables included pH, divalent cations, and the presence of polysorbate-80.

Reviewer's Comment

The Applicant's evaluation of laboratory conditions which affect eravacycline in vitro activity above led to the determination that both the pH of test medium and testing in urine impact in vitro activity of eravacycline and tigecycline against *E. coli* and *K. pneumoniae*. The MICs of eravacycline and tigecycline were typically 2- to 8-fold higher in urine relative to Cation-adjusted Mueller Hinton Broth (CAMHB). In both CAMHB and urine, the MICs for eravacycline and tigecycline increased with decreasing pH of the test medium. The Applicant reported that with the exception of *E. faecalis* ATCC 29212, where eravacycline MICs were 4-fold higher in medium containing 5-10% human serum than in medium without serum, eravacycline MICs in medium containing human serum were identical to or within 2-fold of those observed without serum.

Agar Dilution Comparison to Microbroth Dilution

It was reported that for *E. faecalis*, hazy growth or slightly cloudy wells were observed during broth microdilution testing of these agents and that if this hazy growth was not taken into consideration when interpreting the broth microdilution MIC, the essential agreement rate between the agar dilution and broth microdilution MICs dropped to 50.0%, 87.5%, and 75.0% for eravacycline, tetracycline and tigecycline, respectively (b) (4) 500971).

Freeze-Dried Panels

Freeze dried panels were compared to microbroth, and disk mass evaluation was also done. A study was conducted to determine the appropriate disk mass for use in the disk diffusion testing of eravacycline against target aerobic pathogens (b) (4) 500947). The 20-mcg disk mass was selected for commercial manufacture and was used throughout clinical development.

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Disk Manufacturers

Eravacycline 20 mcg disks were manufactured at both Bio-Rad (Marnes-la-Coquette, France) and Mast Group Ltd. (Merseyside, UK) (MAST 1209012, 1206007, 2012-12-26 BIORAD MEMO). Both manufacturers were able to reliably manufacture 20 mcg eravacycline disks and the two-year stability study conducted at (b) (4) resulted in the recommendation of a shelf life of (b) (4) months when stored at 2-8°C with desiccant. In addition, an independent study conducted at (b) (4) confirmed the stability of eravacycline disks made in house at (b) (4) over a 12-month period after disk storage at 4°C and -20°C (b) (4) 500947-2).

Quality Control for Susceptibility Testing

Studies conducted to establish QC ranges for the *in vitro* susceptibility testing of eravacycline were performed by the Applicant in accordance with guidelines established by CLSI (CLSI M23). Tier 2 multilaboratory studies were used to establish quality control ranges QC ranges for microbroth dilution.

Table 54: Quality Control Ranges for the Broth Microdilution Testing of Eravacycline Against Aerobes and Summary of Tier 2 Results

Organism	QC range (µg/mL)	# of results	# (%) in range
S. aureus ATCC 29213	0.03 – 0.12	240[a]	238 (99.2)
Enterococcus faecalis ATCC 29212	0.015 – 0.06	240[b]	240 (100)
Streptococcus pneumoniae ATCC 49619	0.004 – 0.03	260[c]	260 (100)
E. coli ATCC 25922	0.03 – 0.12	270	270 (100)
Pseudomonas aeruginosa ATCC 27853	2 – 16	270	270 (100)
H. influenzae ATCC 49247	0.12 – 0.5	270	268 (99.3)

Source: adapted from (b) (4) 500948

a. Results from eight laboratories. Results from ninth lab removed due to control drug testing out of QC.
b. Results from eight laboratories. Results from ninth lab removed due to ignoring haze as growth when interpreting endpoint.
c. Results from 10 replicates in one laboratory removed due to control drug testing out of QC.

Table 55: Quality Control Ranges for the Agar Dilution Testing of Eravacycline Against Anaerobes and Summary of Tier 2 Results

Organism	QC range (µg/mL)	Total n	n (%) in range
B. fragilis ATCC 25285	0.06 – 0.25	240[a]	240 (100)
B. thetaiotaomicron ATCC 29741	0.12 – 1	210[b]	210 (100)
Clostridium difficile ATCC 700057	0.06 – 0.25	240[a]	239 (99.6)

Source: adapted from (b) (4) 2338

a. results from one lab removed due to out of range control antibiotic results
b. results from two labs removed due to out of range control antibiotic results

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Table 56: Quality Control Ranges for the Broth Microdilution Testing of Eravacycline Against Anaerobes and Summary of Tier 2 Results

Organism	QC range (µg/mL)	Total n	n (%) in range
B. fragilis ATCC 25285	0.015 – 0.12	270	240 (100)
B. thetaiotaomicron ATCC 29741	0.06 – 0.25	270	268 (99.3)
Clostridium difficile ATCC 700057	0.015 – 0.06	258[a]	257 (99.6)

Source: Adapted from (b) (4) 2419
a. 12 results from one lab removed due to contamination

QC ranges for disk diffusion

The acceptable quality control range for the disk diffusion testing of eravacycline against relevant ATCC® quality control aerobic strains was determined in a nine -laboratory study conducted by the Applicant in accordance with CLSI M23 ((b) (4) 120213).

Table 57: Quality Control Ranges for the Disk Diffusion Testing of Eravacycline Against Aerobes and Summary of Tier 2 Results

Organism	QC range (mm)	# mm	Total n	# (%) in range
S. aureus ATCC 25923	19 – 26	7	540	519 (96.1)
Streptococcus pneumoniae ATCC 49619	23 – 30	9	540	540 (100.0)
E. coli ATCC 25922	16 – 23	7	538[a]	524 (97.4)

Source: (b) (4) 120213
a. 2 replicates from Lab C not tested

Reviewer's Comment

The Quality Control tier 2 testing described by the Applicant above was done according to CLSI guidelines and had a high percentage of quality control results that were in range at greater than 96%. Quality Control Ranges have been published by the CLSI in M100-S28 for MIC and disk for aerobic bacteria and agar and broth methods for anaerobic bacteria. This reviewer recommends the Quality Control published by the CLSI in M100-S28 and that the published quality control values and isolates are referenced on the Agency's breakpoint website as follows:

Disk Diffusion QC Ranges

Eravacycline 20 mcg disk QC

E. coli (b) (4)

S. aureus (b) (4)

(b) (4)

MIC QC Ranges

S. aureus (b) (4)

E. faecalis (b) (4)

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E. coli (b) (4)

(b) (4)

MIC QC Ranges for Anaerobes (b) (4)

B. fragilis (b) (4)

B. thetaiotaomicron (b) (4)

(b) (4)

(b) (4)

Antibacterial Interactions

The potential interactions between eravacycline and other agents (e.g. synergy, antagonism, indifference) were investigated by the Applicant through in vitro fractional inhibitory concentrations (FIC) studies. Potential interactions were then further investigated by time-kill kinetic analysis of the antibacterial agents in combination. FIC was evaluated by using a checkerboard panel in which the combination agents are tested alone or together at varying concentrations. The antimicrobial interactions of eravacycline with other agents for aerobic gram-positive and gram-negative bacteria and for *B. fragilis* were found to be indifferent based on results from FICI analysis for nearly all antibiotic combinations and bacteria evaluated. For some isolates of *P. aeruginosa*, while the mean FICI was <4 indicative of indifference, at certain eravacycline/cefepime concentrations individual FICI values >4 indicative of antagonism were observed.

Reviewer's Comment

This reviewer considered whether it was factual that in vitro studies have not demonstrated antagonism between XERAVA and other commonly used antibacterials (b) (4)

8.1.2 Activity In Vivo (Animal Studies)

Eravacycline was evaluated in multiple preclinical animal infection models including systemic lethal infections in mice, murine kidney infections, neutropenic and immunocompetent murine thigh infections, lung infections in mice, a rat intra-abdominal abscess model, and pulmonary infections in rabbits and monkeys challenged with aerosolized pathogens having potential as bioweapons. These studies evaluated the activity of eravacycline against gram-positive or -negative bacteria including *Escherichia coli* (tetracycline-resistant and ESBL-producing strains),

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K. pneumoniae (ESBL strains), *S. aureus* (methicillin- and tetracycline- resistant strains), *S. pyogenes*, *S. pneumoniae* (tetracycline-resistant strain), *B. fragilis, B. anthracis* and *F. tularensis*. The pharmacokinetics (PK) and pharmacodynamics (PD) of eravacycline were investigated in murine thigh infection models. These studies were conducted in neutropenic mice (tetracycline-resistant MRSA) (Tetraphase 2010-01) or immunocompetent mice (*E. coli* and *K. pneumoniae*) (1284-17B) and assessed for the ability of eravacycline to achieve tissue levels relevant to pathogen MICs [Study HH128339]. In addition, the Applicant investigated the efficacy of i.v. eravacycline at humanized doses in the murine thigh infection model of up to 3 days of dosing (1284-17B). The efficacy of eravacycline was compared with tigecycline, ertapenem or meropenem, levofloxacin, doxycycline, linezolid, and vancomycin. Eravacycline activity was reported to be as active, or more active, than comparators. Specific information on the animal efficacy studies is below:

Mouse systemic infection model
Eravacycline was evaluated in mouse septicemia models which assessed animal survival with eravacycline in comparison to controls.
Study VV055-08608-02 evaluated the efficacy of TP-343 following oral administration against *S. aureus* ATCC 13709. TP-434 did not provide protection against *S. aureus* ATCC 13709 in this study at the concentrations delivered to animals. Tetracycline and linezolid provided PD_{50} values of 6.9 and 3.5 mg/Kg respectively.

For the following studies, mice were infected intraperitoneally with a 48h lethal bacterial load that would result in 0% survival at 48 hours. Antibacterial treatment was given via intravenous injection 60 minutes post-infection in comparison to untreated controls and survival was assessed over a 48 hour period:
-Study VVS055-042908-02: Evaluation of mice infected with *E. coli* isolate ATCC 25922 followed by TP-434 treatment. The PD_{50} for TP-434 was 4.36 mg/Kg. The comparator tigecycline had a PD_{50} of 1.74 mg/Kg.
-Study VVS055-012709-01: Evaluation of TP-434 against ESBL+ *E. coli* EC133 (tetracycline MIC >32mcg/ml). The TP-434, tigecycline and imipenem PD_{50} values were 1.2, 3.5, and less than 0.3 mg/Kg respectively.
-Study VVS055-092308-01: Evaluation of the efficacy of TP-434 against community-associated MRSA 300 isolate, erythromycin and tetracycline resistant VL-191 (NRS384). The TP-434, vancomycin, and tigecycline PD_{50} values were 0.3, 0.3 and 0.35 mg/Kg respectively.
-Study VVS055-040108-01: Evaluation of the TP-434C against *S. aureus* ATCC 13709. TP-434C demonstrated a PD_{50} of 0.3 mg/Kg and comparator tigecycline had a PD_{50} of approximately 0.07 mg/Kg.
-Study VVS055-043008-01: Evaluation of TP-434 against Tet^R *S. aureus* isolate SA-161. TP-434 demonstrated PD_{50} of 1 mg/Kg. Comparators tigecycline and tetracycline had PD_{50} values of 1 and > 10 mg/Kg respectively.
-Study VVS055-120908-01: Evaluation of TP-434 against *S. pyogenes* isolate SP-162. TP-434 had a PD_{50} of approximately 0.05 mg/Kg. Comparator tigecycline and linezolid has PD_{50} of 0.3 and 0.63 mg/Kg respectively.

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-Study VVS055-120408-01: Evaluation of TP-434 against *S. pyogenes* ATCC 8668. TP-434 had a PD_{50} of 1 mg/Kg, while comparators tigecycline and linezolid had PD_{50} values of 2.5 and > 10 mg/Kg respectively.

The susceptibilities of isolates used in the animal infection models is shown in the table below:

Table 58: Susceptibilities of Strains used in Mouse Infection Models

	MIC (μg/ml)						
Organism	Eravacycline	Tigecycline	Tetracycline	Vancomycin	Linezolid	Levofloxacin	Imipenem
S. aureus ATCC 13709	0.016	0.063	0.25	1	4	0.25	NT[a]
S. aureus SA158 [*tet*(K)]	0.063	0.13	64	2	4	0.25	NT
MRSA SA161 [*tet*(M)]	0.063	0.25	64	1	4	16	NT
MRSA SA192 [*tet*(K) USA300]	0.25	0.13	64	1	4	1	NT
MRSA SA191 [*tet*(M)]	0.5	0.5	>64	1	2	0.25	NT
S. pyogenes ATCC 8668	0.016	≤0.016	0.25	0.5	2	0.5	NT
S. pyogenes ATCC 19615	0.016	≤0.016	0.13	0.5	1	NT	NT
S. pneumoniae SP160 [*tet*(M)]	≤0.016	0.03	32	0.25	0.5	1	NT
E. coli ATCC 25922	0.063	0.13	1	NT	NT	0.03	0.25
E. coli EC133 [ESBL$^+$ *tet*(B) *tet*(D)]	0.13	0.13	>32	NT	NT	>32	0.13
E. coli EC200 [*tet*(B)]	0.13	0.13	>64	NT	NT	0.063	0.25

[a] NT, not tested.

Source: Grossman et al., 2015.

Pyelonephritis model

Eravacycline demonstrated statistically significant reductions in kidney bacterial burden with an uropathogenic *E. coli* isolate or an ESBL-producing *K. pneumoniae* isolate, respectively. *E. coli* isolates tested included EC200 (Tet^R; ATCC BAA-1161) with a 1.30 log_{10} change CFU for TP-4620 (TP-434) from 36 hour controls in comparison to levofloxacin at 2.74 log_{10} change in CFU. Also *K. pneumoniae* KP453 isolate was tested in study VVS055-021610-02-R1 in comparison to meropenem: cilastatin. TP-4620 showed a 2.38 log_{10} reduction in CFU from 36 hour controls at a concentration of 20 mg/Kg, and meropenem-cilastatin showed a 2.38 log_{10} reduction at 30 mg/Kg. In Study VVS055-030310-01-R1 *K. pneumoniae* KP453 (ESBL$^+$) was used for the infection model and CFU per gram of kidney was calculated. TP-434 showed a 1.27 log_{10} CFU change from 36 hour controls relative to meropenem-cilastatin at 3.28 log_{10} CFU reduction.

Thigh infection models

The murine thigh infection model was used for studies of PK/PD and antimicrobial efficacy. The studies are summarized below:

Report 1284-17C: This study evaluated the relationship of eravacyline *f*AUC/MIC to eravacycline efficacy against Enterobacteriaceae isolates previously associated with clinical cure in cIAI adults. The isolates tested were Tet^R and are shown in the table below:

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Table 59: MICs of Eravacycline and Comparators Against a Collection of Enterobacteriaceae isolates

Isolate	Genotype	ERV	TGC	CAZ	TZP	MEM	LVX	TET
EC 473	tet(A)	1	1	0.5	>128	0.031	0.25	>32
EC 474	ND	1	0.5	1	4	≤0.016	32	16
EC 475	tet(A)	1	0.5	0.063	2	≤0.016	8	>32
EC 476	tet(A)	1	0.5	0.063	1	0.031	0.031	>32
KP 566	SHV, TetD	0.25	0.5	ND	2	ND	0.06	>32
KP 567	ND	0.25	0.25	ND	<=0.5	ND	0.015	<=0.25

CAZ, ceftazidime; CIP, ciprofloxacin; EC, *Escherichia coli*; ERV, eravacycline; KP, *Klebsiella pneumoniae*; LVX, levofloxacin; MEM, meropenem; ND, not done or defined; TET, tetracycline; TGC, tigecycline; TZP, piperacillin/tazobactam

Source: Report 1284-17C.

No efficacy of eravacycline was observed in this study and doses resulted in bacterial stasis or growth. There was a lack of correlation between *f*AUC$_{0\text{-}24}$ and efficacy.

The following tables summarize the studies for gram-positive and gram-negative pathogens in the neutropenic murine thigh model including information on the strain type, MICs and comparators for eravacycline.

Table 60: Efficacy of Eravacycline and Comparators in Neutropenic Mouse Thigh Infection Efficacy Studies

Organism, Strain	Resistance Genotype and/or Phenotype	Study Drug	Reduction in CFU[a] vs. 24h vehicle control (mg/kg)			Maximum $\log_{10}$ CFU reduction (dose in mg/kg)	MIC (µg/mL)	Reference Study Report VVS055-
			1 $\log_{10}$	2 $\log_{10}$	3 $\log_{10}$			
S. aureus ATCC 13709	-	eravacycline	0.2	0.2	0.4	5.1 (10)	0.016	*042908-00*
		tigecycline	1.2	1.5	2	4.8 (30)	0.063	
S. aureus SA161	MRSA, *tet*(M) MDR[b]	eravacycline	0.6	1	3	3.5 (10)	0.063	*101408-00*
		tigecycline	3	12.5	17.3	3.6 (20)	0.25	
		vancomycin	0.8	2.9	10	3.5 (30)	1	
S. aureus MRSA300 SA192	CA-MRSA (USA300) *tet*(K), macrolide-R	eravacycline	3.5	9.5	NR	2.1 (10)	0.25	*102108-00*
		tigecycline	3.8	8	NR	2.9 (20)	0.13	
		vancomycin	2.1	19.2	NR	2.8 (30)	1	
S. aureus SA158	*tet*(K)	eravacycline	2.3	8.2	16.2	3.5 (20)	0.063	*010609-00*
		tigecycline	2.1	5.4	9.7	3.2 (20)	0.13	
		vancomycin	2.8	>20	>20	1.7 (20)	2	
Streptococcus pyogenes ATCC 8668	-	eravacycline	5.3	9	NR	2.3 (10)	0.016	*012009-00*
		tigecycline	6	15.8	NR	2.3 (20)	≤0.016	
		linezolid	>20	>20	NR	0.7 (20)	2	

Sources: Study Reports VVS055- as indicated in references above
ATCC = American Type Culture Collection; CA = community acquired; CFU = colony forming unit; MIC = minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; NR = not reached; *tet* = tetracycline
a. CFU per gram of thigh muscle tissue
b. Multidrug-resistant strain (MDR) that is resistant to tetracycline, macrolide, fluoroquinolone, and cephalosporins.

In the gram-positive neutropenic mouse thigh model, eravacycline showed the greatest efficacy in comparison to tigecycline at producing 2-log reductions in CFU for *S. aureus* SA-161 Tet^R and *S. pyogenes* ATCC 8668. There was a 2 $\log_{10}$ CFU reduction or greater with eravacycline treatment in comparison to controls for all isolates tested including MRSA USA300, SA-161, and *S. pyogenes* ATCC 8668.

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Mouse thigh infection models of immunocompetent and neutropenic mice were used to assess eravacycline efficacy against *E. coli* and *K. pneumoniae* isolates. Efficacy was assessed after 24 hours by comparing bacterial burden from thigh tissue of treated animals to untreated vehicle prior to treatment and at 24 hours. The MICs for the strains and the values for stasis and effective exposure index 50 (EI_{50}) are shown in the tables below:

Table 61: Enterobacteriaceae Tested in the Murine Thigh Model

Isolate number		MIC (µg/mL)	
CAIRD	Tetraphase	Eravacycline	Tigecycline
EC 363	EC 355	0.063	0.125
EC 366	EC133	0.125	0.125
KP 404	KP451	0.125	0.25

CAIRD = Center for Anti-infective Research and Development; MIC = minimum inhibitory concentration

Source: Study HH128339

Table 62: Free AUC/MIC Plasma Ratios Associated with Eravacycline Intraperitoneal Administration in the Immunocompetent Murine Thigh Model

Isolate	MIC (µg/mL)	EI_{50}	Stasis	E_{max}
E. coli 363	0.063	38.1	42.7	-0.83
E. coli 366	0.125	188.7	119.7	-1.88
K. pneumoniae 404	0.125	33.4	43.9	-0.41
UNT019-1[a]	0.063	31.4	58.9	-1.09

AUC = area under the plasma concentration-time curve; MIC = minimum inhibitory concentration; EI_{50} = exposure index 50%; E_{max} = maximum effect in log_{10}CFU/thigh.
a. *E. coli* UNT019-1 from Tetraphase 2010-02, eravacycline administered subcutaneously.

Source: Tetraphase-2010-02

In the gram-negative bacteria, eravacycline was reported to be efficacious after single dose administration, however, the mean magnitude associated with stasis had to be recalculated by the Applicant using a more detailed analysis (data not shown).

The following table shows some of the virulence factors of *E. coli* isolates tested. *C. freundii* was also tested in this model.

Table 63: *E. coli* Isolates Used in the Murine Neutropenic Thigh Model with I.P. Administration

E.coli isolate	Phenotype	Median MIC (µg/mL)
ATCC25922	CLSI type strain	0.125
EC355	tet(B), CTX-M-9/14	0.125
EC1135	*tet*(M), ESBL	0.25
1-894-1	Tet^R	0.125
14714-1	ESBL	0.125
102-94090	ESBL	0.25

Source: NC-Andes-2017-01
MIC = minimum inhibitory concentration

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Lung infection model in neutropenic mice

Mixed infection intra-abdominal abscess model in rats

The therapeutic efficacy of eravacycline compared with ertapenem was evaluated in a rat intra-abdominal mixed-infection model using *E. coli* UNT057-1 (CTX-M-15 (MICs of 0.125 to 0.25 mcg/mL) and *B. fragilis* ATCC 25825 (MIC of 0.063 mcg/mL). Data from two separate *in vitro* evaluations demonstrated that eravacycline exhibited activity against both isolates for *E. coli* UNT057-1 (CTX-M-15) and 0.063 mcg/mL for *B. fragilis* ATCC25825.

Although eravacycline exhibited activity *in vitro* against the *E. coli* and *B. fragilis* isolates used in the infection model, the 10, 20 and 40 mg/kg BID regimens of eravacycline did not demonstrate a significant reduction in CFU/abscess *in vivo* compared to the untreated controls (data not shown). The Applicant's suggested that treatment with eravacycline may have been complicated by drug-related morbidity and lethality that has been observed in rats following i.v. administration [Grotti 2009 (Report ECQ00010), Bai 2009 (Report EQC00020)]. The exposures associated with treatment in this study were unknown. The Applicant suggested that a survival endpoint might have been a better assessment of efficacy than early bioburden reduction.

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Reviewer's Comment
Although lung infection models are useful for determining efficacy and whether the drug reached concentrations in the epithelial lining fluid (ELF), this model was not particularly relevant to the indication which is cIAI. Likewise, the animal models involving potential agents of bio-terrorism are not discussed in this review. Additionally, some of the animal models used strains that produced beta-lactamases, which is not a tetracycline-class resistance mechanism. The mixed infection intra-abdominal abscess model in rats is relevant to the indications, however, it did not produce interpretable results. The murine thigh infection and systemic infection models (survival) listed above, were not intra-abdominal infections, however, some of these studies contributed to proof of concept in well-known animal models and using relevant pathogens. This proof of concept was demonstrated through extending animal survival through eravacycline treatment and/or reduction in $\log_{10}$ CFU of the tested pathogen.

8.1.3 Pharmacokinetics/Pharmacodynamics

In vitro chemostat model

An *in vitro* dynamic chemostat system was used to identify the PK/PD index associated with the efficacy of eravacycline against *E. coli*; and to determine the magnitude of the PK/PD index associated with the efficacy of eravacycline using a multiple *E. coli* isolate challenge panel Eravacycline susceptibility studies were conducted in accordance with CLSI guidelines (CLSI M7). Tetracycline was used as an internal standard for susceptibility assays. In order to evaluate the effect of protein binding on eravacycline activity for the five *E coli* isolates, a series of susceptibility studies were carried out in which Mueller Hinton growth medium was supplemented with either mouse or human serum. In these experiments, an initial inoculum of 1.0×10^6 CFU/mL of each of the challenge organisms was used. Bacteria were exposed to changing concentrations of eravacycline simulating free-drug plasma concentrations following intravenous administration of a 1 mg/kg dose in healthy volunteers (Connors et al., 2014)[9]. Specimens were collected for CFU counts at 0, 2, 4, 8, 12, 24, 30, and 48 h. The correlation between efficacy and the PK/PD parameters of AUC/MIC, C_{max}/MIC, and %T>MIC were determined. As with tigecycline (Craig, 1998[10]; Passarell et al.[11], 2008; Meagher et al., 2007[12]),

[9] Connors KP, Housman ST, Pope JS, et al. Phase I, open-label, safety and pharmacokinetic study to assess bronchopulmonary disposition of intravenous eravacycline in healthy men and women. *Antimicrob Agents Chemother*. 2014;58(4):2113-8.

[10] Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis*. 1998;26:1-10.

[11] Passarell JA, Meagher AK, Liolios K, et al. Exposure-response analyses of tigecycline efficacy in patients with complicated intra-abdominal infections. *Antimicrob Agents Chemother*.2008;52(1):204-10.

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the analysis demonstrated that AUC/MIC was the PK/PD index best associated with efficacy based upon data fit and R^2 values.

PK/PD Models In Vivo

The Applicant provided information on the percent probability of PK-PD target attainment by MIC and protein binding method for Enterobacteriaceae (See figure in clinical pharmacology section above). Additionally, two studies were performed to evaluate the efficacy of eravacycline in the neutropenic murine thigh infection model against *E. coli* isolates exhibiting variable resistance mechanisms, as well as to evaluate the relative *f*AUC/MIC magnitude required for eravacycline efficacy (see animal studies above). The Agency's clinical pharmacology review team determined the PTA inadequate to support the breakpoints due to variability in the PK/PD target in animal models and the uncertainty in plasma protein binding. Therefore, the PTA will not be further discussed in this section. See clinical pharmacology section for additional information, and impact on breakpoint determination at the clinical microbiology final recommendations section of this review.

8.2 Clinical Microbiology

8.2.1 Clinical Microbiology Analysis Of Efficacy

Specimens for Culture

Aerobic and anaerobic specimens for culture at the time of the initial surgical procedure (or during re-intervention in the case of prior treatment failures) were collected from the site of infection by aspiration and/or tissue sample and directly inoculated into transport media during the surgical intervention. A set of blood cultures (aerobic and anaerobic) was taken from at least two separate venipuncture sites at screening before the initiation of study drug. The blood and intra-abdominal specimens were cultured, and the species identified according to local laboratory practice by a qualified local or regional laboratory. Pure cultures of isolate(s) were sent to a central, reference laboratory for confirmation of species identification and susceptibility analysis to eravacycline, ertapenem and other comparator antibacterial drugs. Shipping materials were provided by the central laboratory and adhered to local and other international regulations for transportation of biological materials.

Microbiological Efficacy

Per-pathogen microbiological response categories were eradication, presumptive eradication, persistence, persistence with decreased susceptibility, presumed persistence, and indeterminate as defined in the study protocols. These categories were further classified as

[12] Meagher AK, Passarell JA, Cirincione BB, et al. Exposure-response analyses of tigecycline efficacy in patients with complicated skin and skin-structure infections. *Antimicrob Agents Chemother*. 2007;51(6):1939-45.

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favorable (eradication, presumed eradication), unfavorable (persistence, persistence with decreased susceptibility, presumed persistence), and indeterminate.

The pathogenic organisms identified at baseline from an intra/extra-abdominal specimen or blood culture was presented by study and pooled across studies. The number and percentage of subjects with gram-negative aerobes, gram-positive aerobes, and anaerobes was presented by genus and species, antibiotic resistance, and confirmed beta- lactamase, carbapenemase, and AmpC producers for the micro-ITT and ME populations. Antibiotic resistance included pathogens resistant to specific individual antibiotics, multidrug-resistant (MDR) pathogens, 3rd/4th generation cephalosporin-resistant (cefotaxime- and/or ceftazidime- and/or cefepime-resistant), and carbapenem-resistant pathogens. Resistance was defined in the 2016 CLSI guidance M100S26 or, if absent (i.e., tigecycline) the MIC breakpoints are defined in the FDA package insert or another reference documented. Carbapenem-R was defined as resistant to ertapenem, imipenem, and/or meropenem. Multidrug resistance is defined as resistant to at least one member of ≥3 antibiotic classes.

The number and percentage of subjects with mono-microbial (single gram-negative, single gram-positive or single anaerobe pathogen) and poly-microbial infections (gram-negative only, gram-positive only, anaerobes only, and mixed infections [gram-positive and gram-negative; gram-positive and anaerobe; gram-negative and anaerobe; and gram-negative, gram-positive and anaerobe]) were provided for the specimens from the infection site (i.e., intra/extra-abdominal specimen or blood culture) for the micro-ITT and ME populations by study and combined across study. Where central laboratory determinations of genus and species were not available, local/regional identifications were used. Only central laboratory antibiotic susceptibility/MIC results were used.

Microbiological categories for pathogens identified after baseline assessment were superinfection and new infection. Superinfection was defined as emergence of a new pathogen during therapy with emergence of new signs and symptoms of infection (i.e., determined by the Investigator to be clinical failure). A new pathogen was defined as a different genus and species. New infection was defined as eradication of the original pathogen followed by replacement after completion of therapy by a new pathogen with signs and symptoms of infection. Decreasing susceptibility of a pathogen was defined as a >2-times (at least 2 dilutions) increase from baseline to any subsequent study time point in the MIC of the study drug received.

The Clinical cure at test of cure (TOC) for each phase 3 trial by baseline pathogen is shown in the table below for the mITT population as proposed by the Agency in the clinical section of the eravacycline labeling. TOC was 25-31 days after the first dose of study drug was administered.

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Table 65: Clinical Cure Rates at TOC by Selected Baseline Pathogen in Pooled Phase 3 cIAI Trials, Micro-ITT Population

Pathogen	ERV (b) (4) (N=415) n/N1 (%)	(b) (4) Comparators (b) (4) (N=431) n/N1 (%)
Enterobacteriaceae	271/314 (86.3)	289/325 (88.9)
Citrobacter freundii	19/22 (86.4)	8/10 (80.0)
Enterobacter cloacae complex	17/21 (81.0)	23/24 (95.8)
Escherichia coli	220/253 (87.0)	237/266 (89.1)
Klebsiella oxytoca	14/15 (93.3)	16/19 (84.2)
Klebsiella pneumoniae	37/39 (94.9)	42/50 (84.0)
(b) (4)		
Enterococcus faecalis	45/54 (83.3)	47/54 (87.0)
Enterococcus faecium	38/45 (84.4)	48/53 (90.6)
Staphylococcus *aureus*	24/24 (100.0)	12/14 (85.7)
Streptococcus anginosus group (b) (4)	79/92 (85.9)	50/59 (84.7)
(b) (4)		
Anaerobes	186/215 (86.5)	194/214 (90.7)
(b) (4)		
(b) (4)		

Reviewer's Comment

(b) (4)

Bacteroides uniformis was added to the first list of organisms because there was adequate clinical experience for this organism and it was deemed clinically relevant.

Microbiology from Clinical Trials

The largest portion of isolates analyzed were *E. coli*, 231 isolates from combined studies. *E. coli,* and *Klebsiella* isolates including *Klebsiella oxytoca* and *K. pneumoniae* were found to carry a diversity of tetracycline resistant mechanisms including efflux genes as well as the *blaNDM*-family metallo-beta-lactamase gene. The gram-positive isolates *Enterococcus*, *Staphylococcus*, and *Streptococcus,* isolates carried the tetracycline resistance gene *tet*(M) and the efflux pump gene *tet*(L). Genetic characterization is further discussed in the review below.

Reviewer's Comment

(b) (4)

Pathogen distribution for monomicrobial and polymicrobial infections

For the subjects in the micro-ITT population in both studies, the Applicant reported that across all treatment groups, approximately 70% of all infections were polymicrobial. Monomicrobial infections were found in approximately 30% (Table below). The distributions of pathogens across the subsets of subjects with monomicrobial and polymicrobial infections were similar between the two treatment groups. In the subset of subjects with polymicrobial infections, the frequencies of various combinations of co-cultured pathogens were similar between the treatment groups.

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Table 66: Monomicrobial and Polymicrobial Infections in Studies TP-434-008 and TP-434-025 (Micro-ITT Population)

	TP-434-008		TP-434-025		Pooled Phase 3 cIAI	
	ERV 1.0 mg/kg q12h IV (N=220)	ETP 1.0 g q24 IV (N=226)	ERV 1.0 mg/kg q12h IV (N=195)	MER 1.0 g q8h IV (N=205)	ERV 1.0 mg/kg q12h IV (N=415)	All Comparators (N=431)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Mono-microbial Infection	63 (28.6)	64 (28.3)	48 (24.6)	74 (36.1)	111 (26.7)	138 (32.0)
Single Gram-negative pathogen	42 (19.1)	43 (19.0)	22 (11.3)	45 (22.0)	64 (15.4)	88 (20.4)
Single Gram-positive pathogen	18 (8.2)	19 (8.4)	19 (9.7)	21 (10.2)	37 (8.9)	40 (9.3)
Single Anaerobe pathogen	3 (1.4)	2 (0.9)	7 (3.6)	8 (3.9)	10 (2.4)	10 (2.3)
Poly-microbial Infection	157 (71.4)	162 (71.7)	147 (75.4)	131 (63.9)	304 (73.3)	293 (68.0)
Gram-negative aerobes only [1]	13 (5.9)	14 (6.2)	12 (6.2)	9 (4.4)	25 (6.0)	23 (5.3)
Gram-positive aerobes only [1]	8 (3.6)	9 (4.0)	5 (2.6)	1 (0.5)	13 (3.1)	10 (2.3)
Anaerobes only [1]	0	2 (0.9)	1 (0.5)	1 (0.5)	1 (0.2)	3 (0.7)
Gram-negative and Gram-positive	33 (15.0)	34 (15.0)	27 (13.8)	18 (8.8)	60 (14.5)	52 (12.1)
Gram-negative and Anaerobe	45 (20.5)	45 (19.9)	31 (15.9)	35 (17.1)	76 (18.3)	80 (18.6)
Gram-positive and Anaerobe	9 (4.1)	8 (3.5)	5 (2.6)	8 (3.9)	14 (3.4)	16 (3.7)
Gram-negative, Gram-positive and Anaerobe	49 (22.3)	50 (22.1)	66 (33.8)	59 (28.8)	115 (27.7)	109 (25.3)

Source: *ISM Table 5.1*
N = Number of subjects in the micro-ITT Population. n = Number of subjects within a specific category. Percentages are calculated as 100 x (n/N).
ERV = Eravacycline. ETP = Ertapenem. MER = Meropenem.
[1] Subjects are considered to have a poly-microbial Gram-negative, Gram-positive, or anaerobe infection if more than one pathogen, including pathogens with the same genus and species but differentiated based on susceptibility profile, within an overall group is identified.

Reviewer's Comment

The investigation of monomicrobial and polymicrobial infections is relevant to cIAI (peritonitis). Primary bacterial peritonitis is usually associated with monomicrobial infections with gram-positive cocci or Enterobacteriaceae. Secondary bacterial peritonitis is commonly due to Enterobacteriaceae, gram- positive Enterococci, Staphylococci and anaerobes. Resistant organisms are usually present in polymicrobial infections. The molecular characterization of the isolates from the phase 3 studies is discussed in the tables below.

Table 67: Clinical Response at the TOC Visit Excluding Subjects Who Had a Carbepenem-Resistant Pathogen at Baseline in the Comparator Group-Pivotal Studies and Pooled Analysis-Micro-ITT Population

	Study TP-434-008		Study TP-434-025		Pooled	
Response	Eravacycline 1.0 mg/kg q12h (N=220) n (%)	Ertapenem 1.0 g q24h (N=195) n (%)	Eravacycline 1.0 mg/kg q12h (N=195) n (%)	Meropenem 1.0 g q8h (N=196) n (%)	Eravacycline 1.0 mg/kg q12h (N=415) n (%)	Comparator (N=391) n (%)
Clinical Cure	191 (86.8)	170 (87.2)	177 (90.8)	178 (90.8)	368 (88.7)	348 (89.0)
Difference (95% CI)[a]	-0.4 (-6.9, 6.3)		0.0 (-6.0, 5.9)		-0.3 (-4.6, 4.2)	
Clinical Failure	19 (8.6)	10 (5.1)	7 (3.6)	7 (3.6)	26 (6.3)	17 (4.3)
Indeterminate/Missing	10 (4.5)	15 (7.7)	11 (5.6)	11 (5.6)	21 (5.1)	26 (6.6)

Source: *TP-434 ISE Appendices Table 5.*
Abbreviations: N=Number of subjects in the Micro-ITT population (For Eravacycline group) and who did not have a Carbapenem resistant pathogen at baseline (For Comparator groups); n = Number of subjects with the specific response. Percentages are calculated as 100 x (n/N1).
Difference = Difference in clinical cure rates (Eravacycline minus Comparator).
[a] For Pooled - Confidence intervals are stratified by study and calculated using the adjusted Miettinen-Nurminen method. For Individual Studies - Confidence intervals are calculated using the unadjusted Miettinen-Nurminen method.
Clinical response is based on the Surgical Adjudication Committee assessment (if available).

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Study "Characterization of Molecular Relatedness and Beta-lactam Resistance Mechanisms of Strains Collected in Complicated Intra-abdominal Infections During Phase 3 Clinical trials for Eravacycline": Beta-lactam resistance mechanisms among gram-negative pathogens that displayed a beta-lactamase phenotype (below) and/or carbapenem resistance (above), according to current CLSI guidelines, were evaluated by the Applicant. Isolates of the same bacterial species from a study subject were evaluated by pulsed-field gel electrophoresis (PFGE) to assess genetic relatedness. The following summaries of beta-lactamase-encoding genes were provided by the Applicant for non-fermentative gram-negative bacteria and Enterobacteriaceae.

Table 68: Summary of Positive Results for Beta-lactamase-encoding Genes and OprD Loss Detected Among Non-fermentative Gram-negative Bacilli Isolates

	Carbapenemases					ESBLs					
Organism/group	IMP-1	OXA-23	OXA-72-like	OXA-143	VIM-2	GES-11	OXA-10	OXA-17	PER-1	Chromosomal AmpC overexpression[a]	OprD loss
All non-fermentative Gram-negative	1	3	4	4	1	5	2	1	1	8	1
Acinetobacter baumannii complex[b]		3	4	4	1	5			1	7	
Pseudomonas aeruginosa	1						2	1		1	1

a. Only elevated expression levels were considered positive.
b. OXA-51 was not listed since this gene is intrinsic in *A. baumannii* complex isolates.

Table 4. Summary of the positive results for β-lactamase-encoding genes detected among Enterobacteriaceae isolates.

	Carbapenemase		ESBL								Narrow Spectrum β-lactamase			Plasmidic AmpC	
Organism/group	KPC-2	OXA-48	CTX-M-14	CTX-M-15-like	CTX-M-1-like	CTX-M-3-like	CTX-M-55/79	OXA-1/30	SFO-1-like	SHV-12	SHV-30	SHV-1	SHV-11	TEM-1	CMY-2-like	Chromosomal AmpC overexpression[a]
All Enterobacteriaceae	1	1	2	35	3	3	1	33	1	2	1	5	8	28	5	11
Citrobacter freundii				5				5								7
Citrobacter freundii species complex											1					1
Enterobacter cloacae				4				4	1					3		3
Escherichia coli			2	13	3		1	12		2		1		9	4	
Klebsiella oxytoca				1				1						1		
Klebsiella pneumoniae	1	1		10		1		9				4	8	11		
Proteus mirabilis						2								2	1	
Serratia marcescens				2				2						2		

a. Only "elevated" expression levels (not modestly elevated) were considered positive.

Reviewer's Comment

(b) (4)

Based on the numbers of beta-lactamases from the study reports of Phase 3 clinical trials for cIAI, the following numbers and

types of beta-lactamases from combined Enterobacteriaceae and non-fermentative gram-negative bacilli isolates from Phase 3 clinical trials were considered by this reviewer to be most consistently prevalent in the isolates tested. Eravacycline appeared to maintain activity in the presence of these beta lactamases (N): CTX-M (44), SHV (16), CMY (5), OXA (48), TEM (28) and AmpC (19). Pulse-field Gel Electrophoresis was used to distinguish between isolates of the same species recovered during baseline and follow-up visits. The data is shown below:

Table 69: MIC (mcg/mL) Summary Statistics of Eravacycline for Unique Pathogens Identified at Baseline From Blood and Intra-abdominal Cultures Confirmed Extended-spectrum Beta-lactamase, Amp C Beta-lactamase and Carbapenemase Producing Gram-negative Aerobes in Studies TP-434-008 and TP-434-025 (Micro-ITT-Population)

Pathogen	Pooled Phase 3 cIAI Studies (N=846)			
		MIC (µg/mL)		
	N1	MIC_{50}	MIC_{90}	Range
Enterobacteriaceae	991	0.25	0.5	0.03-2
ESBL	85	0.25	1	0.06-2
Carbapenemase	4	NC	NC	0.5-2
AmpC	20	0.5	0.5	0.12-2
Citrobacter freundii	33	0.25	0.5	0.12-1
ESBL	6	NC	NC	0.25-1
CTX-M-15-Like	5	NC	NC	0.25-0.5
SHV-30	1	NC	NC	1-1
AmpC	7	NC	NC	0.25-1
Elevated Expression	7	NC	NC	0.25-1
Enterobacter cloacae complex	51	0.5	0.5	0.12-1
ESBL	10	0.5	0.5	0.25-1
CTX-M-15-Like	9	NC	NC	0.25-0.5
SFO-1-Like	1	NC	NC	1-1
AmpC	4	NC	NC	0.5-0.5
Elevated Expression	4	NC	NC	0.5-0.5
Escherichia coli	630	0.12	0.25	0.03-2
ESBL	39	0.25	0.5	0.06-0.5
CTX-M-1-Like	2	NC	NC	0.12-0.5
CTX-M-3-Like	2	NC	NC	0.06-0.25
CTX-M-5	1	NC	NC	0.12-0.12
CTX-M-14	2	NC	NC	0.12-0.25
CTX-M-15-Like	28	0.25	0.5	0.06-0.5
CTX-M-32	1	NC	NC	0.25-0.25
CTX-M-55/79	1	NC	NC	0.5-0.5
SHV-12	3	NC	NC	0.06-0.25
AmpC	8	NC	NC	0.12-0.5
CMY-2-Like	7	NC	NC	0.12-0.5
CMY-42	1	NC	NC	0.25-0.25
Klebsiella oxytoca	34	0.25	0.25	0.12-1
ESBL	1	NC	NC	0.12-0.12
CTX-M-15-Like	1	NC	NC	0.12-0.12
Klebsiella pneumoniae	106	0.25	1	0.06-2
ESBL	24	1	1	0.12-2
CTX-M-2	1	NC	NC	0.12-0.12
CTX-M-3-Like	1	NC	NC	1-1
CTX-M-15-Like	21	1	1	0.12-2
SHV-12	1	NC	NC	0.5-0.5

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Pathogen	Pooled Phase 3 cIAI Studies (N=846)			
		MIC (µg/mL)		
	N1	MIC_{50}	MIC_{90}	Range
Carbapenemase	4	NC	NC	0.5-2
KPC-2	2	NC	NC	0.5-0.5
OXA-48	2	NC	NC	0.5-2
Proteus mirabilis	34	1	2	0.5-2
ESBL	2	NC	NC	1-1
CTX-M-3-Like	2	NC	NC	1-1
AmpC	1	NC	NC	2-2
CMY-2-Like	1	NC	NC	2-2
Serratia marcescens	6	NC	NC	1-2
ESBL	3	NC	NC	1-2
CTX-M-15-Like	3	NC	NC	1-2
Non-*Enterobacteriaceae*	163	2	8	0.015-16
ESBL	8	NC	NC	0.25-16
Carbapenemase	7	NC	NC	0.06-16
AmpC	7	NC	NC	0.12-0.5
Acinetobacter baumannii complex	25	0.25	0.5	0.03-1
ESBL	6	NC	NC	0.25-0.25
GES-11	5	NC	NC	0.25-0.25
PER-1	1	NC	NC	0.25-0.25
Carbapenemase	6	NC	NC	0.06-1
VIM-2	1	NC	NC	0.06-0.06
OXA-23	2	NC	NC	0.5-1
OXA-72-Like	3	NC	NC	0.12-0.5
AmpC	7	NC	NC	0.12-0.5
Elevated Expression	7	NC	NC	0.12-0.5
Pseudomonas aeruginosa	81	4	8	0.25-16
ESBL	2	NC	NC	8-16
OXA-10	2	NC	NC	8-16
Carbapenemase	1	NC	NC	16-16
IMP-1	1	NC	NC	16-16

Adapted from *ISM Table 8.1.1a*
N = Number of subjects in the micro-ITT Population.
N1 = Number of unique pathogens with MIC data available in the specific category.
NC= not calculated for pathogens where N1 <10
ESBL = extended spectrum β-lactamase; MIC = minimum inhibitory concentration; MIC_{50} = concentration inhibiting 50% of isolates; MIC_{90} = concentration inhibiting 90% of isolates

8.2.2 Interpretive Criteria

Provisional Antimicrobial Susceptibility Testing (AST) Interpretive criteria
Provisional AST interpretive criteria were not used for analysis of data from the clinical trials due to limited availability of relevant PK/PD data to allow selection of breakpoints at the time the studies were conducted.

Correlation of Broth MICs to Disk Zone Size
The performance of commercially manufactured 20 mcg eravacycline disks was evaluated by performing susceptibility testing on target gram-positive and -negative pathogens by broth microdilution and disk diffusion using concurrent inocula at a reference testing laboratory [redacted] (b) (4)). In this study, a total of 1,441 isolates were evaluated. This included 607 Enterobacteriaceae (11 species), 175 non-fermentative gram-negative bacilli (5 species), 150 *S. aureus*, 54 coagulase-negative staphylococci, 129 enterococci, 100 *Streptococcus pneumoniae*, 100 beta-hemolytic streptococci (3 species groups), 46 viridans

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group streptococci (multiple species), 28 *Moraxella catarrhalis*, and 51 *H. influenzae*. Using disk lots from both Bio-Rad and Mast, the Applicant reported no difference between disk lots from different manufacturers (b) (4) 2038).

When testing eravacycline disks manufactured by Mast, the Applicant reported that there was good correlation between broth microdilution MICs and disk zone size by pathogen and by organism groups. However, the Applicant also stated that with exception of the non-fermenters, there were not enough resistant organisms included in the study to get correlates across the entire spectrum of the MIC distributions. The Applicant used the error-rate bounding analysis method (Metzler and DeHaan, 1974)[13], to evaluate MIC and disk correlation studies, however, the Agency is proposing different MIC and disk zone diameter values. See analysis below:

Reviewer's Comment
Data provided by the Applicant was displayed in scattergrams (not shown) with zone diameters on the x axis and MICs on the y axis. The error rate-bounded method was used to form a table with the total number of isolates tested and the number of minor, major, or very major discrepancies that were recorded for the isolates. This is the method described by CLSI in their document M23-A4 and the CLSI guidelines for acceptable discrepancy rates are below:

Table 70: CLSI Guideline for Acceptable Discrepancy Rates for MIC-Disk Correlation Studies (Without Intermediate Range)

MIC Range	Very Major	Major	Minor
≥R+1	<2%	NA	<5%
R+S	<10%	<10%	<40%
≤ S-1	NA	<2%	<5%

Source: Adapted from CLSI document M23-A4.

Reviewer's Comment
The aim of this analysis was to minimize discrepancy rates to best fit within CLSI guidelines. Minimizing error rates is important to prevent negative consequences for patients which could result from errors such as calling strains susceptible when they are known to be resistant. The guideline above was selected by this reviewer because there is no intermediate range and the interpretive criteria distinguish susceptible and resistant populations. It was unclear why the Applicant used an analysis which included an intermediate range for some of their analysis (Report (b) (4) 2038) when they were not proposing an intermediate breakpoint. The analysis used by the Agency is shown in the tables below for each pathogen type.

[13] Metzler CM, DeHaan RM. Susceptibility tests of anaerobic bacteria: statistical and clinical considerations. *J Infect Dis*. 1974;130(6):588-94.

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MIC-Disk Correlations for Enterobacteriaceae

Table 71: Discrepancy Rates for MIC-Disk Correlation for Enterobacteriaceae Using an MIC Susceptible Breakpoint of ≤0.5 mcg/mL and a Susceptible Zone Diameter Breakpoint of ≥ 15 mm

MIC Range	n	Discrepancy Rates		
		Very Major	Major	Minor
≥ R +1	50	1 (2%)	NA	---
R+S	435	38 (8.7%)	49 (11%)	---
≤ S-1	1258	NA	32 (2.5%)	---
Total	1743	39 (2%)	81(4.6%)	---

Source: Reviewer's Table.

Reviewer's Comment
The analysis of the disk diffusion correlation for eravacycline against Enterobacteriaceae showed that CLSI guidelines for acceptable discrepancy rates could not be met using the MIC susceptible breakpoint of ≤0.5 mcg/mL and a susceptible zone diameter of ≥ 15 mm, but were close. The major error rates were just above CLSI recommendations in the R+S and ≤S-1 regions of the scattergram. It was not possible to eliminate this error rate without increasing the very major errors to unacceptable values based on CLSI criteria in the ≥R+1 region of the scattergram. It is not likely that error rates can be reduced by eliminating *Proteus mirabilis* (b) (4) because the MIC values were high for these organisms, and the error rates that are too high in the scattergram are in the lower region of the graph (in association with MICs less than 0.25 mcg/mL).

Attempts to use disk criteria of S ≥ 14 mm still maintained major error rates that were outside of CLSI recommendations. At disk criteria of S ≥ 14 mm and smaller zone diameters, there was an increase in very major error rates to unacceptable values for the ≥ R+1 region of the scattergram. CLSI stated in M23-A4 document that if there are no intermediate ranges for MIC and disk interpretive criteria, that the minor discrepancy rates are not a consideration. Therefore, no minor error rates were calculated for this analysis. As 300 Enterobacteriaceae is the preferred number of isolates, the Applicant provided a sufficient number for this analysis (N=1743 isolates). The reviewer's recommended disk breakpoints are S≥ 15 mm for Enterobacteriaceae.

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Table 72: Discrepancy Rates for MIC-Disk Correlation for *Staphylococcus aureus* Using an MIC Susceptible Breakpoint of ≤0.06 mcg/mL and a Susceptible Zone Diameter Breakpoint of ≥ 28mm

MIC Range	n	Discrepancy Rates		
		Very Major	Major	Minor
≥ R +1	18	0	NA	----
R+S	269	0	207 (77%)	----
≤ S-1	51	NA	50 (98%)	----
Total	150	0	257 (76%)	----

Source: Reviewer's Table.

Reviewer's Comment
The disk correlation analysis for *S. aureus* was not able to meet CLSI guidelines for acceptable discrepancy rates. Using an susceptible MIC breakpoint of ≤0.06 mcg/mL and a disk diffusion susceptible breakpoint of ≥20 mm, the very major errors in the ≥R+1 section of the scattergram were too high at 50%. If the breakpoint for disk is changed to susceptible ≥28 mm, the very major errors can be eliminated, however, the major error rates in the R+S and ≤S-1 will exceed CLSI recommended guidelines at 77% and 98% respectively. The recommended number of isolates was used for this analysis was greater than 100, and therefore was an acceptable number. No disk diffusion criteria are recommended.

Table 73: Discrepancy Rates for MIC-Disk Correlation for *Enterococcus* spp. Using an MIC Susceptible Breakpoint of ≤0.06 mcg/mL and a Susceptible Zone Diameter Breakpoint of ≥ 22 mm

MIC Range	n	Discrepancy Rates		
		Very Major	Major	Minor
≥ R+1	3	0	NA	-----
R+S	241	28 (11.6%)	47 (19.5%)	-----
≤ S-1	191	NA	27 (14%)	-----
Total	435	28 (6.4%)	74 (17%)	-----

Source: Reviewer's Table.

Reference ID: 4312284

Reviewer Comment
An MIC susceptible breakpoint of ≤ 0.06 mcg/mL for *Enterococcus* spp. and a disk susceptible breakpoints of ≥ 22 mm were used for the analysis. Very major errors in the R + S and major errors in the R+S and ≤S-1 region of the scattergram were too high using these criteria. If disk diffusion breakpoints of susceptible ≥ 23 mm or greater zone diameter breakpoints were used, in an attempt to reduce the very major errors, the major error rate would increase further. The analysis for disk discrepancy *Enterococcus* spp. did have the recommended number of isolates of greater than 100. No disk diffusion criteria are recommended.

Table 74: Discrepancy Rates for MIC-Disk Correlation for Viridans Group Streptococci Using an MIC Susceptible Breakpoint of ≤0.06 mcg/mL and a Susceptible Zone Diameter Breakpoint of ≥ 25 mm

MIC Range	n	Discrepancy Rates		
		Very Major	Major	Minor
≥ R+1	10	0	NA	-----
R+S	68	8 (8.8%)	12 (17.6%)	-----
≤ R-1	317	NA	9 (2.8%)	-----
Total	395	8 (2%)	21 (5.3%)	-----

Source: Reviewer's Table.

Reviewer's Comment
The Agency's analysis of disk diffusion correlation with MIC ≤0.06 mcg/mL for viridans group streptococci produced the error rates shown above. The disk diffusion susceptible breakpoint used above was ≥ 25 mm. Using these criteria, the major error rates in the R+S and ≤ S-1 regions of the scattergram did not meet CLSI recommendations for acceptable error rates. At disk susceptible breakpoints of ≥ 24 mm and ≥26 mm, the very major error rate was too high in the R+S or the major error rates increased respectively. A sufficient number of isolates was used for this analysis. No disk criteria are recommended.

Reviewer's Comment
No scattergram analysis is shown for anaerobes as they use different methods for susceptibility testing (e.g. agar dilution rather than disk testing). The Agency's recommendation on disk diffusion criteria to correlate with proposed MIC breakpoints are in the final recommendation of this section.

Susceptibility test interpretive criteria for eravacycline

Reference ID: 4312284

The Applicant considered the totality of the data in determining the proposed breakpoints, including efficacy in human clinical trials, MIC frequency distributions from surveillance and clinical studies, efficacy in animal models of infection, and in vitro PK/PD models and PTA modeling. Based on clinical efficacy in intra-abdominal studies, the Applicant is seeking clinical indication labeling for the following organisms: *C. freundii, E. coli, Enterobacter cloacae, K. oxytoca, K. pneumoniae,* (b) (4), *S. aureus, Enterococcus faecalis*, *Enterococcus faecium, Streptococcus anginosis* group, (b) (4), *B. caccae, B. fragilis, B. ovatus, B. thetaiotaomicron, B. vulgatus, Clostridium perfringens* and *Parabacteroides distasonis.* The table below lists the Applicant's proposed interpretive criteria (breakpoints) that would be used by clinical laboratories performing susceptibility tests with eravacycline. These breakpoints are proposed based on the clinical cutoff, *in vitro* susceptibility distributions and determination of an epidemiological cutoff (ECOFF). ECOFF has been defined by EUCAST to describe the upper MIC limit of the susceptible peak in an MIC distribution, the wild-type (WT) population (Kahlmeter et al., 2003)[14].

Table 75: Applicant's Proposed Interpretive Criteria for MIC Testing with Eravacycline

Pathogen	MIC (µg/mL)	Zone diameter (mm)
Enterobacteriaceae	(b) (4)	
(b) (4)		
Staphylococcus aureus		
(b) (4)		
Anaerobes		

The epidemiological cutoff values for the organisms proposed for clinical indication labelling was determined using the ECOFF calculator on the CLSI website (https://clsi.org/education/microbiology/ecoffinder/) based upon the publication by Turnidge (Turnidge et al., 2006)[15]. ECOFF (97.5%) values were calculated for the 2014-2016 surveillance data, the isolates obtained in the two Phase 3 cIAI trials and for the combined datasets. In cases where the fitted function returned an incomplete curve or the distribution curve was bimodal, the proposed breakpoint was determined visually.

Reviewer's Comment

[14] Kahlmeter G, Brown DF, Goldstein FW, et al. European harmonization of MIC breakpoints for antimicrobial susceptibility testing of bacteria. *J Antimicrob Chemother*. 2003;52:145-8.

[15] Turnidge J, Kalhmeter G, Kronvall G. Statistical characterization of bacterial wild-type MIC value distributions and the determination of epidemiological cut-off values. *Clin Microbiol Infect* 2006;12:418-25

Reference ID: 4312284

(b) (4)

The data provided by the Applicant was re-evaluated by clinical microbiology and other disciplines. The Agency's clinical microbiology perspective is summarized below.

Reviewer's Comment
The Agency's clinical pharmacology review team found the PK-PD target attainment by MIC and protein binding to be variable and inadequate, the Agency's proposed breakpoints were primarily based on the clinical data. The information on in vitro data for the targeted organisms may be found in the in vitro activity section of this review, and the relevant clinical data is below.

Clinical cutoff
The microbiological responses are displayed below for all patients from Phase 3 cIAI studies that were treated with eravacycline. The favorable microbiological response rates were high overall.

Table 76: Microbiologically Favorable Response at TOC by Baseline Eravacycline MIC (mcg/mL) to key Gram-negative Aerobic Baseline Pathogens for All Patients Randomized to Eravacycline Treatment Arms for Phase 3 cIAI Studies (Micro-ITT)

Eravacycline MIC (µg/mL)	Number of eradications at each MIC/ number of pathogens at that MIC (% eradication)					
	C. freundii	*E. cloacae*	*E. coli*	*K. oxytoca*	*K. pneumoniae*	*A. baumannii*
0.06			36/40 (90.0)		1/1 (100.0)	
0.12	3/5 (60.0)	1/1 (100)	89/104 (85.6)	6/7 (85.7)	5/5 (100.0)	1/1 (100)
0.25	11/11 (100)	6/6 (100.0)	70/76 (92.1)	7/7 (100.0)	17/17 (100.0)	6/6 (100.0)
0.5	4/5 (80.0)	10/13 (76.9)	22/26 (84.6)		8/8 (100.0)	4/4 (100.0)
1	1/1 (100)	1/1 (100)	2/2 (100.0)	1/1 (100.0)	6/7 (85.7)	2/2 (100.0)
2			1/1 (100)		1/1 (100.0)	

Source *ISM Table 31.1*

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Table 77: Microbiologically Favorable response at TOC by Baseline Eravacycline MIC (mcg/mL) to key Gram-positive Aerobic Baseline Pathogens for All Patients Randomized to Eravacycline Treatment Arms for Phase 3 cIAI Studies (Micro-ITT)

Table 78: Microbiologically Favorable Response at TOC by Baseline Eravacycline MIC (mcg/mL) to key Anaerobic Baseline Pathogens for All Patients Randomized to Eravacycline Treatment Arms for Phase 3 cIAI Studies (Micro-ITT)

The following table shows the microbiologically favorable responses at TOC for each study and combined. There were 7 isolates in the Phase 3 cIAI studies of other Enterobacteriaceae species that tested with an eravacycline MIC of (b) (4) mcg/mL: *M. morganii* (n=1), *S. marcescens* (n=1) and *P. mirabilis* (n=5); all had favorable microbiological responses in clinical trials (b) (4)

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Table 79: Microbiologically Favorable Response at the TOC Visit of Pathogens Identified at Baseline for Patients Treated with Eravacycline in Phase 3 Trials for cIAI (Micro-ITT Population)

Pathogen	Number of eradications/ number of patients (% eradication)		
	TP-434-008	TP-434-025	Pooled Phase 3 cIAI
Overall	**192/220 (87.3)**	**179/195 (91.8)**	**371/415 (89.4)**
Gram-negative aerobes			
Citrobacter freundii	14/15 (93.3)	5/7 (71.4)	19/22 (86.4)
Enterobacter cloacae	11/14 (78.6)	7/7 (100.0)	18/21 (85.7)
Escherichia coli	109/127 (85.8)	114/126 (90.5)	223/253 (88.1)
Klebsiella oxytoca	7/7 (100.0)	7/8 (87.5)	14/15 (93.3)
Klebsiella pneumoniae	17/18 (94.4)	21/21 (100.0)	38/39 (97.4)
Acinetobacter baumannii	8/8 (100.0)	5/5 (100.0)	13/13 (100.0)
Gram-positive aerobes			
Staphylococcus aureus[a]	8/8 (100.0)	16/16 (100.0)	24/24 (100.0)
Enterococcus faecalis	16/23 (69.6)	29/31 (93.5)	45/54 (83.3)
Enterococcus faecium[b]	13/16 (81.3)	26/29 (89.7)	39/45 (86.7)
Streptococcus anginosus group	43/47 (91.5)	39/45 (86.7)	82/92 (89.1)
Streptococcus mitis group	18/18 (100.0)	12/13 (92.3)	30/31 (96.8)
Streptococcus salivarius group	8/8 (100.0)	2/2 (100.0)	10/10 (100.0)
Anaerobic pathogens			
Bacteroides caccae	9/11 (81.8)	5/6 (83.3)	14/17 (82.4)
Bacteroides fragilis	40/44 (90.9)	34/40 (85.0)	74/84 (88.1)
Bacteroides ovatus	14/19 (73.7)	19/24 (79.2)	33/43 (76.7)
Bacteroides thetaiotaomicron	25/26 (96.2)	28/30 (93.3)	53/56 (94.6)
Bacteroides vulgatus	11/12 (91.7)	27/28 (96.4)	38/40 (95.0)
Clostridium perfringens	7/9 (77.8)	7/7 (100.0)	14/16 (87.5)
Parabacteroides distasonis	6/8 (75.0)	16/16 (100.0)	22/24 (91.7)

Source: *ISM Table 28.1*
[a] Includes 1 subject with a MRSA isolate
[b] Includes 1 subject with a VRE isolate

(b) (4)

however these were reanalyzed by the Agency using guideline for acceptable discrepancy rates by CLSI. See analysis above. The interpretive criteria for zones were based on the correlation of MIC and disk diffusion

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results using data from both preclinical and clinical isolates focusing on the pathogens for the clinical indication of cIAI. In the Agency's analysis, disk diffusion breakpoints that minimized the error rates to within CLSI guideline of acceptability were not found for all organisms with MIC breakpoints. See MIC-disk correlation analysis above.

In summary, microbiological and clinical responses by pathogen in the clinical trials and *in vitro* MIC distributions for isolates from the clinical trials and surveillance suggested revised breakpoints from those proposed by the Applicant. The MIC distributions of all listed bacterial species, (b) (4) showed monomodal distributions without a second peak with resistant variants. Final Clinical Microbiology Recommendations are below.

8.2.3 Final Clinical Microbiology Recommendations

From a clinical microbiology perspective, the information provided by the Applicant supports the efficacy of eravacycline for the treatment of susceptible bacteria for the indication of cIAI. The following is a summary of the Agency's proposed clinical microbiology labeling changes and rationale:

- Subsection 12.4 has been updated in accordance with the FDA documents titled, "Microbiology Data for Systemic Antibacterial Drugs-Development, Analysis, and Presentation: Guidance for Industry" and "Systemic Antibacterial and Antifungal Drugs: Susceptibility Test Interpretive Criteria Labeling for NDAs and ANDAs: Guidance for Industry".
- (b) (4) Only the details of specifically relevant resistance factors were included in the resistance section of 12.4 including target site modifications to the 16s rRNA and certain 30S ribosomal proteins such as S10.
- (b) (4)
- The first and second lists of organisms were edited according to relevance to the indication, and sufficient number of organisms. *Bacteroides uniformis* was added to the first list because of sufficient clinical experience. (b) (4)
- Susceptibility interpretive criteria by MIC were reevaluated based on surveillance data, animal models, evaluation of PK/PD, and clinical outcome. The Agency's breakpoint decisions for the organism groups listed below were based primarily on the clinical outcome. PK/PD data was not very reliable due to lack of clarity on the effect of variable protein binding and target attainment analysis.
  The following contains the MIC breakpoint rationale by organism group:
  - Enterobacteriaceae- This reviewer recommended breakpoints for Enterobacteriaceae of of 0.5 mcg/mL. (b) (4)

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- o [redacted]
- o *S. aureus*- The number of isolates met inclusion in the first list (24). [redacted] This reviewer recommends breakpoints of [redacted] mcg/mL. The Agency's breakpoints were based on clinical experience at a breakpoint of 0.06 mcg/mL.
- o [redacted] Adequate data was provided for both *E. faecium* (39) and *E. faecalis* (46), and the label should indicate these species. [redacted]
- o [redacted] Breakpoints were given for *S. anginosus* group as they were most relevant to the indications, [redacted] *S. salivarius* group [redacted] meets the criteria for inclusion in the second list because of in vitro activity.
- o Anaerobes- the MIC_{90} for these organisms [redacted] The Agency's recommended breakpoint is 0.5 mcg/mL based on the collective clinical data. A statement is included in labeling that specifies for what species of Anaerobes clinical efficacy was demonstrated. There are some Anaerobes for which the breakpoints do not apply or for which there is insufficient information

- [redacted]. The disk breakpoints are S≥ 15 mm for Enterobacteriaceae.
- The Agency's proposed MIC and disk breakpoints are below:

Table 80: Susceptibility Test Interpretive Criteria for Eravacycline

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameters in mm)

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	S ≤	S≥
Enterobacteriaceae[a]	0.5	15
Enterococcus faecalis and *Enterococcus faecium*	0.06	---
Staphylococcus aureus	0.06	---
Streptococcus anginosus group[b]	0.06	---
Anaerobes[c]	0.5	NA

S=susceptible

[a] Clinical efficacy was shown for *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae.*
[b] Clinical efficacy was shown for *S. anginosus, S. constellatus, S. intermedius*.
[c] Clinical efficacy was shown for *Clostridium perfringens*, *Parabacteroides distasonis*, *Bacteroides caccae*, *Bacteroides fragilis*, *Bacteroides ovatus*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus.*
Source: Reviewer's Table.

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9 Review of Safety

9.1 Safety Review Approach

Eravacycline was developed as both intravenous (IV) and oral (PO) formulations. The IV formulation is proposed for use in the treatment of cIAI; therefore, clinical data from the IV formulation of eravacycline is considered in this review of safety. Clinical reports from the following studies were reviewed:

- 9 Phase 1 studies (single or multiple IV administration)
  - Single ascending dose study in healthy volunteers (TP-434-P1-SAD-1)
  - Thorough QTc study in healthy volunteers (TP-434-004)
  - Mass balance recovery study in healthy volunteers (TP-434-012)
  - PK study in subjects with hepatic impairment and healthy volunteers (TP-434-013)
  - PK study in subjects with renal impairment and healthy volunteers (TP-434-014)
  - Multiple ascending dose study in healthy volunteers (TP-434-P1-MAD-1)
  - PK study of bronchopulmonary disposition in healthy volunteers (TP-434-006)
  - Drug-drug interaction with itraconazole study in healthy volunteers (TP-434-016)
  - Drug-drug interaction with rifampin study in healthy volunteers (TP-434-020)
- 1 Phase 2 study in subjects with cIAI (TP-434-P2-cIAI-1, IV administration)
- 2 Phase 3 studies in subjects with cIAI (TP-434-008 and TP-434-025, IV administration)
- 1 Phase 3 study in subjects with cUTI (TP-434-010, IV and PO administration)

The 120-day safety update submitted to this NDA provided summary level safety data from a second Phase 3 study in subjects with cUTI (TP-434-021, IV administration). The clinical study report and datasets from this study were not available for review. Table 81 provides an overview of the clinical studies referenced in the clinical review of safety.

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Table 81: Summary of Clinical Trials Used to Evaluate Safety

Study ID	Study Design	Purpose	Regimen/Schedule/Duration	Population	Subject Exposure
Phase 1 Trials with Single Dose IV Eravacycline					
TP-434-P1-SAD-1	Phase 1, Single-center, Randomized, Double-blind, Placebo-controlled, Single Dose, Dose-escalation, IV Formulation	Safety/PK	7 Dose Groups for administration of ERV or matching placebo • 0.1 mg/kg 30-min IV- single dose • 0.25 mg/kg 30-min IV- single dose • 0.5 mg/kg 30-min IV- single dose • 1 mg/kg 30-min IV- single dose • 1.5 mg/kg 30-min IV- single dose • 2 mg/kg 30-min IV- single dose • 3 mg/kg 30-min IV- single dose Follow-up to day 9	Healthy males and females age 18-50 years	42 – ERV (each dose group = 6) 14 – Placebo (each dose group = 2)
TP-434-004[a]	Phase 1, Single center, Randomized, 3-Period Crossover, Placebo and Positive control, Single Dose, IV Formulation	Safety/PK; TQTc study	3-Period crossover separated by ≥14 day washout period • Regimen A: ERV 1.5 mg/kg IV + Placebo PO • Regimen B: Placebo IV + Moxifloxacin 400 mg PO Regimen C: Placebo IV + PO Follow-up to day 3 or 4 of each period	Healthy males and females age 18-55 years	54 – ERV 1.5 mg/kg IV 57 – Moxifloxacin PO 55 – Placebo IV + PO
TP-434-012[b]	Phase 1, Single-center, Non-randomized, Open-label, Single Dose, IV and PO Formulations	Mass balance recovery	• 100 mg [^{14}C]-ERV PO containing NMT 4.8 MBq (130 µCi) ^{14}C • 60 mg [^{14}C]-ERV IV containing NMT 3.8 MBq (105 µCi) ^{14}C Follow-up to day 11	Healthy males age 30-65 years	5 –ERV PO formulation 5 –ERV IV formulation

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Study ID	Study Design	Purpose	Regimen/Schedule/Duration	Population	Subject Exposure
TP-434-013	Phase 1, Single-center, Non-randomized, Open-label, Single Dose, IV Formulation	Safety/PK in subjects with hepatic impairment	ERV 1.5 mg/kg IV – single dose Follow-up at 2 weeks	Males and females age ≥18 years with hepatic impairment and healthy controls	24 – ERV 1.5 mg/kg IV (hepatic impairment = 18) (healthy controls = 6)
TP-434-014	Phase 1, Single-center, Non-randomized, Open-label, Single Dose, IV Formulation	Safety/PK in subjects with renal impairment	ERV 1.5 mg/kg IV – single dose Follow-up at 2 weeks	Males and females age ≥18 years with ESRD and healthy controls	12 – ERV 1.5 mg/kg IV (ESRD = 6) (healthy controls = 6)
Phase 1 Trials with Multiple Dose IV Eravacycline					
TP-434-P1-MAD-1	Phase 1, Single-center, Randomized, Double-blind, Placebo-controlled, Multiple Dose, Dose-escalation, IV Formulation	Safety/PK	4 Dose Groups for administration of ERV or matching placebo • 0.5 mg/kg 30-min IV q24h – 10 doses • 1.5 mg/kg 30-min IV q24h – 10 doses • 1.5 mg/kg 60-min IV q24h – 10 doses • 1 mg/kg 60-min IV q12h – 19 doses Follow-up to day 24	Healthy males and females age 18-50 years	24 – ERV (each dose group = 6) 8 – Placebo, any IV dose (each dose group = 2)
TP-434-006	Phase 1, Single center, Open-label, Multiple Dose, IV Formulation	Safety/PK; Lung Penetration	ERV 1 mg/kg IV q12h – 7 doses Follow-up to day 20	Healthy males and females age 18-65 years	20 – ERV 1 mg/kg IV q12h

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Study ID	Study Design	Purpose	Regimen/Schedule/Duration	Population	Subject Exposure
TP-434-016[b]	Phase 1, Single-center, Non-randomized, Open-label, Drug-drug Interaction, IV and PO Formulations	Drug-Drug Interaction	• ERV 1 mg/kg IV on Day 1 and Day 10 + Itraconazole 200 mg PO q12h on Day 8 and q24h from Days 9 to 15 • ERV 200 mg PO on Day 1 and Day 11 + Itraconazole 200 mg PO q12h on Day 8 and q24h from Days 9 to 15 Follow-up until 2 weeks after last dose of study drug	Healthy males and females age 18-55 years	12 – ERV 1 mg/kg IV 12 – ERV PO formulation
TP-434-020[b]	Phase 1, Single-center, Open-label Drug-drug Interaction, IV and PO Formulations	Drug-Drug Interaction	• ERV 1 mg/kg IV on Day 1 and Day 17 + rifampin 600 mg PO q24h from Days 8 to 17 • ERV 200 mg PO on Day 1 and Day 13 + rifampin 600 mg PO q24h from Days 8 to 13 Follow-up until 2 weeks after last dose of study drug	Healthy male and females age 18-55 years	12 – ERV 1 mg/kg IV 12 – ERV PO formulation
Phase 2 and 3 trials conducted for cIAI indication					
TP-434-P2-cIAI-1	Phase 2, Multicenter, Randomized, Double-blind, Double-dummy, Ertapenem-controlled, 2 dose regimens of IV Formulation	Efficacy and Safety/PK in subjects with cIAI	• ERV 1 mg/kg IV q12h for 4-14 days • ERV 1.5 mg/kg IV q24h for 4-14 days • Ertapenem 1 g IV q24h for 4-14 days Follow-up until 28 to 42 days after last dose of study drug	Males and females age 18-75 years with cIAI	56 – ERV 1 mg/kg IV q12h 53 – ERV 1.5 mg/kg IV q24h 30 – Ertapenem
TP-434-008	Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Ertapenem-controlled, IV Formulation	Efficacy and Safety in subjects with cIAI	• ERV 1 mg/kg IV q12h for 4-14 days • Ertapenem 1 g IV q24h for 4-14 days Follow-up to day 38 to 50	Males and females age ≥18 years with cIAI	270 – ERV 1 mg/kg IV q12h 268 – Ertapenem

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Study ID	Study Design	Purpose	Regimen/Schedule/Duration	Population	Subject Exposure
TP-434-025	Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Meropenem-controlled, IV Formulation	Efficacy and Safety in subjects with cIAI	• ERV 1 mg/kg IV q12h for 4-14 days • Meropenem 1 g IV q8h for 4-14 days Follow-up to day 38 to 50	Males and females age ≥18 years with cIAI	250 – ERV 1 mg/kg IV q12h 249 – Meropenem
Phase 3 trials conducted for other indications					
TP-434-010	Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Levofloxacin-controlled, IV and PO Formulations	Efficacy and Safety in subjects with cUTI	• ERV 1.5 mg/kg IV q24h for 3-7 days and transition to 200 mg PO q12h to maintain 7 days of total treatment • ERV 1.5 mg/kg IV q24h for 3-7 days and transition to 250 mg PO q12h to maintain 7 days of total treatment • Levofloxacin 750 mg IV q24h for 3-7 days and transition to 750 mg PO q24h to maintain 7 days of total treatment Follow-up until 2 to 3 weeks after last dose of study drug	Males and females age ≥18 years with cUTI	502 – ERV 1.5 mg/kg IV q24h + 200 mg PO q12h 45 – ERV 1.5 mg/kg IV q24h + 250 mg PO q12h 498 – Levofloxacin IV + PO
TP-434-021[c]	Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Ertapenem-controlled, IV Formulation	Efficacy and Safety in subjects with cUTI	• ERV 1.5 mg/kg IV q24h for 5-10 days • Ertapenem 1 g IV q24h for 5-10 days Both treatment groups with oral levofloxacin transition to maintain up to 10 days of total treatment Follow-up over a period of 4 weeks	Males and females age ≥18 years with cUTI	601 – ERV 1.5 mg/kg IV q24h 600 – Ertapenem

Abbreviations: ESRD = end-stage renal disease; ERV = eravacycline; IV = intravenous; MAD = multiple-ascending dose; MBq = megabecquerel; min = minute; NMT = not more than; PO = oral; SAD = single ascending dose; TQTc = thorough QTc study.

[a] Study TP-434-004 (3-period, 3-way crossover) was a crossover study; thus, the number of subjects for each regimen are not independent within this study.

[b] Studies TP-434-012, TP-434-016, and TP-434-020 had 2 formulation regimens (IV and Oral). A unique set of subjects was allocated to each dosing regimen.

[c] The 120-day safety update report provided a summary of the draft safety data gathered during Study TP-434-021. Final datasets were not available.

Source: Clinical Reviewer's analysis.

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This safety review will focus primarily on the data from the Phase 2 cIAI study (TP-434-P2-cIAI-1) and two Phase 3 cIAI studies (TP-434-008 and TP-434-025). Where relevant, data from the 9 Phase 1 studies with IV eravacycline and a Phase 3 cUTI study (TP-434-010) that evaluated an IV-to-PO regimen will also be presented. Available information from a second Phase 3 cUTI study (TP-434-021) was limited.

Certain adverse events were selected for detailed analysis based on observations from the eravacycline development program and the safety labeling for drugs in the tetracycline class (i.e., tigecycline) and other antibacterial drugs indicated for the treatment of cIAI. Adverse events of special interest included acute pancreatitis, acute renal failure, hypersensitivity, anaphylactic reaction, hepatic disorders, pseudomembranous colitis (*Clostridium difficile* infection), infusion site complications, thrombophlebitis, nausea and vomiting, pseudotumor cerebri/elevated intracranial pressure, and photosensitivity.

9.2 Review of the Safety Database

The Applicant's pooled safety analysis was derived from 20 clinical studies (NDA data cut-off point November 15, 2017). These clinical studies evaluated an IV or PO dose form, and the data was pooled as follows:

- **All Phase 1 Pool** – Integrated pool of all Phase 1 healthy volunteers who received eravacycline, regardless of dose or route of administration. Data tables for additional pools of Phase 1 data, by route of administration, and single or multiple doses were also prepared.
    - **Single Dose IV**: Studies TP-434-P1-SAD-1, TP-434-004, TP-434-012, TP-434-013, and TP-434-014.
    - **Multiple Dose IV**: Studies TP-434-P1-MAD-1, TP-434-006, TP-434-016, and TP-434-020.
    - **Single Dose PO**: Studies TP-434-Oral-P1-SAD-1 and TP-434-012.
    - **Multiple Dose PO**: Studies TP-434-002-P1-MAD-Oral, TP-434-003, TP-434-007, TP-434-009, TP-434-015, TP-434-016, TP-434-017, and TP-434-020.

Note: Studies TP-434-012, TP-434-016, and TP-434-020 had two formulation regimens, and a unique set of subjects was allocated to either the IV or PO regimen.

Note: Subjects with hepatic or renal impairment in Studies TP-434-013 and TP-434-014 were excluded from pooled analyses (i.e., only healthy subjects from these studies included)

Reviewers' Comment: *This reviewer considered the safety data in the Single Dose IV Pool and Multiple Dose IV Pool to be relevant with respect to the cIAI indication. Collectively, these analysis pools will be referred to as the Phase 1 IV Pool (N=181). Although subjects with hepatic impairment in Study TP-434-013 (N=18) or renal impairment in Study TP-434-014 (N=6) were excluded from the Phase 1 IV Pool, the safety data from these subjects were consistent with the pooled data from the healthy volunteers.*

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The other pools of Phase 1 data included additional subjects exposed to only the oral formulation (N=177). The safety data in these subjects were not considered relevant with respect to the cIAI indication and will not be presented in this safety review.

The Applicant presented safety data from 3 additional Phase 1 studies (TP-434-022, TP-434-023, and TP-434-027) separately from the All Phase 1 Pool results. Studies TP-434-022, TP-434-023, and TP-434-027 were not include in the pooled analyses due to the timing of completion of these studies. These studies are part of the development program for PO eravacycline and the majority of the subjects (N=132) were exposed to PO eravacycline or an IV to PO transition dosing regimen. Safety data from these studies were consistent with the pooled data and will not be presented in this safety review.

- **cIAI Only Phase 2/Phase 3 Pool** – integrated pool of all Phase 2 and Phase 3 subjects with cIAI by dose of eravacycline received (IV only) in 3 randomized double-blinded studies.
    - A Phase 2 study (TP-434-P2-cIAI-1) in subjects with cIAI comparing IV eravacycline (2 dose regimens) and IV ertapenem
    - A pivotal Phase 3 study (TP-434-008) in subjects with cIAI comparing IV eravacycline and IV ertapenem
    - A pivotal Phase 3 study (TP-434-025) in subjects with cIAI comparing IV eravacycline and IV meropenem

Reviewers' Comment: *The clinical reviewer considered the two Phase 3 cIAI studies appropriate for pooling. The studies were of similar design and evaluated the proposed dose of IV eravacycline. The results from the Phase 2 study were presented separately due to differences in the study design (i.e. 2 dose regimens evaluated) and small number of enrolled subjects.*

- **All Phase 2/Phase 3 Pool** – Integrated pool of Phase 2 and Phase 3 subjects exposed to eravacycline, regardless of dose, in 4 randomized double-blinded studies. Three of the studies were included in the cIAI Only Phase 2/Phase 3 Pool, and the fourth study was a Phase 3 study (TP-434-010) comparing IV-to-PO eravacycline regimen and IV-to-PO levofloxacin regimen in subjects with cUTI.

Reviewers' Comment: *Pooling of the controlled trials in subjects with cIAI or cUTI were not considered appropriate due to the differences in the patient population and dosing regimens evaluated in these studies. The results from the controlled trials conducted for cIAI were the focus of this safety review.*

9.2.1 Overall Exposure

Table 82 provides a summary of the overall exposures in the clinical studies used to evaluate safety of IV eravacycline. The safety database consisted of 1982 subjects exposed to IV eravacyline, and 632 of these subjects received the proposed dose for cIAI (1 mg/kg). The 120-

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day safety update submitted to the NDA on April 25, 2018 included top-line safety data for a second Phase 3 cUTI study (Study TP-434-021). The final datasets for Study TP-434-021 were not available.

Table 82: Safety Database for Intravenous Eravacycline Development Program

Clinical Trial Group Study ID	Brief purpose	IV Eravacycline N (pro. dose)	Active Control N	Placebo N
Phase 1 Studies (IV only) – Completed				
Single Dose IV		137 (6)	57	69
TP-434-P1-SAD-1	Safety/PK of single ascending doses	42 (6)	–	14
TP-434-004	Thorough QTc study	54 (0)	57	55
TP-434-012	Mass balance recovery and metabolite characterization	5 (0)	–	–
TP-434-013[1]	Single dose PK in subjects with hepatic impairment vs. healthy controls	24 (0)	–	–
TP-434-014[1]	Single dose PK in subjects with renal impairment vs. healthy controls	12 (0)	–	–
Multiple Dose IV		68 (50)	–	8
TP-434-P1-MAD-1	Safety/PK of multiple ascending doses	24 (6)	–	8
TP-434-006	Bronchopulmonary disposition	20 (20)	–	–
TP-434-016	Drug-drug interaction with itraconazole	12 (12)	–	–
TP-434-020	Drug-drug interaction with rifampin	12 (12)	–	–
Phase 2 cIAI Study – Completed				
TP-434-P2-cIAI-1	Controlled trial conducted for cIAI	109 (56)	30	–
Phase 3 cIAI Studies – Completed				
TP-434-008	Controlled trial conducted for cIAI	270 (270)	268	–
TP-434-025	Controlled trial conducted for cIAI	250 (250)	249	–
Phase 3 cUTI Study – Completed				
TP-434-010	Controlled trial conducted for cUTI	547 (0)	498	–
Phase 3 cUTI Study – Ongoing				
TP-434-021[2]	Controlled trial conducted for cUTI	601 (0)	600	–
	Grand Total	**1982 (632)**	**1702**	**77**

Pro. = proposed dose of 1 mg/kg
[1] Subjects with hepatic or renal impairment in Studies TP-434-013 and TP-434-014 were excluded from the pooled analyses (i.e., only healthy subjects from these studies were included)
[2] Study TP-434-021 was completed after the NDA submission. Final datasets were not available.
Source: Clinical Reviewer's Analysis.

There were 181 healthy volunteers treated with eravacycline in the Phase 1 IV Pool. These subjects received at least one dose of either <1 mg/kg (16%), 1 mg/kg (31%), 1.5 mg/kg (46%), or 2-3 mg/kg (7%). The study drug exposure in the Phase 1 Single Dose IV and Multiple Dose IV Pools are summarized in Table 83.

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Table 83: Study Drug Exposure – Phase 1 IV Pool

Parameter	Phase 1 IV Pool	
	Eravacycline Single Dose IV N=113	Eravacycline Multiple Dose IV N=68
Average Daily Dose (mg/day)		
Mean (SD)	109 (55)	105 (41)
Min, Max	6, 312	30, 184
Cumulative Number of Active Doses		
Mean (SD)	1 (0)	7 (5)
Min, Max	1, 1	1, 19
Number of Days Dosing Occurred		
Mean (SD)	1 (0)	5 (3)
Min, Max	1,1	1, 10
Number of Days Dosing Occurred Category, n (%)[2]		
<4.0 days	113 (100)	24 (35)
4.0 to 7.0 days	0	23 (34)
>7.0 days	0	21 (31)

Source: Adapted from Pooled analysis tables – Integrated safety, Table 1.38.1

The Phase 2 cIAI study had 56 subjects treated with eravacycline 1 mg/kg q12h, 52 subjects treated with eravacycline 1.5 mg/kg q24h, and 30 subjects treated with ertapenem 1 gram q24h. The study drug exposure in each treatment group are summarized in Table 84. The subjects treated with eravacycline 1 mg/kg q12h received an average daily dose of 140 mg per day, while those treated with eravacycline 1.5 mg/kg q24h received an average daily dose of 101 mg per day. The mean duration of treatment was 6 days for each treatment group, including ertapenem. Only 2 subjects (1 subject in each eravacycline dose group) received greater than 7 days of study treatment.

Table 84: Study Drug Exposure – Phase 2 cIAI study

Parameter	Study TP-434-P2-cIAI-1		
	Eravacycline 1 mg/kg q12h N=56	Eravacycline 1.5 mg/kg q24h N=53	Ertapenem N=30
Average Daily Dose (mg/day)			
Mean (SD)	140 (29)	101 (20)	1000 (0)
Min, Max	72, 210	60, 144	1000, 1000
Cumulative Number of Active Doses			
Mean (SD)	11 (3)	6 (1)	6 (2)
Min, Max	2, 20	2, 8	1, 7
Treatment Duration (days)[1]			
Mean (SD)	6 (2)	6 (1)	6 (2)
Min, Max	1,10	2, 8	1, 7

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Parameter	Study TP-434-P2-cIAI-1		
	Eravacycline 1 mg/kg q12h N=56	Eravacycline 1.5 mg/kg q24h N=53	Ertapenem N=30
Treatment Duration Category, n (%)[1]			
<4 days	3 (5)	1 (2)	2 (7)
4 to 7 days	52 (93)	51 (96)	28 (93)
>7 days	1 (2)	1 (2)	0

[1] Treatment Duration is the number of 24h-dosing cycles completed (active doses only). In this calculation, the last dosing cycle was counted if at least half of the full daily dose was administered.
Source: Clinical Reviewer's Analysis

The Phase 3 cIAI studies had 520 subjects treated with eravacycline 1 mg/kg q12h (52% from Study TP-434-008 and 48% from Study TP-434-025), 268 subjects treated with ertapenem 1 gram q24h (all from Study TP-434-008), and 249 subjects treated with meropenem 1 gram q8h (all from Study TP-434-025). The study drug exposures in each treatment group are summarized in Table 85. The eravacycline-treated subjects in both studies received an average daily dose of 162 mg. The mean treatment duration was 7 days in both treatment groups in Study TP-434-008. In Study TP-434-025, the mean treatment duration was 6 days in the eravacycline group and 7 days in the meropenem group. In the pooled analysis, at least 20% of subjects in both treatment groups received greater than 7 days of study treatment.

Table 85: Study Drug Exposure – Phase 3 cIAI Studies

Parameter	Study TP-434-008		Study TP-434-025		Pooled Analysis	
	ERV 1 mg/kg q12h N=270	Ertapenem N=268	ERV 1 mg/kg q12h N=250	Meropenem N=249	ERV 1 mg/kg q12h N=520	Comparator N=517
Average Daily Dose (mg/day)						
Mean (SD)	162 (30)	1000 (0)	162 (34)	2987 (153)	162 (32)	
Min, Max	94, 246	1000, 1000	64, 274	909, 3030	64, 274	
Cumulative Number of Active Doses						
Mean (SD)	14 (5)	7 (2)	13 (5)	20 (9)	13 (5)	
Min, Max	3, 28	1, 14	1, 28	1, 42	1, 28	
Treatment Duration (days)[1]						
Mean (SD)	7 (3)	7 (2)	6 (3)	7 (3)	7 (3)	7 (3)
Min, Max	2, 14	1, 14	1, 14	0, 14	1, 14	0, 14
Treatment Duration Category, n (%)[1]						
<4 days	6 (2)	5 (2)	13 (5)	10 (4)	19 (4)	15 (3)
4 to 7 days	202 (75)	207 (77)	193 (77)	187 (75)	395 (76)	394 (76)
>7 days	62 (23)	56 (21)	44 (18)	52 (21)	106 (20)	108 (21)

Abbreviations: ERV=eravacycline; Comparator=ertapenem or meropenem
[1] Treatment Duration is the number of 24h-dosing cycles completed (active doses only). In this calculation, the last dosing cycle was counted if at least half of the full daily dose was administered.
Source: Clinical Reviewer's Analysis

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The first Phase 3 cUTI study, TP-434-010, evaluated an IV-to-PO regimen. This study included 547 eravacycline-treated subjects (1.5 mg/kg q24h IV + 200/250 mg q12h PO) and 498 levofloxacin-treated subjects. The average daily IV dose in the eravacycline group was 114 mg (range, 61 to 218 mg). For each treatment group, the mean duration of IV therapy was 4 days (range, 1 to 7 days) and 80% transitioned to oral study drug to complete up to 8 days of total therapy.

Reviewers' Comment: *The dosing, duration, and number of subjects in the safety database are sufficient to conduct a safety review for the cIAI indication. The mean duration of exposure was balanced across treatment groups in the Phase 2 and Phase 3 studies.*

9.2.2 Relevant characteristics of the safety population:

Table 86 summarize the demographic and baseline characteristics in the Phase 1 IV Pool. The mean ages were 34.7 years and 33.9 years in the Single Dose IV and Multiple Dose IV Pools, respectively. The majority in the Single Dose IV and Multiple Dose IV Pools were male, White, not Hispanic or Latino ethnicity, and enrolled in the United States. All had a creatinine clearance ≥60 mL/min and normal liver function.

Table 86: Demographic and Baseline Characteristics - Phase 1 IV Pool (Safety Population)

Parameter	Phase 1 IV Pool	
	Eravacycline Single Dose IV N=113 n (%)	**Eravacycline Multiple Dose IV N=68 n (%)**
Age (years)		
Mean (SD)	34.7 (12.0)	33.9 (10.6)
Min, Max	18, 59	19, 55
Gender, n (%)		
Male	79 (69.9)	52 (76.5)
Female	34 (30.1)	16 (23.5)
Race, n (%)		
White	67 (59.3)	49 (72.1)
Black/African American	42 (37.2)	15 (22.1)
Other[1]	4 (3.5)	4 (5.9)
Ethnicity, n (%)		
Hispanic/Latino	4 (3.7)	58 (85.3)
Not Hispanic/Latino	104 (92.0)	9 (13.2)
Missing	5 (4.4)	1 (1.5)
Region, n (%)		
Europe	5 (4.4)	0
North America	108 (95.6)	68 (100)
Body Mass Index, n (%)		

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Parameter	Phase 1 IV Pool	
	Eravacycline Single Dose IV N=113 n (%)	Eravacycline Multiple Dose IV N=68 n (%)
<25 kg/m^2	28 (24.8)	29 (42.6)
25 - <30 kg/m^2	63 (55.8)	32 (47.1)
≥30 kg/m^2	22 (19.5)	7 (10.3)

[1] Other includes: Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, and Multiple (Black/African American and White).
Source: Adapted from Pooled analysis tables – integrated safety, Table 1.2.1; Clinical Reviewer's Analysis

Tables 87 summarize the demographic and baseline characteristics for the treatment groups in the Phase 2 cIAI study. Demographic and baseline characteristics were similar across the treatment groups. The mean age was 41.8 years in the eravacycline 1 mg/kg group, 43.2 years in the eravacycline 1.5 mg/kg group, and 42.0 years in the ertapenem group. The majority of subjects were male, White, not Hispanic or Latino ethnicity, and enrolled in India. At baseline, >85% of subjects in each treatment group had a creatinine clearance ≥60 mL/min. None of the subjects had severe hepatic impairment (Child Pugh Class C).

Table 87: Demographic and Baseline Characteristics - Phase 2 cIAI Study (Safety Population)

Parameter	Study TP-434-P2-cIAI-1		
	Eravacycline 1 mg/kg q12h N=56	Eravacycline 1.5 mg/kg q24h N=53	Ertapenem N=30
Age (years)			
Mean (SD)	41.8 (17.2)	43.2 (17.9)	42.0 (17.9)
Min, Max	18, 74	18, 74	18, 74
Age categories, n (%)			
18 – 64 years	51 (91.1)	44 (83.0)	26 (86.7)
≥65 years	5 (8.9)	9 (17.0)	4 (13.3)
Gender, n (%)			
Male	42 (75.0)	37 (69.8)	21 (70.0)
Female	14 (25.0)	16 (30.2)	9 (30.0)
Race, n (%)			
White	36 (64.3)	37 (69.8)	22 (73.3)
Asian	20 (35.7)	16 (30.2)	8 (26.7)
Ethnicity, n (%)			
Hispanic/Latino	1 (1.8)	1 (1.9)	0
Not Hispanic/Latino	55 (98.2)	52 (98.1)	30 (100)
Region, n (%)			
Europe	36 (64.3)	37 (69.8)	21 (70.0)
North America	0	0	1 (3.3)
India	20 (35.7)	16 (30.2)	8 (26.7)
Body Mass Index, n (%)			

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Parameter	Study TP-434-P2-cIAI-1		
	Eravacycline 1 mg/kg q12h N=56	Eravacycline 1.5 mg/kg q24h N=53	Ertapenem N=30
<25 kg/m^2	39 (69.6)	35 (66.0)	19 (63.3)
25 - <30 kg/m^2	17 (30.4)	18 (34.0)	11 (36.7)
APACHE II Score, n (%)			
<10	47 (83.9)	35 (66.0)	26 (86.7)
≥10	9 (16.1)	18 (34.0)	4 (13.3)
Creatinine Clearance, n (%)			
15 - <60 ml/min	3 (5.4)	5 (9.4)	2 (6.7)
≥60 ml/min	50 (89.2)	46 (86.8)	27 (90.0)
Missing	3 (5.4)	2 (3.8)	1 (3.3)
Child-Pugh Class, n (%)			
Class A	37 (66.1)	33 (62.3)	21 (70.0)
Class B	11 (19.6)	12 (22.6)	6 (20.0)
Missing	8 (14.3)	8 (15.1)	3 (10.0)

Source: Adapted from Pooled analysis tables – integrated safety, Table 1.2.4; Clinical Reviewer's Analysis

Tables 88 summarize the demographic and baseline characteristics for the treatment groups in the Phase 3 cIAI studies. Demographic and baseline characteristics were similar across the treatment groups. The mean age was 54.8 years in both treatment groups in Study TP-434-008. In Study TP-434-025, the mean age was 52.1 years in the eravacycline group and 52.8 years in the comparator group. The majority of subjects in all of the treatment groups were male, White, not Hispanic or Latino ethnicity, and enrolled in Europe. At baseline, >85% of subjects in each treatment group had a creatinine clearance ≥60 mL/min. The Child Pugh Class assessment was missing in a greater proportion of subjects in Study TP-434-025 compared to Study TP-434-008 (22% vs. 8%). None of the subjects had severe hepatic impairment or were Child Pugh Class C.

Table 88: Demographic and Baseline Characteristics – Phase 3 cIAI Studies (Safety Population)

Parameter	Study TP-434-008		Study TP-434-025		Pooled Analysis	
	ERV 1 mg/kg q12h N=270	ERT N=268	ERV 1 mg/kg q12h N=250	MER N=249	ERV 1 mg/kg q12h N=520	Comparator N=517
Age (years)						
Mean (SD)	54.8 (16.9)	54.8 (16.1)	52.1 (17.7)	52.8 (18.2)	53.5 (17.3)	53.8 (17.2)
Min, Max	19, 93	20, 87	18, 88	19, 87	18, 93	19, 87
Age categories, n (%)						
18 – 64 years	182 (67.4)	193 (72.0)	180 (72.0)	173 (69.5)	362 (69.6)	366 (70.8)
≥65 years	88 (32.6)	75 (28.0)	70 (28.0)	76 (30.5)	158 (30.4)	151 (29.2)
≥75 years	34 (12.6)	36 (13.4)	25 (10.0)	33 (13.3)	59 (11.3)	69 (13.3)
Gender, n (%)						

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Parameter	Study TP-434-008		Study TP-434-025		Pooled Analysis	
	ERV 1 mg/kg q12h N=270	ERT N=268	ERV 1 mg/kg q12h N=250	MER N=249	ERV 1 mg/kg q12h N=520	Comparator N=517
Male	156 (57.8)	163 (60.8)	139 (55.6)	129 (51.8)	295 (56.7)	292 (56.5)
Female	114 (42.2)	105 (39.2)	111 (44.4)	120 (48.2)	225 (43.3)	225 (43.5)
Race, n (%)						
White	263 (97.4)	257 (95.9)	249 (99.6)	249 (100)	512 (98.5)	506 (97.9)
Non-White[1]	6 (2.2)	11 (4.1)	1 (0.4)	0	7 (1.3)	11 (2.1)
Missing	1 (0.4)	0	0	0	1 (0.2)	0
Ethnicity, n (%)						
Hispanic/Latino	8 (3.0)	8 (3.0)	4 (1.6)	0	12 (2.3)	8 (1.5)
Not Hispanic/ Latino	261 (96.7)	260 (97.0)	239 (95.6)	238 (95.6)	500 (96.2)	498 (96.3)
Unknown/ Not Reported	1 (0.4)	0	7 (2.8)	11 (4.4)	8 (1.5)	11 (2.1)
Region, n (%)						
Europe	252 (93.3)	248 (92.5)	242 (96.8)	245 (98.4)	494 (95.0)	493 (95.4)
North America	18 (6.7)	19 (7.1)	8 (3.2)	4 (1.6)	26 (5.0)	23 (4.4)
South Africa	0	1 (0.4)	0	0	0	1 (0.2)
Body Mass Index, n (%)						
<25 kg/m^2	87 (32.2)	110 (41.0)	92 (36.8)	86 (34.5)	179 (34.4)	196 (37.9)
25 - <30 kg/m^2	102 (37.8)	82 (30.6)	78 (31.2)	94 (37.8)	180 (34.6)	176 (34.0)
≥30 kg/m^2	81 (30.0)	76 (28.4)	80 (32.0)	69 (27.7)	161 (31.0)	145 (28.0)
APACHE II Score, n (%)						
<10	217 (80.4)	206 (76.9)	202 (80.8)	200 (80.3)	419 (80.6)	406 (78.5)
≥10	51 (18.9)	59 (22.0)	48 (19.2)	49 (19.7)	99 (19.0)	108 (20.9)
Missing	2 (0.7)	3 (1.1)	0	0	2 (0.4)	3 (0.6)
Creatinine Clearance, n (%)						
<15 ml/min	1 (0.4)	0	0	0	1 (0.2)	0
15 - <60 ml/min	27 (10.0)	21 (7.8)	14 (5.6)	12 (4.8)	41 (7.9)	33 (6.4)
≥60 ml/min	239 (88.5)	238 (88.8)	232 (92.8)	233 (93.6)	471 (90.6)	471 (91.1)
Missing	3 (1.1)	9 (3.4)	4 (1.6)	4 (1.6)	7 (1.3)	13 (2.5)
Child-Pugh Class, n (%)						
Class A	202 (74.8)	190 (70.9)	179 (71.6)	171 (68.7)	381 (73.3)	361 (69.8)
Class B	47 (17.4)	58 (21.6)	19 (7.6)	20 (8.0)	66 (12.7)	78 (15.1)
Missing	21 (7.8)	20 (7.5)	52 (20.8)	58 (23.3)	73 (14.0)	78 (15.1)

Abbreviations: ERV=eravacycline; ERT=ertapenem; MER=meropenem; Comparator=ertapenem or meropenem
[1] Non-white includes: Asian, Black/African American, and Other.
Source: Adapted from Pooled analysis tables – integrated safety, Table 1.2.4; Clinical Reviewer's Analysis

Demographic and baseline characteristics were similar across eravacycline- and levofloxacin-treated subjects in the Phase 3 cUTI study that evaluated a IV-to-PO regimen. The mean age was 54 year (range, 18 to 89 years) in the eravacycline group and 52.3 years (range, 18 to 88 years) in the levofloxacin group. Most subjects in the eravacycline and levofloxacin groups were

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female (64% and 67%, respectively), White (96% in each treatment group), not Hispanic or Latino ethnicity (97% and 96%, respectively), and enrolled in Europe (93% and 92%, respectively). At baseline, >80% of eravacycline- and levofloxacin-treated subjects had creatinine clearance ≥60 mL/min. None of the subjects had severe hepatic impairment or were Child Pugh Class C.

Reviewers' Comment: *Demographic characteristics at baseline were generally balanced between treatment groups in the Phase 2 and Phase 3 studies.*

9.2.3 Adequacy of the safety database:

The Phase 1 IV Pool included 181 healthy volunteers who received at least one dose of IV eravacycline. These healthy volunteers enrolled in 2 countries (United States and Great Britain). The United States contributed the greatest number of participants, including 108 (96%) healthy subjects in the Single Dose IV Pool and 68 (100%) healthy subjects in the Multiple Dose IV Pool.

The Phase 2 cIAI study included 139 adults who received at least one dose of study drug for treatment of cIAI. The adults with cIAI enrolled in 6 countries (United States, Bulgaria, India, Latvia, Lithuania, and Romania). Table 89 summarizes the enrollment by country in each treatment group. India contributed the greatest number of participants. The United States contributed 1 subject, and this subject was treated with ertapenem.

Table 89: Enrollment by Country - Phase 2 cIAI Study (Safety Population)

	Study TP-434-P2-cIAI-1		
Parameter	Eravacycline 1 mg/kg q12h N=56	Eravacycline 1.5 mg/kg q24h N=53	Ertapenem N=30
United States	0	0	1 (3.3)
India	20 (35.7)	16 (30.2)	8 (26.7)
Lithuania	13 (23.2)	17 (32.1)	7 (23.3)
Latvia	9 (16.1)	8 (15.1)	4 (13.3)
Romania	9 (16.1)	6 (11.3)	6 (20.0)
Bulgaria	5 (8.9)	6 (11.3)	4 (13.3)

Source: Clinical Reviewer's Analysis

The Phase 3 cIAI study included 1037 adults who received at least one dose of study drug for treatment of cIAI. The adults with cIAI enrolled in 13 countries (United States, Bulgaria, Czech Republic, Estonia, Georgia, Germany, Hungary, Latvia, Lithuania, Romania, Russia, South Africa, and Ukraine). Table 90 summarizes the enrollment by country in each treatment group. Bulgaria contributed the greatest number of participants. The United States contributed 26 (5.0%) eravacycline-treated subjects and 23 (4.4%) comparator-treated subjects.

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Table 90: Enrollment by Country – Phase 3 cIAI Studies (Safety Population)

	Study TP-434-008		Study TP-434-025		Pooled Analysis	
Region	ERV 1 mg/kg q12h N=270	ERT N=268	ERV 1 mg/kg q12h N=250	MER N=249	ERV 1 mg/kg q12h N=520	Comparator N=517
United States	18 (6.7)	19 (7.1)	8 (3.2)	4 (1.6)	26 (5.0)	23 (4.4)
Bulgaria	45 (16.7)	44 (16.4)	52 (20.8)	41 (16.5)	97 (18.7)	85 (16.4)
Ukraine	38 (14.1)	38 (14.2)	39 (15.6)	43 (17.3)	77 (14.8)	81 (15.7)
Romania	42 (15.6)	42 (15.7)	23 (9.2)	34 (13.7)	65 (12.5)	76 (14.7)
Latvia	25 (9.3)	23 (8.6)	34 (13.6)	33 (13.3)	59 (11.3)	56 (10.8)
Estonia	32 (11.9)	34 (12.7)	20 (8.0)	11 (4.4)	52 (10.0)	45 (8.7)
Russia	28 (10.4)	24 (9.0)	21 (8.4)	13 (5.2)	49 (9.4)	37 (7.2)
Lithuania	26 (9.6)	26 (9.7)	22 (8.8)	18 (7.2)	48 (9.2)	44 (8.5)
Czech Republic	14 (5.2)	16 (6.0)	13 (5.2)	16 (6.4)	27 (5.2)	32 (6.2)
Hungary	-	-	10 (4.0)	20 (8.0)	10 (1.9)	20 (3.9)
Georgia	-	-	8 (3.2)	16 (6.4)	8 (1.5)	16 (3.1)
Germany	2 (0.7)	1 (0.4)	0	0	2 (0.4)	1 (0.2)
South Africa	-	1 (0.4)	-	-	0	1 (0.2)

Abbreviations: ERV=eravacycline; ERT=ertapenem; MER=meropenem; Comparator=ertapenem or meropenem
Source: Clinical Reviewer's Analysis

The Phase 3 cUTI study that evaluated an IV-to-PO regimen included 1045 adults who received at least one dose of study drug for treatment of cUTI. The adults with cUTI enrolled in 18 countries (United States, Bulgaria, Colombia, Czech Republic, Estonia, Georgia, Greece, Hungary, Israel, Italy, Latvia, Mexico, Moldova, Poland, Romania, Russia, South Africa, and Ukraine). Ukraine contributed the greatest number of participants, including 95 (17%) eravacycline-treated subjects and 94 (19%) levofloxacin-treated subjects. The United States contributed 5 (1%) eravacycline-treated subjects and 13 (3%) levofloxacin-treated subjects.

Reviewers' Comment: *Geographic distribution of study subjects were generally balanced between treatment groups in the Phase 2 and Phase 3 studies. Although the predominance of data in the Phase 3 cIAI studies was from countries in Eastern Europe, the data is considered applicable to the US population/practice of medicine. For this class of drug and indication, there are no known major differences in the disease course, standard of care, or patient characteristics that could significantly affects its use in the US as compared with other populations.*

9.3 Adequacy of Applicant's Clinical Safety Assessments

9.3.1 Issues Regarding Data Integrity and Submission Quality

There were no meaningful concerns noted by this reviewer regarding the quality and integrity of the datasets. Inspections by the Office of Scientific Investigations did not reveal any

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significant irregularities in the conduct of the trial at the selected study sites (Section 4.1 of this review).

9.3.2 Categorization of Adverse Events

No significant issues were identified with respect to the Applicant's process for recording, coding, and categorizing adverse events. Standard regulatory definitions were used to categorize treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs). Adverse events reported by the subject or through the Investigator's observation, physical examination, or other diagnostic procedures were recorded and entered on the appropriate eCRF. TEAEs, which included clinical laboratory test variables that were reported as adverse events, were followed from the first dose of study drug until the completion of study participation.

All adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20. Originally, adverse events were coded using the most updated MedDRA version available when the studies were performed (i.e., MedDRA Versions 14, 16, and 20 used in Studies TP-434-P2-cIAI-1, TP-434-008, and TP-434-025, respectively). The number and percentage of subjects reporting TEAEs was tabulated by MedDRA system organ class (SOC) and preferred term (PT). Subjects were counted only once within each SOC and preferred term.

Adverse events were categorized by severity (mild, moderate, or severe) and received causality assessment from the Investigator. The following definitions were used to report the severity of adverse events:

- Mild – Adverse event usually transient and required no special treatment and did not interfere with the subject's daily activities.
- Moderate – Adverse event produced a low level of inconvenience to the subject and may have interfered with daily activities. These events were usually ameliorated by simple therapeutic measures.
- Severe – Adverse event interrupted daily activities and required systemic drug therapy or other medical treatment OR adverse event placed the subject in the view of the Investigator at immediate risk of death from the reaction as it occurred OR adverse event resulted in death of the subject.

The number and percentage of subjects reporting TEAEs was tabulated by MedDRA system organ class (SOC) and preferred term (PT). Subjects were counted only once within each SOC and preferred term. Standardized MedDRA Queries (SMQs) and customized medical queries (CMQs) were used to identify TEAEs of special interest. The selected queries were chosen based on potential side effects observed with drugs of the tetracycline class, broad spectrum antibiotics, and/or eravacycline. The following SMQs and CMQs were conducted:

- Acute Pancreatitis SMQ (MedDRA narrow and broad algorithm)
    - The MedDRA-specified algorithm used to identify episodes of acute pancreatitis required a narrow term (any Category A term) or a combination of 2 broad terms

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(any Category B term plus any Category C term). Category A terms were specific for the diagnosis of acute pancreatitis (i.e., pancreatitis, pancreatitis acute, pancreatitis necrosis). Category B and C terms were non-specific signs and symptoms that when both are present could represent a diagnosis of acute pancreatitis. The event terms for laboratory abnormalities (i.e., lipase increased, amylase increased), and clinical symptoms (i.e., abdominal pain, nausea, vomiting) were in Categories B and C, respectively.

- Acute Renal Failure SMQ (MedDRA narrow)
- Hypersensitivity SMQ (MedDRA narrow)
- Anaphylactic Reaction SMQ (MedDRA narrow)
- Hepatic Disorders SMQ (Drug-related MedDRA narrow and broad)
- Pseudomembranous colitis SMQ (MedDRA narrow and broad)
- Infusion site Complications CMQ
    - Include the PTs of catheter/infusion/injection site dermatitis, catheter/infusion/injection site edema, catheter/infusion/injection site erythema, catheter/infusion/injection site extravasation, catheter/infusion/injection site hypersensitivity, catheter/infusion/injection site induration, catheter/infusion/injection/vessel puncture site inflammation, catheter/infusion/injection site mass, catheter/infusion/injection/vessel puncture site pain, catheter/injection site pruritus, catheter/infusion/injection site phlebitis, catheter/infusion/injection site rash, catheter site related/infusion/injection/vessel puncture site reaction, catheter/infusion/injection site swelling, catheter/infusion/injection site urticaria, catheter/infusion/injection site vasculitis, catheter/infusion/injection site warmth, infusion/injection site discomfort, infusion/injection site irritation, infusion/injection/vessel puncture site thrombosis, phlebitis, phlebitis superficial, thrombophlebitis, and thrombophlebitis superficial.
- Thrombophlebitis SMQ (MedDRA narrow and broad)
- Nausea and Vomiting CMQ
    - Include the PTs of fecal vomiting, nausea, post-tussive vomiting, procedural nausea, procedural vomiting, regurgitation, retching, vomiting, vomiting projective, and vomiting psychogenic.
- Pseudotumor Cerebri / Elevated Intracranial Pressure CMQ
    - Include the PTs of idiopathic intracranial hypertension, intracranial pressure increased, and papilledema.
- Photosensitivity CMQ
    - Include the PTs of administration/application/infusion/injection site photosensitivity reaction, photodermatosis, photosensitivity reaction, polymorphic light eruption, retinopathy solar, solar dermatitis, solar urticaria, and sunburn.

Reviewers' Comment: *The analysis of adverse events performed by the applicant is considered adequate. For the Infusion site Complications CMQ, this reviewer included the additional event*

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terms of vessel puncture site swelling, vessel puncture site erythema, and infusion site hypoaesthesia.

9.3.3 Routine Clinical Tests

The routine clinical testing required to evaluated the safety concerns of IV eravacycline was adequately addressed in the design and conduct of the clinical studies. Safety assessment included monitoring of TEAEs and SAEs, vital sign measurements (blood pressure, heart rate, respiratory rate, and temperature), physical examination findings, abdominal examination, 12-lead ECG parameters, and changes in clinical chemistry, hematology, coagulation, and urinalysis laboratory values. The schedules for the noteworthy procedures performed in the Phase 2 and Phase 3 cIAI studies are presented in Table 91 and Table 92, respectively.

Table 91: Noteworthy Procedures in the Phase 2 cIAI Study

Procedure	Screening Within 36h of First Dose	Day 1	Day 2	Day 3	Day 4-14[1]	EOT[1]	TOC (EOT + 10-14 Days)	FU (EOT + 24-42 Days)
Informed consent	X							
Medical history	X							
APACHE II score	X							
Vital signs	X	X	X	X	X	X	X	X
Physical exam	X					X	X	X
Abdominal exam[2]	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Pregnancy test	X					X	X	X
Intra-abdominal cultures[3]		X	X	X	X	X	X	X
Blood Cultures[4]	X	X	X	X	X	X	X	X
Intra-abdominal cultures[3]		X	X	X	X	X	X	X
Safety Laboratory Tests[5]	X	X	X	X	X	X	X	X
12-lead ECG[6]	X	X	X	X	X	X	X	X
Study drug administration[7]		X	X	X	X			
PK assessments		X	X	X	X			
Adverse event monitoring		X	X	X	X	X	X	X
Clinical response						X	X	X

Abbreviations: ECG=electrocardiogram; EOT=End of Treatment; TOC=Test of Cure; FU=Follow-up.
[1] EOT assessments were performed at premature withdrawal, treatment failure, or within 24 hours from last dose.
[2] Abdominal examinations were performed at least once daily until resolution of all signs and symptoms of cIAI.

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[3] Samples from the site of infection for both aerobic and anaerobic culture were to be collected by aspiration at the time of initial surgical procedure, subsequent surgical re-intervention(s), and if there were signs and symptoms at the EOT, TOC, and FU visits (if applicable).
[4] Two blood samples (consisting of a set of aerobic and anaerobic bottles) taken from two separate locations for culture were to be obtained at the investigator's discretion, if clinical indicated and followed until negative.
[5] Safety laboratory tests (chemistry, hematology, coagulation, and urinalysis) were to be performed at Screening, on Days 1, 2, 3, 4, and every 3 days thereafter while the subject remained on study drug therapy. These tests were to continue through the EOT, and be performed at TOC and FU visits. Chemistry and hematology labs were performed at Screening, Dose Cycles 1 to 4; every three 24-hour dosing cycles thereafter while on study drug; and at EOT, TOC, and FU Visits.
[6] Electrocardiogram performed at Baseline (within 4 hours prior to administration of Dose 1 bag 1) and within 2 hours after completion of Dose 3 bag 1, Dose 5 bag 1, Dose 7 bag 1, and Dose 15 bag 1, if still on study drug; and at EOT, TOC, and FU Visits.
[7] The expected minimum treatment duration was 4 days (unless clinical failure) and the expected maximum treatment duration was 14 days (7 days for subjects in India).
Source: Adapted from clinical study report for TP-434-P2-cIAI-1.

Table 92: Noteworthy Procedures in the Phase 3 cIAI Studies

Procedure	Screening Within 48h of First Dose	Day 1 (Dose Cycle 1)	Day 2 (Dose Cycle 2)	Day 3 (Dose Cycle 3)	Day 4-14 (Dose Cycles 4-14)	EOT[1]	TOC (Days 25-31)	FU (Days 38-50)
Informed consent	X							
Medical history	X							
APACHE II score	X							
Vital signs	X	X	X	X	X	X	X	X
Physical exam	X					X	X	X
Abdominal exam[2]	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Pregnancy test	X					X	X	X
Blood Cultures[3]	X							
Intra-abdominal cultures[4]	X		X	X	X	X	X	X
Chemistry/ Hematology[5]	X	X	X	X	X	X	X	X
Coagulation	X	X				X	X	X
Urinalysis[6]	X	X				X		
12-lead ECG	X					X		
Study drug administration[7]		X	X	X	X			
PK assessments		X						
Adverse event monitoring		X	X	X	X	X	X	X
Clinical response						X	X	X

Abbreviations: ECG=electrocardiogram; EOT=End of Treatment; TOC=Test of Cure; FU=Follow-up.
[1] EOT assessments were performed at premature withdrawal, treatment failure, or within 24 hours from last dose.

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[2] Abdominal examinations were performed at least once daily until resolution of all signs and symptoms of cIAI.
[3] Aerobic and anaerobic blood cultures were obtained at Screening and repeated if clinically indicated (i.e., positive culture, worsening signs/symptoms, relapse, or new infection).
[4] Intra-abdominal cultures were collected from the site of infection at the time of the initial surgical procedure, subsequent surgical re-interventions, and if there were signs and symptoms of infection (if applicable). If it was not possible to obtain a tissue biopsy or aspirate, then a swab may have been obtained. Samples collected from superficial swabs and abdominal drains were not allowed.
[5] The expected minimum treatment duration was four 24-hour dosing cycles unless clinical failure or clinical cure occurred earlier. Maximum treatment duration was fourteen 24-hour dosing cycles.
[6] Chemistry and hematology labs were performed at Screening, Dose Cycles 1 to 4; every three 24-hour dosing cycles thereafter while on study drug; and at EOT, TOC, and FU Visits.
[7] Urine microscopy for RBC, WBC, crystals, and casts were performed at Screening, Dose Cycle 1, and EOT Visit.
Source: Adapted from clinical study report for TP-434-008 and TP-434-025.

9.4 Safety Results

Overall Incidence
The overall incidence of TEAEs, SAEs, discontinuation of study drug due to adverse events, and deaths in the Phase 1 IV Pool are summarized in Table 93. Overall, most of the TEAEs were reported as mild or moderate in severity, non-serious, and resolved without leading to discontinuation of study drug.

Table 93: Overview of TEAEs - Phase 1 IV Pool (Safety Population)

TEAE Category	Phase 1 IV Pool	
	Eravacycline Single Dose IV N=113 n (%)	Eravacycline Multiple Dose IV N=68 n (%)
Any TEAE	44 (38.9)	49 (72.1)
Any severe TEAE[1]	0	0
Any SAE	0	0
Any TEAE leading to discontinuation of study drug	N/A	2 (2.9)
Any TEAE resulting in Death	0	0

[1] Severe is defined as severe, life-threatening, or fatal. TEAEs with missing severity are included as severe.
Source: Adapted from Pooled analysis tables – Integrated safety, Table 1.3.1

The overall incidence of TEAEs, SAEs, discontinuation of study drug due to adverse events, and deaths in the Phase 2 cIAI study is summarized in Table 94. TEAEs were generally well balanced between the eravacycline 1 mg/kg and ertapenem groups; however, each TEAE category occurred in a greater percentage of subjects in the eravacycline 1.5 mg/kg group compared to the other treatment groups. Overall, most of the TEAEs were mild or moderate in severity, non-serious, and resolved without leading to discontinuation of study drug.

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Table 94: Overview of TEAEs - Phase 2 cIAI Study (Safety Population)

TEAE Category	Study TP-434-P2-cIAI-1		
	Eravacycline 1 mg/kg q12h N=56 n (%)	Eravacycline 1.5 mg/kg q24h N=53 n (%)	Ertapenem N=30 n (%)
Any TEAE	16 (28.6)	19 (35.8)	8 (26.7)
Any severe TEAE[1]	1 (1.8)	4 (7.5)	2 (6.7)
Any SAE	1 (1.8)	6 (11.3)	1 (3.3)
Any TEAE leading to discontinuation of study drug	0	2 (3.8)	2 (6.7)
Any TEAE resulting in Death	0	3 (5.7)	0

[1] Severe is defined as severe, life-threatening, or fatal. TEAEs with missing severity are included as severe.
Source: Adapted from Pooled analysis tables – Integrated safety, Table 1.3.1; Clinical Reviewer's Analysis

The overall incidence of TEAEs, SAEs, discontinuation of study drug due to adverse events, and deaths in the Phase 3 cIAI studies is summarized in Table 95. In each Phase 3 cIAI study, a greater percentage of subjects in the eravacycline group compared with the ertapenem or meropenem groups experienced at least 1 TEAE. The other TEAE categories were generally well balanced between the treatment groups in each study. Overall, most of the TEAEs were mild or moderate in severity, non-serious, and resolved without leading to discontinuation of study drug.

Table 95: Overview of TEAEs - Phase 3 cIAI Studies (Safety Population)

TEAE Category	Study TP-434-008		Study TP-434-025		Pooled Analysis	
	ERV 1 mg/kg q12h N=270 n (%)	ERT N=268 n (%)	ERV 1 mg/kg q12h N=250 n (%)	MER N=249 n (%)	ERV 1 mg/kg q12h N=520 n (%)	Comparator N=517 n (%)
Any TEAE	112 (41.5)	71 (26.5)	89 (35.6)	73 (29.3)	201 (38.7)	144 (27.9)
Any severe TEAE[1]	15 (5.6)	16 (6.0)	12 (4.8)	13 (5.2)	27 (5.2)	29 (5.6)
Any SAE	17 (6.3)	16 (6.0)	15 (6.0)	16 (6.4)	32 (6.2)	32 (6.2)
Any TEAE leading to discontinuation of study drug	7 (2.6)	6 (2.2)	4 (1.6)	5 (2.0)	11 (2.1)	11 (2.1)
Any TEAE resulting in Death	4 (1.5)	6 (2.2)	4 (1.6)	1 (0.4)	8 (1.5)	7 (1.4)

Abbreviations: ERV=eravacycline; ERT=ertapenem; MER=meropenem; Comparator=ertapenem or meropenem
[1] Severe is defined as severe, life-threatening, or fatal. TEAEs with missing severity are included as severe.
Source: Adapted from Pooled analysis tables – Integrated safety, Table 1.3.1; Clinical Reviewer's Analysis

The overall incidence of TEAEs, SAEs, discontinuation of study drug due to adverse events, and deaths in the Phase 3 cUTI studies are summarized in Table 96. TEAE were generally well

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balanced between the treatment groups in each study. Overall, most of the TEAEs were mild or moderate in severity, non-serious, and resolved without leading to discontinuation of study drug.

Table 96: Overview of TEAEs - Phase 3 cUTI Studies (Safety Population)

TEAE Category	Study TP-434-010 (IV-to-PO regimen)		Study TP-434-021 (IV regimen only)	
	Eravacycline 1.5 mg/kg q24h IV + 200/250 mg q12h PO N=547 n (%)	Levofloxacin 750 mg q24h IV + 750 mg PO q24h PO N=498 n (%)	Eravacycline 1.5 mg/kg q24h N=601 n (%)	Ertapenem N=600 n (%)
Any TEAE	211 (38.6)	113 (22.7)	235 (39.1)	133 (22.2)
Any severe TEAE[1]	19 (1.8)	6 (0.6)	21 (3.5)	11 (1.8)
Any SAE	9 (1.6)	7 (1.4)	11 (1.8)	6 (1.0)
Any TEAE leading to discontinuation of study drug	19 (3.5)	11 (2.2)	12 (2.0)	4 (0.7)
Any TEAE resulting in Death	1 (0.2)	0	3 (0.5)	2 (0.3)

Abbreviations: ERV=eravacycline; ERT=ertapenem; MER=meropenem; Comparator=ertapenem or meropenem
[1] Severe is defined as severe, life-threatening, or fatal. TEAEs with missing severity are included as severe.
Source: Adapted from Pooled analysis tables – Integrated safety, Table 1.3.1; 120 Day Safety Update Report.

9.4.1 Deaths

A listing of all deaths that occurred in the development program are presented in Table 97. A total of 24 deaths were reported, including 15 subjects from the eravacycline groups and 9 subjects from the comparator groups. Eighteen of these subjects were from the clinical studies for cIAI, including 3 deaths from Study TP-434-P2-cIAI-1 (all in the eravacyline 1.5 mg/kg dose group), 10 death from Study TP-434-008 (4 eravacycline-treated subjects versus 6 ertapenem-treated subjects), and 5 deaths from Study TP-434-025 (4 eravacycline-treated subjects versus 1 meropenem-treated subject). Four eravacycline-treated subjects and 1 comparator-treated subject in the clinical studies for cIAI experienced a fatal SAE that was also responsible for premature discontinuation of study treatment (i.e., drug withdrawn by investigator or interrupted). None of the adverse events leading to death in the development program for cIAI or cUTI were considered to be related to study drug by the study site investigators.

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Table 97: Deaths in the Eravacycline Development Program

Subject ID	Age/Sex	Diagnosis	Treatment End Study Day	Fatal SAE Preferred Term	AE Onset Study Day	Death Study Day	Study Drug Action Taken
Study TP-434-P2-cIAI-1, Eravacycline 1.5 mg/kg q24h IV							
001-021-2001	74/M	Gastric/duodenal perforation; Peritonitis	2	Duodenal ulcer hemorrhage	2	3	Drug withdrawn
001-021-2028	74/M	Peritonitis	4	Atrial fibrillation	5	6	Drug withdrawn
001-025-2044	60/M	Perforation of intestine	8	Embolism	9	9	N/A
Study TP-434-008, Eravacycline 1 mg/kg q12h IV							
008-073-0005	45/M	Perforation of intestine; Peritonitis	2	Acute respiratory failure	2	3	Drug withdrawn
008-079-0001	59/F	Complicated cholecystitis; Intra-abdominal abscess; Peritonitis	8	Pancreatitis necrotizing	21	50	N/A
008-102-0007	74/M	Peritonitis; Intra-abdominal abscess	15	Multiple organ dysfunction syndrome	34	34	N/A
008-145-0025	71/M	Complicated appendicitis; Intra-abdominal abscess	10	Cerebrovascular accident	13	15	N/A
Study TP-434-025, Eravacycline 1 mg/kg q12h IV							
025-097-0006	66/M	Intra-abdominal abscess	14	Pulmonary embolism	21	21	N/A
025-118-0001	75/F	Gastric/duodenal perforation; Peritonitis	4	Respiratory failure	3	16	Drug withdrawn
025-123-0022	54/F	Gastric/duodenal perforation; Peritonitis	7	COPD	6	7	No change
025-328-0007	78/F	Complicated cholecystitis; Intra-abdominal abscess	11	Pneumonia	11	13	N/A

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Subject ID	Age/Sex	Diagnosis	Treatment End Study Day	Fatal SAE Preferred Term	AE Onset Study Day	Death Study Day	Study Drug Action Taken
Study TP-434-010, Eravacycline 1.5 mg/kg q24h IV + 200/250 mg q12h PO							
010-229-0003	57/F	cUTI	4	DIC	6	13	Oral drug withdrawn
Study TP-434-021, Eravacycline 1.5 mg/kg q24h IV							
021-222-0003	46/M	Pyelonephritis	4	Aneurysm ruptured; Hemorrhagic stroke	4	17	Drug withdrawn
021-234-0010	73/M	Pyelonephritis	5	Myocardial Infarction	21	21	N/A
021-367-0004	83/M	cUTI	5	Pneumonia	38	40	N/A
Study TP-434-008, Ertapenem							
008-072-0030	60/F	Perforation of intestine; Peritonitis	2	Pulmonary embolism	2	2	Drug interrupted
008-093-0003	67/F	Intra-abdominal abscess	11	Pulmonary embolism	15	15	No change
008-097-0001	75/M	Intra-abdominal abscess	8	Respiratory disorder	4	20	No change
008-107-0002	40/F	Complicated appendicitis	9	Acute respiratory distress syndrome	15	15	N/A
008-110-0003	79/M	Complicated cholecystitis; Intra-abdominal abscesses	13	Cardiopulmonary failure	35	35	N/A
008-111-0003	63/F	Perforation of intestine	9	Supraventricular tachycardia	12	13	N/A
Study TP-434-025, Meropenem							
025-102-0001	81/F	Intra-abdominal abscess; Other cIAI	15	Cardiac arrest	21	21	N/A
Study TP-434-021, Ertapenem							
021-222-0021	70/M	cUTI	6	Circulatory collapse	16	16	N/A
021-379-0004	82/M	cUTI	2	Cardiorenal syndrome	2	3	Drug withdrawn

Source: Clinical Reviewer's Analysis

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Reviewers' Comment: *The adverse events leading to death did not follow a particular pattern and were generally associated with pre-existing conditions.*

None of the subjects in the Phase 1 studies with IV eravacycline experienced adverse events leading to death.

The Phase 2 cIAI study had 3 subjects (5.7%) treated with eravacycline 1.5 mg/kg q24h experience adverse events leading to death. Brief narratives for these eravacycline-treated subjects are presented below. None of the subjects treated with eravacycline 1 mg/kg q12h or ertapenem in Study TP-434-P2-cIAI-1 had adverse events leading to death.

Narratives of Deaths in the Eravacycline-treated Subjects in Study TP-434-P2-cIAI-1 (n=3)

i. Subject (b) (6): This was a 74-year-old male with duodenal ulcer perforation and peritonitis who received a 2-day course of ERV 1.5 mg/kg q24h. Baseline APACHE II score was 16, and the subject underwent surgical repair of a single perforated duodenal ulcer to treat the cIAI. One day after starting study drug, the subject experienced a SAE of duodenal ulcer hemorrhage (bleeding from another duodenal ulcer), which resulted in death. The subject developed generalized weakness, nausea, and decreased arterial pressure on the day of event onset. A subsequent endoscopic examination revealed bleeding from a second, unrepaired duodenal ulcer. Despite endoscopic hemostasis, bleeding restarted and the subject was transfused with blood and blood plasma. Study drug was discontinued because of the adverse event. The following day the subject died as a result of duodenal ulcer hemorrhage. An autopsy was performed and confirmed the cause of death as profuse bleeding from an unrepaired duodenal ulcer. The investigator considered the SAE to be unrelated to study drug.

   Reviewers' Comment: *While the contribution of eravacyline to this fatal event cannot be excluded, this reviewer agrees with the assessment of causality provided by the Applicant.*

ii. Subject (b) (6): This was 74-year-old male with peritonitis who received a 4-day course of ERV 1.5 mg/kg q24h. His relevant medical history included atrial fibrillation and cardiac failure. Baseline APACHE II score was 15, and the subject underwent a segmental resection of the small intestine with side-to-side anastomosis to treat the cIAI. Postoperatively, the subject experienced several episodes of tachysystolic atrial fibrillation. Four days after starting study drug, the subject experienced a SAE of atrial fibrillation (thrombosis of intestinal arteries secondary to intermittent atrial fibrillation), which resulted in death. A laparotomy performed on the day of event onset showed superior mesenteric arterial thrombosis and necrosis of complete small intestine. On the same day, the subject also experienced non-serious adverse events of abdominal pain, vomiting, and ileus, which remained ongoing. Study drug was discontinued because of the serious and non-serious adverse events. The following day the subject developed asystole and died as a result of atrial fibrillation. An autopsy was performed and revealed myocardial infarction which may have contributed to his cardiac arrhythmias and episodes of thrombotic

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embolization in the greater blood circulatory system. Although the source of the thrombotic embolization was not found, evidence for the possible effects of the embolism include multiple large scars found in both kidneys and the protracted course of ischemic lesions in the small intestine. The investigator considered the serious and non-serious adverse events to be unrelated to study drug.

Reviewers' Comment: *This reviewer agrees with the investigator's assessment that the serious and non-serious adverse events experienced in this subject were not related to study drug.*

iii. Subject (b) (6) This was a 60-year-old male with perforation of intestine who received a 7-day course of ERV 1.5 mg/kg q24h. His relevant medical history included hypertension and diabetes mellitus. Baseline APACHE II score was 12, and the subject underwent a laparotomy to treat the cIAI. Five days after starting study drug, the subject experienced non-serious adverse events of tachypnea and hypotension, which remained ongoing. Study drug was discontinued on Day 8 because there was no improvement in his general condition. The following day the subject started metronidazole and cefopefrazone + sulbactam treatment and experienced a SAE of embolism (possible thromboembolism), which resulted in death. The subject developed sudden bradycardia, hypotension and apneic spells on the day of event onset. He was intubated for mechanical ventilation. Later that day he developed a cardiac arrest and died as a result of embolism. An autopsy was not performed. The investigator considered the SAE and non-serious adverse events to be unrelated to study drug.

Reviewers' Comment: *This reviewer agrees with the investigator's assessment that the serious and non-serious adverse events experienced in this subject were not related to study drug.*

The Phase 3 cIAI studies had 8 (1.5%) eravacycline-treated subjects and 7 (1.4%) comparator-treated subjects experience TEAEs leading to death. Brief narratives for the eravacycline-treated subjects (4 in Study TP-434-008 and 4 in Study TP-434-025) are presented below.

Narratives of Deaths in the Eravacycline-treated Subjects in Study TP-434-008 (n=4)

i. Subject (b) (6): This was a 45-year-old male with perforation of intestine and peritonitis who received a 1.5-day course of ERV 1 mg/kg q12h. His relevant medical history included hypertension and obesity. Baseline APACHE II score was 15, and the subject underwent a laparotomy to treat the cIAI. Cultures of the peritoneal fluid grew *Escherichia coli* and *Clostridium perfringens*. Blood cultures also revealed *E. coli*. One day after starting study drug, the subject experienced a SAE of acute respiratory failure, which resulted in death. The subject developed tachypnea, dyspnea, and hypoxia on the day of event onset. He was subsequently intubated for mechanical ventilation. Study drug was discontinued because of the adverse event. The following day the subject died as a result of acute respiratory failure. The leading cause of death reported on the death certificate was

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multiple system organ failure (respiratory and circulatory). Other causes of death included septic shock, and the existing cIAI. It was not reported if an autopsy was performed. The investigator considered the SAE to be unrelated to study drug.

Reviewers' Comment: *This reviewer agrees with the investigator's assessment that the SAE experienced in this subject was not related to study drug.*

ii. Subject (b) (6) This was a 59-year-old female with complicated cholecystitis, peritonitis, and an intra-abdominal abscess who received a 7-day course of ERV 1 mg/kg q12h. Baseline APACHE II score was 7, and the subject underwent a laparotomy to treat the cIAI. Notable laboratory findings at screening included elevated lipase of 624 U/L (reference range, 7 - 60 U/L) and elevated amylase of 636 U/L (reference range, 28 - 100 U/L). Both lipase and amylase decreased during the course of treatment. The hospital course was notable for the non-serious adverse events of vomiting from Day 4 to Day 6 and nausea from Day 6 to Day 7. The investigator considered the non-serious adverse events to be unrelated to study drug. Study drug therapy was completed on Day 8 and no abnormal findings were observed on physical examination. She was discharged from the hospital on Day 15 with abdominal drainage tubes still present.

Thirteen days after study drug therapy was completed, the subject experienced SAEs of pancreatitis necrotizing (acute necrotizing destructive pancreatitis) and peritonitis (diffuse purulent peritonitis), which were life-threatening and required hospitalization. The subject presented with fever, nausea, vomiting, abdominal pain and rigidity. She underwent urgent laparotomy with debridement, necrectomy, lavage, and drainage. Aspiration and tissue cultures were positive for *Klebsiella pneumoniae*, and the postoperative diagnosis included recurrent acute necrotizing pancreatitis with hemorrhagic purulent peritonitis. Other treatments included cefoperazone + sulbactam (Day 21 – 32), metronidazole (Day 22 – 33), meropenem (Day 32 – 42), and vancomycin (Day 32 – 42). The SAEs were ongoing when subject completed the final study visit on Day 39. The investigator considered the SAEs to be unrelated to study drug. Based on the baseline elevations of lipase and amylase which improved during study treatment, the investigator considered it more likely the subject had acute pancreatitis of another cause prior to starting ERV treatment.

Six weeks after the study drug therapy was completed and 11 days after the final study visit, the SAE of pancreatitis necrotizing had a fatal outcome. On Day 47, the subject underwent her third laparotomy and experienced hypotension and tachycardia requiring pharmacologic intervention. Re-laparotomy findings included necrosis of the pancreas head, and a total necrosectomy was performed. Other treatment included imipenem/cilastatin (Day 47 – 50) and blood products. Her urine and blood cultures revealed *K. pneumoniae*, *Staphylococcus aureus*, and *Acinetobacter baumannii* (later revealed to be susceptible to only tobramycin). Despite resuscitation, she progressively deteriorated with tachycardia, hypotension, progressive anemia, leukopenia, and thrombocytopenia. She experienced hemodynamic failure and died on the third post-

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operative day (Day 50). The cause of death reported on the death certificate was cardiac arrest. It was not reported if an autopsy was performed. The investigator considered the fatal outcome was related to an exacerbation of pancreatitis which was present at screening, and unrelated to study drug. The event of peritonitis had not recovered at the time of death.

Reviewers' Comment: *This reviewer agrees with the investigator's assessment that the serious and non-serious adverse events experienced in this subject were not related to study drug. Please see Section 9.5.1 for additional information with respect to necrotizing pancreatitis in Subject* (b) (6)

iii. Subject (b) (6): This was a 74-year-old male with peritonitis and intra-abdominal abscess (splenic and parasplenic) who received a 14-day course of ERV 1 mg/kg q12h. His relevant medical history included gastric neoplasia, pulmonary emphysema, reflux esophagitis, and anemia. Baseline APACHE II score was 11, and the subject underwent a laparotomy with splenectomy to treat the cIAI. Three days after starting study drug, the subject experienced a SAE of esophageal fistula, which prolonged hospitalization. He continued on study drug and completed therapy on Day 15. The subject was considered to have recovered from the event of esophageal fistula 1 week after the study drug therapy was completed. According to the investigator, the SAE of esophageal fistula was related to an abscess that eroded the esophagus wall, and unrelated to study drug.

Eight days after study drug therapy was completed, the subject experienced a SAE of hematoma infection (right subphrenic suprainfected hematoma), which prolonged hospitalization. On the same day, he underwent an exploratory laparotomy and had the subphrenic hematoma evacuated. Postoperatively, the subject was placed in the intensive care ward and mechanically ventilated. He was also started on metronidazole, meropenem, and colistin. The subject was considered to have recovered from the event of hematoma infection on the same day. According to the investigator, the SAE of hematoma infection was related to duodenal stump bleeding, and unrelated to study drug.

Nineteen days after study drug therapy was completed, the subject experienced a SAE of multiple organ dysfunction syndrome (multiple organ failure), which resulted in death. His condition had deteriorated during the 10 days leading up to the event, including becoming comatose with unstable respiratory status, worsening anemia, severe thrombocytopenia, leukocytosis, and increased nitrogen retention. On the day of event onset, the subject developed progressive bradycardia. He later developed asystole and died as a result of multiple organ failure. An autopsy was not performed. The investigator considered the SAE of multiple organ dysfunction syndrome to be related to sepsis, and unrelated to study drug.

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Reviewers' Comment: *This reviewer agrees with the investigator's assessment that the serious and non-serious adverse events experienced in this subject were not related to study drug.*

iv. Subject (b) (6): This was a 71-year-old male with complicated appendicitis and intra-abdominal abscess who received a 9-day course of ERV 1 mg/kg q12h. His relevant medical history included diabetes mellitus, arterial hypertonia, chronic atrial fibrillation, cardiovascular insufficiency, and gout. Baseline APACHE II score was 7, and the subject underwent laparoscopic surgery to treat the cIAI. He completed study drug therapy and was discharged from the hospital on Day 10. Three days after study drug therapy was completed, the subject experienced a SAE of cerebrovascular accident (cerebral insult), which resulted in death. On the day of event onset, the subject was found comatose at home and hospitalized. A computerized tomography was performed and the subject was diagnosed with a cerebrovascular accident. Five days after study drug therapy was completed, the subject died as a result of cerebrovascular accident. An autopsy was not performed. According to the investigator, the SAE was related to concurrent illnesses of diabetes mellitus and arterial hypertonia, and unrelated to study drug.

Reviewers' Comment: *This reviewer agrees with the investigator's assessment that the SAE experienced in this subject was not related to study drug.*

Narratives of Deaths in the Eravacycline-treated Subjects in Study TP-434-025 (n=4)

i. Subject (b) (6): This was a 66-year-old male with intra-abdominal abscess who received a 13-day course of ERV 1 mg/kg q12h. His relevant medical history included sinus tachycardia and chronic pyelonephritis. Baseline APACHE II score was 14, and the subject underwent a laparotomy, sigmoid colostomy, and ischiorectal abscessectomy to treat the cIAI. An incision and lavage of the scrotum was also performed due to the presence of a phlegmon. The subject completed study drug therapy on Day 14 and treatment with vancomycin and imipenem were started the following day. Her course during study drug therapy was notable for multiple non-serious adverse events, including fever from Day 2 to Day 6, wound infection from Day 2 to Day 8, abdominal abscess on Day 5, testicular necrosis from Day 5 to Day 13, and another wound infection on Day 10 that remained ongoing. Wound debridement, necrectomy, and lavage were notable interventions performed on Days 3 and 5. A left orchiectomy was also performed on Day 13 due to purulent-necrotic changes in the testicle. The investigator considered all the non-serious adverse events to be unrelated to study drug.

Seven days after study drug therapy was completed, the subject experienced a SAE of pulmonary embolism (pulmonary embolism), which resulted in death. The subject died a result of pulmonary embolism on the same day as event onset. An autopsy was performed and the immediate cause of death was acute heart failure due to massive pulmonary embolism. Pathological conditions included ischiorectal abscess and phlegmon-necrosis of the perineum type Fournier. Other important conditions that contributed to the onset of

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death included chronic kidney disease. The investigator considered the SAE to be unrelated to study drug. An alternative causality was reported as a complication of the intra-abdominal infection.

Reviewers' Comment: *This reviewer agrees with the investigator's assessment that the serious and non-serious adverse events experienced in this subject were not related to study drug.*

ii. Subject (b) (6): This was a 75-year-old female with gastric perforation and peritonitis who received a 3-day course of ERV 1 mg/kg q12h. Her relevant medical history included chronic obstructive pulmonary disease (COPD), hypertension, hypokalemia, hyponatremia, hypochloremia, asthenia, cachexia, and esophageal disorder. Baseline APACHE II score was 12, and the subject underwent surgical repair of a perforated stomach ulcer to treat the cIAI. Two days after starting study drug, the subject experienced a SAE of respiratory failure (respiratory insufficiency), which resulted in death. Study drug was discontinued due to the SAE, and the subject subsequently started treatment with piperacillin/tazobactam and methylprednisolone. Despite an aggressive ventilation regimen, her respiratory failure rapidly progressed. Twelve days after the last dose of study drug, the subject died as a result of respiratory failure. It was not reported if an autopsy was performed. The investigator considered the SAE to be unrelated to study drug. According to the investigator, the SAE was related to concurrent illnesses of COPD, cachexia, and malnutrition.

Reviewers' Comment: *This reviewer agrees with the investigator's assessment that the SAE experienced in this subject was not related to study drug.*

iii. Subject (b) (6): This was a 54-year-old female with gastric/duodenal perforation and peritonitis who received a 6-day course of ERV 1 mg/kg q12h. Her relevant medical history included COPD. Baseline APACHE II score was 12, and the subject underwent a laparotomy to treat the cIAI. Her liver function tests at screening were notable for an elevated ALT of 51 U/L (reference range, 0 - 33 U/L) and elevated AST of 82 U/L (reference range, 14 - 34 U/L). Three days after starting study drug, the subject experienced the non-serious adverse event of toxic encephalopathy, which remained ongoing. Her AST increased to 96 U/L on the same day and decreased to 76 U/L the following day. Study drug was continued throughout. The investigator considered the toxic encephalopathy and the transient worsening of AST to be unrelated to study drug.

Five days after starting study drug, the subject experienced a SAE of chronic obstructive pulmonary disease (COPD exacerbation), which resulted in death. On the day of event onset, the subject underwent a therapeutic bronchoscopy to remove purulent sputum and afterwards was placed on a mechanical ventilator. The COPD exacerbation and large amount of purulent sputum resulted in congestive pneumonia, which was confirmed on pneumonography. Study drug was discontinued on Day 7 when the subject was considered

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a treatment failure and linezolid, moxifloxacin, and ornidazole were started. She was also diagnosed with sepsis (reported as a non-serious adverse event) and developed arterial hypotension and oliguria. She died later that day due to worsening symptoms of respiratory insufficiency and arterial hypotension. The toxic encephalopathy and sepsis remained ongoing at the time of death. An autopsy was not performed. The investigator considered the serious and non-serious adverse events to be unrelated to study drug. According to the investigator, the SAE was related to the pre-existing condition of COPD.

Reviewers' Comment: *This reviewer agrees with the investigator's assessment that the serious and non-serious adverse events experienced in this subject were not related to study drug.*

iv. Subject (b) (6) This was a 78-year-old female with complicated cholecystitis and intra-abdominal abscess who received a 10-day course of ERV 1 mg/kg q12h. Her relevant medical history included cerebrovascular accident, hemiplegia, and hypertensive heart disease. Baseline APACHE II score was 12, and the subject underwent laparoscopic surgery to treat the cIAI. Study drug therapy was completed on Day 11. Later that day the subject experienced a SAE of pneumonia, which resulted in death. The subject developed respiratory distress and had a chest x-ray confirm the diagnosis of pneumonia. She was transferred to the intensive care unit where treatment with cefuroxime and metronidazole was started. The subject's pneumonia resulted in septic shock, acute renal failure, acute respiratory distress and eventually respiratory failure. Two days after study drug therapy was completed, the subject died as a result of pneumonia. An autopsy was not performed. The investigator considered the SAE to be unrelated to study drug.

Reviewers' Comment: *This reviewer agrees with the investigator's assessment that the SAE experienced in this subject was not related to study drug.*

The first Phase 3 cUTI study (TP-434-010) had 1 (0.2%) eravacycline-treated subject experience an adverse event leading to death. A brief narrative for the eravacycline-treated subject is presented below. None of the levofloxacin-treated subjects in Study TP-434-010 experienced adverse events leading to death.

Narratives of Deaths in the Eravacycline-treated Subjects in Study TP-434-010 (n=1)

i. Subject (b) (6): This was a 57-year-old-female with cUTI with partial obstructive uropathy who received a 4-day course of ERV 1.5 mg/kg q24h IV and transition then transitioned to PO study drug (200 mg q12h). Her relevant medical history included hypothyroidism and hepatitis C virus infection. She experienced the SAE of disseminated intravascular coagulation (DIC) on Day 6. Study drug was discontinued that day due to the adverse event. The event was associated with anemia, thrombocytopenia, increased INR, increased serum creatinine, and increased total bilirubin. She required multiple blood product transfusions as well as prednisolone treatment due to worsening laboratory abnormalities related to DIC, sepsis, and multiple organ failure. Her cUTI was also treated

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with ceftriaxone (Days 7 to 10) and later meropenem (Days 11 to 12). By Day 12, diagnostic impressions included possible central nervous system hemorrhage and hepatic failure. Imaging studies, such as computed tomography or magnetic resonance imaging, could not be performed because the subject exceeded the weight limitation for these devices. The subject died on Day 13 from hemorrhage and multiple organ failure. An autopsy was not performed. The investigator considered the SAE of DIC unrelated to study drug. According to the investigator, the event was related to failure of treatment of cUTI and sepsis, as well as the subject's pre-existing condition of hepatitis C virus infection.

Reviewers' Comment: *This reviewer agrees with the investigator's assessment that the SAE experienced in this subject was not related to study drug.*

The second Phase 3 cUTI study (TP-434-021) had 3 (0.5%) eravacycline-treated subjects and 2 (0.3%) ertapenem-treated subjects experience adverse events leading to death. Brief narratives for the eravacycline-treated subjects are presented below.

Narratives of Deaths in the Eravacycline-treated Subjects in Study TP-434-021 (n=3)

i. Subject (b) (6): This was a 46-year-old male with pyelonephritis who received a 4-day course of ERV 1.5 mg/kg q24h. On Day 4, he experienced the SAEs of aneurysm ruptured and hemorrhagic stroke (rupture of anterior communicating artery aneurism, hemorrhagic stroke), which resulted in death. The subject developed headache, increased blood pressure, vomiting, and impaired consciousness that led to coma. A computed tomography angiogram (CTA) was performed that day and revealed a hemorrhagic stroke due to rupture of a saccular aneurysm of the anterior communicating artery. Study drug was discontinued due to the adverse event. His condition remained poor over the next two days with bradycardia, increased blood pressure, and decreased consciousness. On Day 8 he underwent an open surgical repair of the anterior communicating artery aneurysm. Despite this treatment, he died 9 days later. The investigator considered the SAEs to be unrelated to study drug. According to the investigator, the SAE was related to a previously undiagnosed cerebral artery aneurysm.

Reviewers' Comment: *This reviewer agrees with the investigator's assessment that the SAE experienced in this subject was not related to study drug.*

ii. Subject (b) (6): This was a 73-year old male with pyelonephritis who received a 5-day course of ERV 1.5 mg/kg q24h followed by 3 days of cefixime. His relevant medical history included hypertension, diabetes mellitus, angina pectoris, coronary stent, chronic ischemic cardiopathy, stroke, ureteral stricture, and prostate adenoma. On Day 15, the subject experienced the non-serious adverse event of renal colic. The event was treated as an outpatient with antispasmodic drugs and an NSAID. He experienced an SAE of renal colic the following day, which was assessed as severe and required hospitalization. He complained of severe right lumbar pain and had mild hydronephrosis on ultrasound. On Day 21, the subject experienced an SAE of myocardial infarction, which resulted in a cardiac

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arrest and death. No autopsy was performed. The investigator considered the SAEs of renal colic and myocardial infarction to be unrelated to study drug. According to the investigator, the events were related to the concurrent illnesses of right hydronephrosis and angina pectoris, respectively.

Reviewers' Comment: *This reviewer agrees with the investigator's assessment that the SAEs experienced in this subject were not related to study drug.*

iii. Subject (b) (6): This was a 83-year-old male diagnosed with cUTI with partial obstructive uropathy who a received a 5-day course of ERV 1.5 mg/kg q24h followed by 3 days of cefixime. On Day 1, he underwent percutaneous nephrostomy insertion to treat the primary study condition of left hydronephrosis. His relevant medical history included chronic obstructive pulmonary disease, ischemic heart disease, pyelectasia, nephrolithiasis, atrial fibrillation and cholelithiasis. On Day 8, he experienced a SAE of deep vein thrombosis (thrombosis of the left femoral vein), which required hospitalization. Symptoms associated with the event included significant edema and pain of the left extremity. Ultrasound of the extremity revealed thrombosis of left femoral vein. He received treatment with low molecular weight heparin and the event resolved 17 days later. The investigator considered the SAE of deep vein thrombosis to be unrelated to study drug.

On Day 36, the subject experienced a SAE of decubitus ulcer, which required hospitalization for wound care. According to the investigator, the event likely developed because the subject was in bed due to thrombosis of the left femoral vein.

On Day 38, the subject experienced a SAE of pneumonia, which required hospitalization and was fatal. The subject presented for a scheduled nephrostomy tube change where he was noted to be very weak with cachexia and have an abnormal lung examination. Chest x-ray findings were suggestive of pneumonia with pleural effusion. He received supplemental oxygen, corticosteroids, and antibiotics. Despite ongoing treatment, his condition progressively worsened and he died on Day 40. The event of decubitus ulcer had not resolved at the time of death. An autopsy confirmed the direct cause of death as bilateral pneumonia of the lower lobes. The investigator considered the SAEs of decubitus ulcer and pneumonia to be unrelated to the study drug.

Reviewers' Comment: *This reviewer agrees with the investigator's assessment that the SAEs experienced in this subject were not related to study drug.*

9.4.2 Serious Adverse Events

None of the subjects in the Phase 1 IV Pool experienced SAEs. However, the Phase 1 IV Pool only included healthy subjects and excluded the subjects with hepatic or renal impairment in Studies TP-434-013 and TP-434-014, respectively. In Study TP-434-013, a single-dose PK study of eravacycline conducted in healthy subjects and subjects with hepatic impairment, 1 subject

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with severe hepatic impairment (Subject (b) (6)) had a SAE of hepatic encephalopathy. In Study TP-434-014, a single-dose PK study of eravacycline conducted in healthy subjects and subjects with end-stage renal disease, 1 subject with end stage renal disease (Subject (b) (6)) had a SAE of arteriovenous fistula site hemorrhage. Both events required hospitalization, resolved, and were considered by the investigator to be unrelated to study drug.

Reviewers' Comment: *This reviewer agrees with the investigator's assessment that SAEs in Subjects (b) (6) and (b) (6) were unrelated to study drug. Please see Section 9.5.5 for additional information with respect to hepatic encephalopathy reported in Subject (b) (6).*

A summary of SAEs (including deaths) for each treatment group in the Phase 2 cIAI study is presented in Table 98. No SAE occurred in more than 1 subject in any treatment group. The non-fatal SAEs reported in the eravacycline treatment groups included wound infection (1 mg/kg dose group), abdominal wall abscess (1.5 mg/kg dose group), pneumonia (1.5 mg/kg dose group), and ileus (1.5 mg/kg dose group). These events required/prolonged hospitalization and resolved. None of the SAEs reported during the Phase 2 cIAI study were considered by the investigator to be related to study drug.

Table 98: Summary of SAEs - Phase 2 cIAI Study (Safety Population)

System Organ Class Preferred Term	Study TP-434-P2-cIAI-1		
	Eravacycline 1 mg/kg q12h n (%)	Eravacycline 1.5 mg/kg q24h n (%)	Ertapenem n (%)
Total exposed (N)	**56**	**53**	**30**
Any SAE	**1 (1.8)**	**6 (11.3)**	**1 (3.3)**
Infections and Infestations	**1 (1.8)**	**2 (3.8)**	**1 (3.3)**
Wound infection	1 (1.8)	–	–
Abdominal wall abscess	–	1 (1.9)	–
Pneumonia	–	1 (1.9)	–
Subdiaphragmatic abscess	–	–	1 (3.3)
Gastrointestinal disorders	**0**	**2 (3.8)**	**0**
Duodenal ulcer hemorrhage	–	1 (1.9)	–
Ileus	–	1 (1.9)	–
Cardiac disorders	**0**	**1 (1.9)**	**0**
Atrial fibrillation	–	1 (1.9)	–
Vascular disorders	**0**	**1 (1.9)**	**0**
Embolism	–	1 (1.9)	–

Source: Adapted from Pooled analysis tables – Integrated safety, Tables 1.5.4 and 1.11.6; Clinical Reviewer's Analysis

A summary of SAEs (including deaths) for each treatment group in the Phase 3 cIAI studies are summarized in Table 99. The most common SAEs reported in the eravacycline group were pneumonia (4 subjects, 0.8%) and wound dehiscence (4 subjects, 0.8%). None of the other SAEs

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occurred in more than two subjects in any treatment group. Most of the non-fatal SAEs were assessed as serious because they required/prolonged hospitalization. Notable exceptions in the eravacycline group included 2 subjects with life-threatening TEAEs. One subject (Subject (b) (6)) was diagnosed with splenic rupture after they fell and hit their abdomen during post-surgical rehabilitation. The subject required a splenectomy and the event resolved. The other subject (Subject (b) (6) experienced necrotizing pancreatitis and peritonitis that required multiple re-laparotomy procedures. The latter event resulted in death after the final study visit (see summary of deaths). Another 2 subjects in the eravacycline group had non-fatal SAEs that were medically significant (adenocarcinoma of colon; neuroendocrine tumor). These subjects were diagnosed with adenocarcinoma of colon or neuroendocrine tumor based on the pathology sample from the initial surgery (Subject (b) (6) and Subject (b) (6) respectively). None of the SAEs reported in any treatment group during the Phase 3 cIAI studies were considered by the investigator to be related to study drug.

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Table 99: Summary of SAEs - Phase 3 cIAI Studies (Safety Population)

System Organ Class Preferred Term	Studies TP-434-008 and TP-434-025		
	Eravacycline 1 mg/kg q12h n (%)	Ertapenem n (%)	Meropenem n (%)
Total exposed (N)	**520**	**268**	**249**
Any SAE	**32 (6.2)**	**16 (6.0)**	**16 (6.4)**
Gastrointestinal disorders	**10 (1.9)**	**3 (1.1)**	**3 (1.2)**
Duodenal ulcer hemorrhage	1 (0.2)	1 (0.4)	1 (0.4)
Esophageal fistula	1 (0.2)	–	–
Ileus	1 (0.2)	–	1 (0.4)
Intestinal fistula	1 (0.2)	–	1 (0.4)
Diverticular perforation	1 (0.2)	–	–
Gastrointestinal inflammation	1 (0.2)	–	–
Large intestine perforation	1 (0.2)	–	–
Melena	1 (0.2)	–	–
Pancreatitis acute	1 (0.2)	–	–
Pancreatitis necrotizing	1 (0.2)	–	–
Abdominal compartment syndrome	–	1 (0.4)	–
Colonic fistula	–	1 (0.4)	–
Duodenal ulcer	–	–	1 (0.4)
Infections and infestations	**8 (1.5)**	**7 (2.6)**	**1 (0.4)**
Pneumonia	4 (0.8)	1 (0.4)	1 (0.4)
Abdominal abscess	1 (0.2)	2 (0.7)	1 (0.4)
Liver abscess	1 (0.2)	1 (0.4)	–
Peritonitis	1 (0.2)	–	1 (0.4)
Empyema	1 (0.2)	–	–
Hematoma infection	1 (0.2)	–	–
Sepsis	–	1 (0.4)	1 (0.4)
Peritoneal abscess	–	1 (0.4)	–
Septic shock	–	1 (0.4)	–

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System Organ Class Preferred Term	Studies TP-434-008 and TP-434-025		
	Eravacycline 1 mg/kg q12h n (%)	Ertapenem n (%)	Meropenem n (%)
Injury, poisoning and procedural complications	**6 (1.2)**	**2 (0.7)**	**1 (0.4)**
Wound dehiscence	4 (0.8)	1 (0.4)	–
Abdominal wound dehiscence	1 (0.2)	–	–
Splenic rupture	1 (0.2)	–	–
Wound evisceration	1 (0.2)	–	–
Gastrointestinal stoma complication	–	1 (0.4)	–
Suture related complication	–	–	1 (0.4)
Wound decomposition	–	–	1 (0.4)
Respiratory, thoracic and mediastinal disorders	**6 (1.2)**	**6 (2.2)**	**2 (0.8)**
Respiratory failure[1]	2 (0.4)	1 (0.4)	1 (0.4)
Pulmonary embolism	1 (0.2)	2 (0.7)	1 (0.4)
Chronic obstructive pulmonary disease	1 (0.2)	–	–
Hydrothorax	1 (0.2)	–	–
Pleural effusion	1 (0.2)	–	–
Acute respiratory distress syndrome	–	1 (0.4)	–
Pulmonary artery thrombosis	–	1 (0.4)	–
Respiratory disorder	–	1 (0.4)	–
Neoplasms benign, malignant and unspecified	**2 (0.4)**	**0**	**1 (0.4)**
Adenocarcinoma of colon	1 (0.2)	–	–
Neuroendocrine tumor	1 (0.2)	–	–
Gallbladder cancer	–	–	1 (0.4)
General disorders and administration site conditions	**1 (0.2)**	**0**	**1 (0.4)**
Multiple organ dysfunction syndrome	1 (0.2)	–	–
Pyrexia	–	–	1 (0.4)
Metabolism and nutrition disorders	**1 (0.2)**	**0**	**0**
Dehydration	1 (0.2)	–	–
Nervous system disorders	**1 (0.2)**	**0**	**0**
Cerebrovascular accident	1 (0.2)	–	–

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System Organ Class Preferred Term	Studies TP-434-008 and TP-434-025		
	Eravacycline 1 mg/kg q12h n (%)	Ertapenem n (%)	Meropenem n (%)
Renal and urinary disorders	**1 (0.2)**	**0**	**0**
Ureteric rupture	1 (0.2)	–	–
Renal failure	–	–	1 (0.4)
Surgical and medical procedures	**1 (0.2)**	**0**	**0**
Biliary drainage	1 (0.2)	–	–
Vascular disorders	**1 (0.2)**	**0**	**1 (0.4)**
Deep vein thrombosis	1 (0.2)	–	–
Hypotension	–	–	1 (0.4)
Blood and lymphatic system disorders	**0**	**0**	**1 (0.4)**
Splenic hematoma	–	–	1 (0.4)
Cardiac disorders	**0**	**3 (1.1)**	**3 (1.2)**
Atrial fibrillation	–	1 (0.4)	1 (0.4)
Cardiopulmonary failure	–	1 (0.4)	–
Pulseless electrical activity	–	1 (0.4)	–
Supraventricular tachycardia	–	1 (0.4)	–
Cardiac arrest	–	–	1 (0.4)
Myocardial infarction	–	–	1 (0.4)
Hepatobiliary disorders	**0**	**0**	**1 (0.4)**
Cholecystitis acute	–	–	1 (0.4)
Reproductive system and breast disorders	**0**	**0**	**1 (0.4)**
Pelvic fluid collection	–	–	1 (0.4)

[1] Respiratory failure includes: acute respiratory failure and respiratory failure.
Source: Adapted from Pooled analysis tables – Integrated safety, Tables 1.5.4 and 1.11.6; Clinical Reviewer's Analysis

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The Phase 3 cUTI study with the IV-to-PO transition regimen (TP-434-010) had 9 eravacycline-treated subjects (1.6%) and 7 levofloxacin-treated subjects (1.4%) experience a SAE. No SAE occurred in more than 1 subject in any treatment group. The non-fatal SAEs reported in the eravacycline group included the following: deep vein thrombosis, dyspnea, hip fracture, pancreatitis acute, pneumonia aspiration, renal colic, retroperitoneal abscess, and suicide attempt. The latter event occurred in a subject with a history of depression, was life threatening, and not identified as related to study drug. The other non-fatal SAEs reported in the eravacycline group required/prolonged hospitalization. None of the SAEs in the eravacycline group were considered by the investigator to be related to study drug.

9.4.3 Dropouts and/or Discontinuations Due to Adverse Effects

Table 100 summarizes the premature treatment discontinuations and/or early study withdrawals for the Phase 1 IV Pool (Safety Population). In the Phase 1 Single Dose IV Pool, 2 subjects (1.8%) had TEAEs resulting in discontinuation from the study. Both subjects received a single dose of IV eravacycline (0.25 mg/kg or 1 mg/kg) during Study TP-434-P1-SAD-1 and withdrew from the study because of signs and symptoms of the common flu (pyrexia) and in accordance with the Clinical Research Organization's influenza response plan. The events were non-serious and resolved within 1 week. In the Phase 1 Multiple Dose IV Pool, 1 subject (1.5%) had a TEAE resulting in discontinuation of the study drug and study. This subject received a single dose of IV eravacycline (1 mg/kg) during Study TP-434-016 and experienced presyncope in the itraconazole treatment period. The event was non-serious and resolved on the same day. Five additional subjects, all from Study TP-434-P1-MAD-1, had adverse events resulting in discontinuation of the study drug only. Four of the subjects received multiple doses of IV eravacycline (1.5 mg/kg q24h [n=3] or 1 mg/kg q12h [n=1]) and discontinued the study drug because of loss of IV access, which resulted from phlebitis superficial. The fifth subject was also administered multiple doses of IV eravacycline (1 mg/kg q12h), but discontinued the study drug because of decreased appetite, nausea, and vomiting. All the TEAEs resulting in discontinuation of study drug during Study TP-434-P1-MAD-1 were assessed as non-serious and resolved within 1 or 2 weeks.

Table 100: Subject Disposition - Phase 1 IV Pool (Safety Population)

TEAE Category	Phase 1 IV Pool	
	Eravacycline Single Dose IV N=113 n (%)	Eravacycline Multiple Dose IV N=68 n (%)
Number of Subjects Prematurely Discontinuing Study Drug		
n (%)	N/A	7 (10.3)
Reason for Premature Discontinuation of Study Drug		
Adverse Event	N/A	6 (8.8)
Subject's Decision	N/A	1 (1.5)
Number of Subjects Prematurely Withdrawing from Study		

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TEAE Category	Phase 1 IV Pool	
	Eravacycline Single Dose IV N=113 n (%)	Eravacycline Multiple Dose IV N=68 n (%)
n (%)	3 (2.7)	2 (2.9)
Reason for Premature Withdrawal from Study		
Adverse Event	2 (1.8)	1 (1.5)
Subject's Decision	0	1 (1.5)
Lost to Follow-Up	1 (0.9)	0

Source: Adapted from Pooled analysis tables – Integrated safety, Table 1.1.1; Clinical Reviewer's Analysis

Table 101 summarizes the premature treatment discontinuations and/or early study withdrawals during the Phase 2 cIAI study. The subjects who prematurely withdrew from the study due to Adverse Event had either a fatal SAE (3 subjects in the eravacycline 1.5 mg/kg group) or a non-fatal SAE (1 subject in the eravacycline 1.5 mg/kg group). The latter subject experienced the SAE of abdominal wall abscess on Day 27 that required re-hospitalization and resolved 1 week later.

Table 101: Subject Disposition - Phase 2 cIAI Study (Safety Population)

	Study TP-434-P2-cIAI-1		
	Eravacycline 1 mg/kg q12h N=56 n (%)	Eravacycline 1.5 mg/kg q24h N=53 n (%)	Ertapenem N=30 n (%)
Number of Subjects Prematurely Discontinuing Study Drug			
n (%)	3 (5.4)	2 (3.8)	2 (6.7)
Reason for Premature Discontinuation of Study Drug			
Adverse Event	0	2 (3.8)	2 (6.7)
Subject's Decision	3 (5.4)	0	0
Number of Subjects Prematurely Withdrawing from Study			
n (%)	7 (12.5)	10 (18.9)	3 (10.0)
Reason for Premature Withdrawal from Study			
Lost to Follow-Up	3 (5.4)	5 (9.4)	2 (6.7)
Adverse Event	0	4 (7.5)	0
Subject's Decision	4 (7.1)	0	0
Investigator's Decision	0	1 (1.9)	1 (3.3)

Source: Adapted from Pooled analysis tables – Integrated safety, Tables 1.1.4 and 1.14; Clinical Reviewer's Analysis

Reviewers' Comment: *There were minor discrepancies between this reviewer's analysis and that of the Applicant. For example, in the "adverse event" category, this reviewer included 4 patients in the eravacycline 1.5 mg/kg dose group who prematurely withdrew from the study due to adverse events. These patients experienced SAEs which resulted in death or required re-*

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hospitalization (3 patients and 1 patient, respectively). The Applicant's disposition table included these patients in a different reason for premature withdrawal from study ("other").

The TEAEs that led to premature discontinuation of study drug during the Phase 2 cIAI study is presented in Table 102.

Table 102: TEAEs that Led to Premature Discontinuation of Study Drug - Phase 2 cIAI Study (Safety Population)

System Organ Class Preferred Term	Study TP-434-P2-cIAI-1		
	Eravacycline 1 mg/kg q12h n (%)	Eravacycline 1.5 mg/kg q24h n (%)	Ertapenem n (%)
Total exposed (N)	**56**	**53**	**30**
Any TEAE Leading to Discontinuation of Study Drug	**0**	**2 (3.8)**	**2 (6.7)**
Gastrointestinal disorders	**0**	**2 (3.8)**	**0**
Abdominal pain	–	1 (1.9)	–
Duodenal ulcer hemorrhage	–	1 (1.9)	–
Ileus	–	1 (1.9)	–
Vomiting	–	1 (1.9)	–
Cardiac disorders	**0**	**1 (1.9)**	**0**
Atrial fibrillation	–	1 (1.9)	–
General disorders and administration site conditions	**0**	**0**	**1 (3.3)**
Application site hypersensitivity	–	–	1 (3.3)
Immune system disorders	**0**		**1 (3.3)**
Hypersensitivity	–	–	1 (3.3)

Source: Adapted from Pooled analysis tables – Integrated safety, Tables 1.7.4; Clinical Reviewer's Analysis

Table 103 summarizes the premature treatment discontinuations and/or early study withdrawals during the Phase 3 cIAI studies. All of the eravacycline-treated subjects who prematurely withdrew from the study due to Adverse Event had fatal SAEs. A single meropenem-treated subject prematurely withdrew from the study on Day 1 due to the non-serious adverse event of vomiting. The other comparator-treated subjects who prematurely withdrew from the study all experienced fatal SAEs.

Table 103: Subject Disposition - Phase 3 cIAI studies

	Study TP-434-008		Study TP-434-025		Pooled Analysis	
	ERV 1 mg/kg q12h N=270 n (%)	ERT N=268 n (%)	ERV 1 mg/kg q12h N=250 n (%)	MER N=249 n (%)	ERV 1 mg/kg q12h N=520 n (%)	Comparator N=517 n (%)

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	Study TP-434-008		Study TP-434-025		Pooled Analysis	
	ERV 1 mg/kg q12h N=270 n (%)	ERT N=268 n (%)	ERV 1 mg/kg q12h N=250 n (%)	MER N=249 n (%)	ERV 1 mg/kg q12h N=520 n (%)	Comparator N=517 n (%)
Number of Subjects Prematurely Discontinuing Study Drug						
n (%)	15 (5.6)	13 (4.9)	11 (4.4)	7 (2.8)	26 (5.0)	20 (3.9)
Reason for Premature Discontinuation of Study Drug						
Adverse Event	7 (2.6)	6 (2.2)	4 (1.6)	5 (2.0)	11 (2.1)	11 (2.1)
Subject's Decision	4 (1.5)	0	2 (0.8)	2 (0.8)	6 (1.2)	2 (0.4)
Insufficient Therapeutic Effect	4 (1.5)	5 (1.9)	1 (0.4)	0	5 (1.0)	5 (1.0)
Investigator's Decision	0	0	2 (0.8)	0	2 (0.4)	0
Non-Compliance	0	1 (0.4)	1 (0.4)	0	1 (0.2)	1 (0.2)
Other[1]	0	1 (0.4)	1 (0.4)	0	1 (0.2)	1 (0.2)
Number of Subjects Prematurely Withdrawing from Study						
n (%)	24 (8.9)	13 (4.9)	13 (5.2)	8 (3.2)	37 (7.1)	21 (4.1)
Reason for Premature Withdrawal from Study						
Lost to Follow-Up	15 (5.6)	3 (1.1)	6 (2.4)	4 (1.6)	21 (4.0)	7 (1.4)
Adverse Event	3 (1.1)	6 (2.2)	4 (1.6)	2 (0.8)	7 (1.3)	8 (1.5)
Subject's Decision	3 (1.1)	0	1 (0.4)	2 (0.8)	4 (0.8)	2 (0.4)
Non-Compliance	2 (0.7)	3 (1.1)	2 (0.8)	0	4 (0.8)	3 (0.6)
Other[2]	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)

Abbreviations: ERV = eravacycline; ERT = ertapenem; MER = meropenem; Comparator = ertapenem or meropenem

[1] Premature Discontinuation of Study Drug due to Other includes: subject met discharge criteria (1 subject, ERV group) and subjects' baseline pathogen was Enterococcus resistant to one of the treatment arms (1 subject, ertapenem/comparator group).

[2] Premature Withdrawal from Study due to Other includes: follow-up visit not scheduled (1 subject, ERV group) and baseline pathogen was Enterococcus resistant to one of the treatment arms (1 subject, ertapenem/comparator group).

Source: Adapted from Pooled analysis tables – Integrated safety, Tables 1.1.4 and 1.14; Clinical Reviewer's Analysis

Reviewers' Comment: *There were minor discrepancies between this reviewer's analysis and that of the Applicant. For example, in the "adverse event" category, this reviewer included an additional eravacycline-treated subject from Study TP-434-025 who prematurely discontinued the study drug due to an adverse event (peritoneal adhesions). This eravacycline-treated subject (Subject* (b) (6) *experienced non-serious peritoneal adhesions associated with ileus from Day 4 through Day 12. The Applicant's disposition table did not include this subject; however, the subject was included in the Applicant's analysis of adverse events leading to study drug discontinuation (Pooled analysis tables – Integrated safety, Table 1.14). In the "subject decision" category, this reviewer included 2 additional eravacycline-treated subjects from Study TP-434-008 who prematurely discontinued the study drug due to withdrawal of consent. The Applicant's disposition table included these subjects in a different reason for premature withdrawal from the study treatment ("other").*

Reference ID: 4312284

The TEAEs that led to premature discontinuation of study drug during the Phase 3 cIAI studies is presented in Table 104.

Table 104: TEAEs that Led to Premature Discontinuation of Study Drug - Phase 3 cIAI Studies (Safety Population)

System Organ Class Preferred Term	Studies TP-434-008 and TP-434-025		
	Eravacycline 1 mg/kg q12h n (%)	Ertapenem n (%)	Meropenem n (%)
Total exposed (N)	**520**	**268**	**249**
Any TEAE Leading to Discontinuation of Study Drug	**11 (2.1)**	**6 (2.2)**	**5 (2.0)**
Gastrointestinal disorders	**4 (0.8)**	**1 (0.4)**	**4 (1.6)**
Diverticular perforation	1 (0.2)	–	–
Nausea	1 (0.2)	–	–
Pancreatitis acute	1 (0.2)	–	–
Peritoneal adhesions	1 (0.2)	–	–
Intra-abdominal hemorrhage	–	1 (0.4)	–
Vomiting	–	–	2 (0.8)
Duodenal ulcer	–	–	1 (0.4)
Ileus	–	–	1 (0.4)
Respiratory, thoracic and mediastinal disorders	**3 (0.6)**	**2 (0.7)**	**0**
Respiratory failure[1]	2 (0.4)	–	–
Dyspnea	1 (0.2)	–	–
Hydrothorax	–	1 (0.4)	–
Pulmonary embolism		1 (0.4)	
General disorders and administration site conditions	**1 (0.2)**	**1 (0.4)**	**1 (0.4)**
Drug intolerance	1 (0.2)	–	–
Infusion site pain	–	1 (0.4)	–
Infusion site urticaria	–	–	1 (0.4)
Immune system disorders	**1 (0.2)**	**0**	**0**
Hypersensitivity	1 (0.2)	–	–
Injury, poisoning and procedural complications	**1 (0.2)**	**0**	**0**
Wound dehiscence	1 (0.2)	–	–
Renal and urinary disorders	**1 (0.2)**	**0**	**0**
Dysuria	1 (0.2)	–	–
Infections and infestations	**0**	**2 (0.7)**	**0**
Abdominal abscess	–	2 (0.7)	–
Musculoskeletal and connective tissue disorders	**0**	**0**	**1 (0.4)**
Back pain	–	–	1 (0.4)

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System Organ Class Preferred Term	Studies TP-434-008 and TP-434-025		
	Eravacycline 1 mg/kg q12h n (%)	Ertapenem n (%)	Meropenem n (%)
Vascular disorders	**0**	**0**	**1 (0.4)**
Hypertension	–	–	1 (0.4)

[1] Respiratory failure includes: acute respiratory failure and respiratory failure
Source: Adapted from Pooled analysis tables – Integrated safety, Tables 1.7.4; Clinical Reviewer's Analysis

Reviewers' Comment: *There were minor discrepancies between this reviewer's analysis and that of the Applicant. For example, there were 2 additional subjects in the eravacycline group (Study TP-434-008) and 1 additional subject in the ertapenem group who premature discontinued the study treatment due to an adverse event. One of the eravacycline-treated subjects (Subject* (b) (6) *) experienced the non-serious adverse event of dysuria from Day 2 through Day 38. The other eravacycline-treated subject (Subject* (b) (6) *) experienced the serious adverse event of acute respiratory failure which resulted in death. The ertapenem-treated subject (Subject experienced a serious adverse event of pulmonary embolism which resulted in death. Although none of these events were considered related to study drug by the investigator, the subjects narratives for each indicated that the study drug was permanently discontinued/interrupted because of the adverse event. The Applicant's disposition table include these subjects in premature discontinuation of study drug due to adverse event (Pooled analysis tables – Integrated safety, Table 1.1.4).*

The Phase 3 cUTI study with the IV-to-PO transition regimen had 42 eravacycline-treated subjects (7.7%) and 26 levofloxacin-treated subjects (5.2%) who prematurely discontinued the study drug. The most common reason was adverse event (19 subjects in the eravacycline group and 11 subjects in the levofloxacin group). In the eravacycline group, 1 (0.2%) discontinuation was associated with a fatal SAE (disseminated intravascular coagulation), 3 (0.5%) discontinuations were associated with non-fatal SAEs (hip fracture, retroperitoneal abscess, and dyspnea), and 15 (2.7%) discontinuations were associated with one or more non-serious TEAEs. The non-fatal SAEs required/prolonged hospitalization and resolved. The non-serious TEAEs also resolved and included 8 cases of nausea, 2 cases of diarrhea, 2 cases of vomiting, and 1 case each of atrial fibrillation, dizziness, influenza, nightmare, and rash. In the levofloxacin group, 3 (0.6%) discontinuations were associated with non-fatal SAEs (pericardial effusion, pneumonia, and psoas abscess) and 8 (1.6%) discontinuations were associated with one or more non-serious TEAEs. The non-serious TEAEs included 3 cases of diarrhea, 2 cases of nausea, and 1 case each of vomiting, abdominal pain upper, Clostridium difficile colitis, hypersensitivity, and toxic skin eruption. All the TEAEs that led to premature discontinuation of levofloxacin treatment were resolving or resolved by study completion.

9.4.4 Significant Adverse Events

Reference ID: 4312284

There were no additional significant adverse events identified within the Safety populations in clinical studies with IV eravacycline.

9.4.5 Treatment Emergent Adverse Events and Adverse Reactions

The most common TEAEs reported in the Phase 1 IV Pool were nausea, infusion site reactions, and headache. These events were reported in 53 subjects (29.3%), 39 subjects (21.5%), and 27 subjects (14.9%), respectively. Infusion site reactions included phlebitis, phlebitis superficial/erythema, infusion/vessel puncture site pain, infusion site erythema, infusion site discomfort, infusion site extravasation, and infusion site swelling. Other common TEAEs that occurred in ≥2% of subjects in the Phase 1 IV Pool were vomiting/retching (10.5%), diarrhea (5.0%), pain in extremity (3.9%), abdominal pain upper/lower (3.3%), dizziness (3.3%), dysgeusia (2.2%), and oropharyngeal pain (2.2%).

Table 105 summarizes the common TEAEs reported during the Phase 2 cIAI study, and defined as TEAEs experienced by at least 2 subjects in any treatment group. Nausea and lipase increased were the most frequently reported TEAEs. The former was reported in 6 subjects (10.7%) treated with eravacycline 1 mg/kg q12h, 1 subject (1.9%) treated with eravacycline 1.5 mg/kg q24h, and 2 subjects (6.7%) treated with ertapenem. Three of these subjects (1 in the eravacycline 1 mg/kg group and 2 in the ertapenem group) also experienced the TEAE of lipase increased. The other subjects who experienced lipase increased (3 in each eravacycline group) did not report nausea or another TEAE in the Gastrointestinal disorders SOC.

Table 105: TEAEs Experienced by at least 2 Subjects in Any Treatment Group – Phase 2 cIAI Study (Safety Population)

Preferred term	Study TP-434-P2-cIAI-1		
	Eravacycline 1 mg/kg q12h N=56 n (%)	Eravacycline 1.5 mg/kg q24h N=53 n (%)	Ertapenem N=30 n (%)
Nausea	6 (10.7)	1 (1.9)	2 (6.7)
Lipase increased	4 (7.1)	3 (5.7)	2 (6.7)
Infusion site reaction[1]	3 (5.4)	1 (1.9)	1 (3.3)
Amylase increased	2 (3.6)	3 (5.7)	1 (3.3)
Vomiting	1 (1.8)	3 (5.7)	0
Abdominal pain	0	2 (3.8)	0
Ileus	0	2 (3.8)	0

[1] Infusion site reaction includes: catheter site pain, thrombophlebitis, and application site hypersensitivity.
Source: Adapted from Pooled analysis tables – Integrated safety, Table 1.17.1; Clinical Reviewer's Analysis

Reviewers' Comment: *Nausea, lipase increased, and infusion site reactions were the only TEAEs reported by 2 or more subjects in any treatment group and more frequently in the eravacycline 1 mg/kg group. The other common TEAEs were reported more frequently in the eravacycline 1.5 mg/kg group.*

Reference ID: 4312284

Table 106 summarizes the common TEAEs reported during the Phase 3 cIAI studies, and defined as TEAEs experienced by at least 1% of eravacycline-treated subjects. The most common TEAEs were infusion site reactions, nausea, and vomiting. The respective events were reported in 40 (7.7%), 34 (6.5%), and 19 (3.7%) of the eravacycline-treated subjects and 10 (1.9%), 3 (0.6%), and 13 (2.5%) of the comparator-treated subjects across both Phase 3 studies. Infusion site reactions in either treatment group included catheter/infusion/injection site phlebitis, catheter/infusion/vessel puncture site pain, infusion site extravasation, infusion site hypoaesthesia, infusion site thrombosis, infusion site urticaria, injection/vessel puncture site erythema, phlebitis, phlebitis superficial, thrombophlebitis, and vessel puncture site swelling.

Reference ID: 4312284

Table 106: TEAEs Experienced by at least 1% of Patients in Eravacycline Treatment Group – Phase 3 cIAI Studies (Safety Population)

Preferred term	Study TP-434-008		Study TP-434-025		Pooled Analysis	
	ERV 1 mg/kg q12h N=270 n (%)	ERT N=268 n (%)	ERV 1 mg/kg q12h N=250 n (%)	MER N=249 n (%)	ERV 1 mg/kg q12h N=520 n (%)	Comparator N=517 n (%)
Infusion site reactions[1]	25 (9.3)	5 (1.9)	15 (6.0)	5 (2.0)	40 (7.7)	10 (1.9)
Nausea	22 (8.1)	2 (0.7)	12 (4.8)	1 (0.4)	34 (6.5)	3 (0.6)
Vomiting	11 (4.1)	8 (3.0)	8 (3.2)	5 (2.0)	19 (3.7)	13 (2.5)
Wound infection	7 (2.6)	2 (0.7)	7 (2.8)	4 (1.6)	14 (2.7)	6 (1.2)
Diarrhea	6 (2.2)	5 (1.9)	6 (2.4)	3 (1.2)	12 (2.3)	8 (1.5)
Anemia[2]	7 (2.6)	8 (3.0)	3 (1.2)	8 (3.2)	10 (1.9)	16 (3.1)
Pyrexia	6 (2.2)	7 (2.6)	4 (1.6)	3 (1.2)	10 (1.9)	10 (1.9)
Hypertension[3]	4 (1.5)	6 (2.2)	5 (2.0)	7 (2.8)	9 (1.7)	13 (2.5)
Pneumonia	4 (1.5)	3 (1.1)	4 (1.6)	3 (1.2)	8 (1.5)	6 (1.2)
Wound dehiscence	6 (2.2)	1 (0.4)	1 (0.4)	0	7 (1.3)	1 (0.2)
Hypotension	4 (1.5)	1 (0.4)	3 (1.2)	1 (0.4)	7 (1.3)	2 (0.4)
Postoperative wound infection	3 (1.1)	1 (0.4)	4 (1.6)	4 (1.6)	7 (1.3)	5 (1.0)
Abdominal pain[4]	4 (1.5)	3 (1.1)	2 (0.8)	2 (0.8)	6 (1.2)	5 (1.0)
Leukocytosis[5]	3 (1.1)	3 (1.1)	3 (1.2)	1 (0.4)	6 (1.2)	4 (0.8)
Pleural effusion	4 (1.5)	0	0	0	4 (0.8)	0
Constipation	3 (1.1)	2 (0.7)	1 (0.4)	0	4 (0.8)	2 (0.4)
Leukopenia[6]	3 (1.1)	0	1 (0.4)	0	4 (0.8)	0
Blood CPK Increased	1 (0.4)	4 (1.5)	3 (1.2)	3 (1.2)	4 (0.8)	7 (1.4)
Dyspnea	3 (1.1)	1 (0.4)	0	0	3 (0.6)	1 (0.2)
Hypokalemia[7]	3 (1.1)	4 (1.5)	0	6 (2.4)	3 (0.6)	10 (1.9)
Atrial fibrillation	0	2 (0.7)	3 (1.2)	2 (0.8)	3 (0.6)	4 (0.8)

Abbreviations: ERV = eravacycline; ERT = ertapenem; MER = meropenem; Comparator = ertapenem or meropenem; CPK = creatine phosphokinase

[1] Infusion site reaction includes: catheter/infusion/injection site phlebitis, catheter/infusion/vessel puncture site pain, infusion site extravasation, infusion site thrombosis, infusion site urticaria, injection/vessel puncture site erythema, phlebitis, phlebitis superficial, thrombophlebitis, and vessel puncture site swelling.

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[2] Anemia includes: anemia, anemia postoperative, hemoglobin decreased, and normochromic normocytic anemia.
[3] Hypertension includes: blood pressure increased, essential hypertension, hypertension, and systolic hypertension.
[4] Abdominal pain includes: abdominal pain and abdominal pain upper.
[5] Leukocytosis includes: leukocytosis and white blood cell count increased.
[6] Leukopenia includes: leukopenia and white blood cell count increased.
[7] Hypokalemia includes: blood potassium decreased and hypokalemia
Source: Adapted from Pooled analysis tables – Integrated safety, Table 1.4.4; Clinical Reviewer's Analysis

Reviewers' Comment: *The TEAEs reported by at least 1% of subjects in the pooled eravacycline group and more frequently in the eravacycline group were infusion site reactions, nausea, vomiting, wound infection, diarrhea, pneumonia, wound dehiscence, hypotension, post-operative wound infection, abdominal pain, and leukocytosis. Some of these common TEAEs (i.e., wound infection, post-operative wound infection, abdominal pain, leukocytosis) could be considered complications of surgical treatment, hospitalization, or the underlying condition.*

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In the Phase 3 cUTI study that evaluated an IV-to-PO regimen, the most common TEAEs were nausea, vomiting, and infusion site reactions. The respective events were reported in 97 (17.7%), 46 (8.4%), and 26 (4.8%) of the eravacycline-treated subjects and 16 (3.2%), 7 (1.4%), and 6 (1.2%) of the levofloxacin-treated subjects. Infusion site reactions in either treatment group included catheter/infusion site erythema, infusion site phlebitis, infusion site thrombosis, thrombophlebitis/thrombophlebitis superficial, infusion site pain, infusion site reaction, infusion site irritation, catheter site inflammation, and infusion site discomfort. Other common TEAEs that occurred in ≥1% of eravacycline-treated subjects and with incidences greater than the levofloxacin group were: headache (3.3% eravacycline group vs. 1.2% levofloxacin group), hypertension/blood pressure increased (2.6% eravacycline group vs. 1.8% levofloxacin group), dyspepsia (2.2% in the eravacycline group vs. 0.4% in the levofloxacin group), abdominal pain/abdominal pain upper (1.8% eravacycline group vs. 0.6% levofloxacin group), and dizziness (1.1% eravacycline group vs. 0.4% levofloxacin group).

Reviewers' Comment: *The common TEAEs reported in this study were similar to the events reported in the other analysis pools. The eravacycline-treated subjects in the Phase 3 cIAI studies also had greater incidences of nausea, vomiting, infusion site reactions, and abdominal pain than the comparator group. Headache and dizziness were common in this Phase 3 cUTI study as well as in the Phase 1 IV Pool.*

9.4.6 Laboratory Findings

Different central clinical laboratories were used in the individual eravacycline Phase 2 and Phase 3 cIAI studies. In order to facilitate comparisons among the studies and to allow accurate calculation of mean values and changes from baseline across the studies, safety laboratory results in the Applicant's integrated analyses were normalized to adjust for the different reference ranges. This reviewer did not use the normalized values when evaluating individual studies for changes relative to the reference range value. Regardless, no meaningful differences in the overall interpretation of clinical laboratory results were identified using the actual laboratory values vs. the normalized results.

Lipase and Amylase

Baseline mean values for lipase and amylase were within the normal ranges for eravacycline-treated subjects and comparator-treated subjects in the Phase 2 and Phase 3 cIAI studies. Mean changes from baseline in the clinical chemistry parameters were generally small and there were no changes from baseline at any timepoint that resulted in mean values outside the normal range. Summary of peak post-baseline lipase and amylase values reported in Studies TP-434-P2-cIAI, TP-434-008, and TP-434-025 are presented in Table 107, Table 108, and Table 109, respectively. Overall, elevations of serum lipase and amylase occurred in the eravacycline and comparator groups at similar frequencies. Please see Section 9.5.1 for assessment of TEAEs meeting the Acute Pancreatitis MedDRA SMQ.

Reference ID: 4312284

Table 107: Summary of Lipase and Amylase Results – Phase 2 cIAI Study (Safety Population)

	Study TP-434-P2-cIAI-1					
	Eravacycline 1 mg/kg q12h		Eravacycline 1.5 mg/kg q24h		Ertapenem	
Lipase (U/L)	**Subject Count**	**% of Subjects**	**Subject Count**	**% of Subjects**	**Subject Count**	**% of Subjects**
Less than 2x ULN	41	73.2%	37	69.8%	22	73.3%
Between 2x and 5x ULN	7	12.5%	6	11.3%	3	10.0%
Between 5x and 10x ULN	5	8.9%	5	9.4%	1	3.3%
Between 10x and 20x ULN	1	1.8%	3	5.7%	1	3.3%
20x ULN or Greater	0	0.0%	1	1.9%	1	3.3%
Missing Test Result	2	3.6%	1	1.9%	2	6.7%
All	56	100.0%	53	100.0%	30	100.0%
Amylase (U/L)						
Less than 2x ULN	47	83.9%	43	81.1%	24	80.0%
Between 2x and 5x ULN	7	12.5%	7	13.2%	4	13.3%
Between 5x and 10x ULN	0	0.0%	2	3.8%	0	0.0%
Missing Test Result	2	3.6%	1	1.9%	2	6.7%
All	56	100.0%	53	100.0%	30	100.0%

Source: Clinical Reviewer's Analysis

Table 108: Summary of Lipase and Amylase Results – Study TP-434-008 (Safety Population)

	Study TP-434-008			
	Eravacycline 1 mg/kg q12h		Ertapenem	
Lipase (U/L)	**Subject Count**	**% of Subjects**	**Subject Count**	**% of Subjects**
Less than 2x ULN	217	80.4%	202	75.4%
Between 2x and 5x ULN	44	16.3%	45	16.8%
Between 5x and 10x ULN	5	1.9%	10	3.7%
Between 10x and 20x ULN	2	0.7%	9	3.4%
20x ULN or Greater	1	0.4%	1	0.4%
Missing Test Result	1	0.4%	1	0.4%
All	270	100.0%	268	100.0%
Amylase (U/L)				
Less than 2x ULN	258	95.6%	243	90.7%
Between 2x and 5x ULN	10	3.7%	21	7.8%
Between 5x and 10x ULN	0	0.0%	3	1.1%
Between 10x and 20x ULN	1	0.4%	0	0.0%
Missing Test Result	1	0.4%	1	0.4%
All	270	100.0%	268	100.0%

Source: Clinical Reviewer's Analysis

Reference ID: 4312284

Table 109: Summary of Lipase and Amylase Results - Study TP-434-025 (Safety Population)

	Study TP-434-025			
	Eravacycline 1 mg/kg q12h		Meropenem	
Lipase (U/L)	**Subject Count**	**% of Subjects**	**Subject Count**	**% of Subjects**
Less than 2x ULN	207	82.8%	208	83.5%
Between 2x and 5x ULN	27	10.8%	27	10.8%
Between 5x and 10x ULN	10	4.0%	10	4.0%
Between 10x and 20x ULN	6	2.4%	1	0.4%
Missing Test Result	0	0.0%	3	1.2%
All	250	100.0%	249	100.0%
Amylase (U/L)				
Less than 2x ULN	235	94.0%	233	93.6%
Between 2x and 5x ULN	13	5.2%	13	5.2%
Between 5x and 10x ULN	2	0.8%	0	0.0%
Missing Test Result	0	0.0%	3	1.2%
All	250	100.0%	249	100.0%

Source: Clinical Reviewer's Analysis

Liver Tests

Baseline mean values for ALT, AST, and total bilirubin were within the normal ranges for eravacycline-treated subjects and comparator-treated subjects in the Phase 2 and Phase 3 cIAI studies. Mean changes from baseline in the clinical chemistry parameters were generally small and there were no changes from baseline at any timepoint that resulted in mean values outside the normal range. Summary of peak post-baseline ALT, AST, and total bilirubin values reported in Studies TP-434-P2-cIAI, TP-434-008, and TP-434-025 are presented in Table 110, Table 111, and Table 112, respectively. Overall, elevations of ALT, AST, or total bilirubin occurred in the eravacycline and comparator groups at similar frequencies. Please see Section 9.5.5 for analysis of potential drug-induced liver injury, including those who met laboratory criteria defined by Hy's Law.

Reference ID: 4312284

Table 110: Summary of Liver Test Results – Phase 2 cIAI Study (Safety Population)

	Study TP-434-P2-cIAI-1					
	Eravacycline 1 mg/kg q12h		Eravacycline 1.5 mg/kg q24h		Ertapenem	
ALT (U/L)	**Subject Count**	**% of Subjects**	**Subject Count**	**% of Subjects**	**Subject Count**	**% of Subjects**
Less than 2x ULN	51	91.1%	46	86.8%	27	90.0%
Between 2x and 5x ULN	3	5.4%	5	9.4%	2	6.7%
Between 5x and 10x ULN	0	0.0%	1	1.9%	0	0.0%
Between 10x and 20x ULN	0	0.0%	1	1.9%	0	0.0%
Missing Test Result	2	3.6%	0	0.0%	1	3.3%
All	56	100.0%	53	100.0%	30	100.0%
AST (U/L)						
Less than 2x ULN	52	92.9%	47	88.7%	28	93.3%
Between 2x and 5x ULN	1	1.8%	5	9.4%	1	3.3%
20x ULN or Greater	0	0.0%	1	1.9%	0	0.0%
Missing Test Result	3	5.4%	0	0.0%	1	3.3%
All	56	100.0%	53	100.0%	30	100.0%
Bilirubin (umol/L)						
Less than 2x ULN	54	96.4%	48	90.6%	29	96.7%
Between 2x and 5x ULN	0	0.0%	5	9.4%	0	0.0%
Missing Test Result	2	3.6%	0	0.0%	1	3.3%
All	56	100.0%	53	100.0%	30	100.0%

Source: Clinical Reviewer's Analysis

Table 111: Summary of Liver Test Results – Study TP-434-008 (Safety Population)

	Study TP-434-008			
	Eravacycline 1 mg/kg q12h		Ertapenem	
ALT (U/L)	**Subject Count**	**% of Subjects**	**Subject Count**	**% of Subjects**
Less than 2x ULN	242	89.6%	231	86.2%
Between 2x and 5x ULN	24	8.9%	32	11.9%
Between 5x and 10x ULN	2	0.7%	4	1.5%
Between 10x and 20x ULN	1	0.4%	0	0.0%
Missing Test Result	1	0.4%	1	0.4%
All	270	100.0%	268	100.0%
AST (U/L)				
Less than 2x ULN	237	87.8%	232	86.6%
Between 2x and 5x ULN	27	10.0%	30	11.2%
Between 5x and 10x ULN	5	1.9%	3	1.1%
Between 10x and 20x ULN	0	0.0%	2	0.7%
Missing Test Result	1	0.4%	1	0.4%
All	270	100.0%	268	100.0%
Bilirubin (umol/L)				
Less than 2x ULN	258	95.6%	260	97.0%
Between 2x and 5x ULN	10	3.7%	6	2.2%
Between 5x and 10x ULN	1	0.4%	0	0.0%
Between 10x and 20x ULN	0	0.0%	1	0.4%
Missing Test Result	1	0.4%	1	0.4%
All	270	100.0%	268	100.0%

Source: Clinical Reviewer's Analysis

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Table 112: Summary of Liver Test Results – Study TP-434-025 (Safety Population)

	Study TP-434-025			
	Eravacycline 1 mg/kg q12h		Meropenem	
ALT (U/L)	**Subject Count**	**% of Subjects**	**Subject Count**	**% of Subjects**
Less than 2x ULN	198	79.2%	202	81.1%
Between 2x and 5x ULN	46	18.4%	42	16.9%
Between 5x and 10x ULN	3	1.2%	2	0.8%
Between 10x and 20x ULN	3	1.2%	0	0.0%
Missing Test Result	0	0.0%	3	1.2%
All	250	100.0%	249	100.0%
AST (U/L)				
Less than 2x ULN	206	82.4%	212	85.1%
Between 2x and 5x ULN	38	15.2%	29	11.6%
Between 5x and 10x ULN	4	1.6%	5	2.0%
Between 10x and 20x ULN	2	0.8%	0	0.0%
Missing Test Result	0	0.0%	3	1.2%
All	250	100.0%	249	100.0%
Bilirubin (umol/L)				
Less than 2x ULN	239	95.6%	240	96.4%
Between 2x and 5x ULN	11	4.4%	6	2.4%
Missing Test Result	0	0.0%	3	1.2%
All	250	100.0%	249	100.0%

Source: Clinical Reviewer's Analysis

Other Chemistry

Baseline mean values for sodium, chloride, potassium glucose, protein, albumin, BUN, and creatinine were within the normal ranges for eravacycline-treated subjects and comparator-treated subjects in the Phase 2 and Phase 3 cIAI studies. Mean changes from baseline in the clinical chemistry parameters were small and there were no changes from baseline at any timepoint that resulted in mean values outside the normal range.

Hematology and Coagulation

Hematology and coagulation laboratory values assessed in the Phase 2 and Phase 3 cIAI trials included hemoglobin, hematocrit, platelet count, WBC count, partial thromboplastin time, prothrombin time, and INR. Overall, the mean values for hematology and coagulation parameters were generally balanced between treatment groups. There were no clear trends in shifts from baseline in any hematology/coagulation parameter for either eravacycline-treated subjects or comparator-treated subjects in the Phase 2 and Phase 3 cIAI studies.

9.4.7 Vital Signs

Vital sign descriptive summary statistics including changes from baseline by study visit for the Phase 1 IV Pool, Phase 2 cIAI study, and the Phase 3 cIAI studies were reviewed. A summary of abnormal post-baseline vital sign values (i.e., heart rate <60 beats/min, heart rate >120 beats/min, systolic blood pressure ≥140 mmHg, and diastolic blood pressure >20 mmHg

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increase from baseline) was also reviewed.

Overall, mean changes in heart rate, systolic blood pressure, diastolic blood pressure, and respiratory rate from baseline were small and similar between eravacycline and comparator treatment arms. The percentage of subjects in the Phase 2 and Phase 3 cIAI studies with vital signs that met the definition of clinically notable is presented in Table 113.

Table 113: Summary of Abnormal Post-Baseline Vital Signs - Phase 2 and Phase 3 cIAI Studies (Safety Population)

	Study TP-434-P2-cIAI-1 (Phase 2 cIAI)			Studies TP-434-008 and TP-434-025 (Phase 3 cIAI Pool)	
Post-baseline Abnormality	**ERV 1 mg/kg q12h N=56**	**ERV 1.5 mg/kg q24h N=53**	**ERT N=30**	**ERV 1 mg/kg q12h N=520**	**Comparator N=517**
Heart Rate, n (%)					
<60 beats/min	3 (5.4)	7 (13.2)	0	34 (6.5)	24 (4.6)
>120 beats/min	0	1 (1.9)	1 (3.3)	7 (1.3)	6 (1.2)
Systolic Blood Pressure, n (%)					
≥140 mmHg	16 (28.6)	17 (32.1)	4 (13.3)	259 (49.8)	243 (47.0)
Diastolic Blood Pressure, n (%)					
Change from baseline >20 mmHg	4 (7.1)	5 (9.4)	2 (6.7)	64 (12.3)	69 (13.3)

Abbreviations: ERV = eravacycline; ERT = ertapenem; Comparators = ertapenem or meropenem
Source: Adapted from Pooled analysis tables – Integrated safety, Table 1..33.4; Clinical Reviewer's Analysis

9.4.8 Electrocardiograms (ECGs)

In the Phase 2 cIAI study, standard 12-lead electrocardiograms (ECGs) were performed at Baseline (within 4 hours of initial dose), during study treatment (2 hours post-infusion of first dose on Days 1, 2, 3, 4, and 8) and at the EOT, TOC, and FU visits. There were no remarkable trends in the ECG intervals (i.e., PR, QRS, and QT) between treatment groups. The incidences of subjects with prolongation of corrected QTc intervals using Fridericia's formula is presented in Table 114. No subjects had a QTcF interval >500 msec post dosing. Five eravacycline-treated subjects (1 in the 1 mg/kg group and 4 in the 1.5 mg/kg group) and 1 ertapenem-treated subjects had >60 msec increase in QTcF between the baseline and EOT visits. The QTcF for all 5 subjects were <450 msec at the EOT visit. None of these subjects had TEAEs in the Cardiac disorders SOC.

Table 114: Calculated QTcF in the Phase 2 cIAI Study - (Safety Population)

QTcF ECG Parameter	**Study TP-434-P2-cIAI-1**		
	Eravacycline 1 mg/kg q12h	**Eravacycline 1.5 mg/kg q24h**	**Ertapenem**

QTcF ECG Parameter	Study TP-434-P2-cIAI-1		
	Eravacycline 1 mg/kg q12h	Eravacycline 1.5 mg/kg q24h	Ertapenem
QTcF (msec) at End of Therapy			
N1	50	48	27
Mean (SD)	401 (26)	395 (40)	397 (33)
Mean Change from Baseline (SD)	+4 (39)	+6 (47)	+3 (28)
Post-baseline Value at End of Therapy Category, n/N1 (%)			
>450 to ≤480 msec	–	1/48 (2.1)	–
>480 to ≤500 msec	–	–	–
>500 msec	–	–	–
Post-baseline Change at End of Therapy Category, n/N1 (%)			
>30 to ≤60 msec	4/50 (8.0)	6/48 (12.5)	3/27 (11.1)
>60 msec	1/50 (2.0)	4/48 (8.3)	1/27 (3.7)

N1=number of subjects with a baseline and post-baseline value
QTcF = Fridericia's formula for QT interval defined as QT divided by the cubed root of RR.
Source: Clinical Reviewer's Analysis

Reviewers' Comment: *QTcF was calculated by this reviewer using the QT and RR intervals reported in the Phase 2 study.*

In the Phase 3 cIAI studies, standard 12-lead ECGs were performed at Screening (within 48 hours of initial dose) and the End-of-therapy visit (premature withdrawal, treatment failure, or within 24-h of last dose). There were no remarkable trends in the ECG intervals (i.e., PR, QRS, and QT) between treatment groups. The incidences of subjects with prolongation of corrected QTc intervals using Fridericia's formula is presented in Table 115. Few subjects exhibited QTcF values during treatment with eravacycline or comparators that would be considered indicative of clinically relevant QT lengthening (>480 to ≤500 msec, or >500 msec). Six eravacycline-treated subjects (3 in Study TP-434-008 and 2 in Study TP-434-025) and 1 ertapenem-treated subject exhibited prolongation of QTcF of >500 msec at the End-of-therapy visit as well as >60 msec increase from the baseline QTcF interval. None of the eravacycline-treated subjects had associated TEAEs in the Cardiac disorders SOC; however, the ertapenem-treated subject experienced non-serious atrial fibrillation that resolved 10 days prior to the end of therapy.

Table 115: Calculated QTcF in the Phase 3 cIAI Studies - (Safety Population)

QTcF ECG Parameter	Study TP-434-008		Study TP-434-025	
	Eravacycline 1 mg/kg q12h	Ertapenem	Eravacycline 1 mg/kg q12h	Meropenem
QTcF (msec) at End of Therapy				
N1	213	209	205	204
Mean (SD)	406 (53)	402 (38)	410 (43)	406 (48)
Mean Change from Baseline (SD)	+8 (53)	+1 (39)	+7 (42)	+3 (48)
Post-baseline Value at End of Therapy, n/N1 (%)				

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QTcF ECG Parameter	Study TP-434-008		Study TP-434-025	
	Eravacycline 1 mg/kg q12h	Ertapenem	Eravacycline 1 mg/kg q12h	Meropenem
>450 to ≤480 msec	17/213 (8.0)	10/209 (4.8)	15/205 (7.3)	17/204 (8.3)
>480 to ≤500 msec	3/213 (1.4)	1/209 (0.5)	6/205 (2.9)	5/204 (2.5)
>500 msec	3/213 (1.4)	2/209 (1.0)	5/205 (2.4)	4/204 (2.0)
Post-baseline Change at End of Therapy, n/N1 (%)				
>30 to ≤60 msec	24/213 (11.3)	23/209 (11.0)	18/205 (8.8)	21/204 (10.3)
>60 msec	16/213 (7.5)	11/209 (5.3)	17/205 (8.3)	13/204 (6.4)

N1=number of subjects with a baseline and post-baseline value
QTcF = Fridericia's formula for QT interval defined as QT divided by the cubed root of RR.
Source: Clinical Reviewer's Analysis

Reviewers' Comment: *QTcF was calculated by this reviewer using the QT and RR intervals reported in the individual clinical studies.*

9.4.9 QT

The Applicant conducted a Through QTc study (Study TP-434-004) in which 1.5 mg/kg dose of eravacycline was compared to a positive control (moxifloxacin) as well as placebo in 60 healthy adult subjects. This study was evaluated by the Agency's Interdisciplinary Review Team for QT studies and they concluded that at a single dose 1.5-fold of the recommended therapeutic dose, eravacycline did not prolong the QTc interval to any clinically relevant extent.

9.4.10 Immunogenicity

Eravacycline is not a protein or peptide product; thus, studies specifically assessing the impact of immunogenicity have not been conducted.

9.5 Analysis of Submission-Specific Safety Issues

9.5.1 Acute Pancreatitis

Drug-induced pancreatitis was of special interest because it is recognized as a rare adverse event associated with antibiotics in the tetracycline class and is specifically listed in the Warnings & Precautions section of the FDA product label for tigecycline. Pancreatitis has also been reported with use of other broad-spectrum antibiotics, including carbapenems and fluoroquinolones. As mentioned in Section 9.3.2, the MedDRA-specified Acute Pancreatitis algorithm (any narrow term or a combination of 2 broad terms) was used to identify events that might represent episodes of acute pancreatitis.

None of the subjects in the Phase 1 IV Pool experienced TEAEs that met the Acute Pancreatitis SMQ criteria.

Subjects in the Phase 2 study that met the Acute Pancreatitis SMQ criteria are summarized in

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Table 116. The Phase 2 cIAI study had 1 eravacycline-treated subject (1 mg/kg q12h group, 1.8%) and 2 ertapenem-treated subjects (6.7%) experience TEAEs that met the Acute Pancreatitis SMQ criteria. An event term specific for the diagnosis of acute pancreatitis (i.e., any narrow preferred term) was not reported in either treatment group. All were non-serious events that resolved. None of the TEAEs led to premature discontinuation of study treatment.

Table 116: Acute Pancreatitis SMQ – Phase 2 cIAI Study (Safety Population)

MedDRA SMQ Preferred Term	Study TP-434-P2-cIAI-1		
	ERV 1 mg/kg q12h N=56 n (%)	ERV 1.5 mg/kg q24h N=53 n (%)	Ertapenem N=30 n (%)
Acute Pancreatitis SMQ[1]	**1 (1.8)**	**0**	**2 (6.7)**
Any Combination of 2 Broad Terms	**1 (1.8)**	**0**	**2 (6.7)**
Nausea + Lipase increased	1 (1.8)	–	2 (6.7)
Nausea + Amylase increased	–	–	1 (3.3)

[1]MedDRA-specified algorithm required a narrow term or a combination of 2 broad terms.
Source: Adapted from Pooled analysis tables – Integrated safety, Table 1.17.4; Clinical Reviewer's Analysis

Reviewers' Comment: *The case identified in the eravacycline-treated subject was non-specific in nature. Nausea is a known side-effect of tetracycline class antibacterial drugs, including eravacycline.*

Subjects in the Phase 3 cIAI studies that met the Acute Pancreatitis SMQ criteria are summarized in Table 117. The Phase 3 cIAI studies had 5 eravacycline-treated subjects (1.0%) and 1 ertapenem-treated subject (0.4%) experience TEAEs that met the Acute Pancreatitis SMQ. Events specific for the diagnosis of acute pancreatitis were reported in 4 eravacycline-treated subjects (0.8%) and 1 ertapenem-treated subject (0.2%). A single eravacycline-treated subject experienced non-specific events (i.e., combination of broad terms only). Two of the TEAEs in the eravacycline-treated subjects were serious. One case resulted in death and the other case prolonged hospitalization, led to premature discontinuation of study treatment, and resolved. The other TEAEs reported in either treatment group were non-serious, resolved, and did not lead to premature discontinuation of study treatment.

Table 117: Acute Pancreatitis SMQ – Phase 3 cIAI Studies (Safety Population)

Preferred Term	Studies TP-434-008 and TP-434-025		
	Eravacycline 1 mg/kg q12h N=520 n (%)	Ertapenem N=268 n (%)	Meropenem N=249 n (%)
Acute Pancreatitis SMQ[1]	**5 (1.0)**	**1 (0.4)**	**0**
Any Narrow Term	**4 (0.8)**	**1 (0.4)**	**0**
Pancreatitis acute	2 (0.4)	1 (0.4)	–

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Preferred Term	Studies TP-434-008 and TP-434-025		
	Eravacycline 1 mg/kg q12h N=520 n (%)	Ertapenem N=268 n (%)	Meropenem N=249 n (%)
Pancreatitis necrotizing	1 (0.2)	–	–
Pancreatic necrosis	1 (0.2)	–	–
Any Combination of 2 Broad Terms	**1 (0.2)**	**0**	**0**
Lipase increased + Nausea	2 (0.4)	–	–
Lipase increased + Vomiting	1 (0.2)	–	–

[1]MedDRA-specified algorithm required a narrow term or a combination of 2 broad terms
Source: Adapted from Pooled analysis tables – Integrated safety, Table 1.17.4; Clinical Reviewer's Analysis

Reviewers' Comment: *Comparatively more eravacycline-treated subjects experienced events from the Acute Pancreatitis SMQ criteria. All the events in the eravacycline-treated subjects were assessed as unrelated to study drug. The case identified in the eravacycline-treated subject using broad terms only was non-specific in nature. Nausea and vomiting are known side-effects of tetracycline class antibiotics, including eravacycline.*

The Phase 3 cUTI study with the IV-to-PO transition regimen (TP-434-010) had 1 eravacycline-treated subject (0.2%) and zero comparator-treated subjects experience a TEAE that met the Acute Pancreatitis SMQ criteria. This subject experienced the SAE of pancreatitis acute, which prolonged the hospitalization. The event resolved and did not lead to premature discontinuation of study treatment.

Detailed subject listing for all the reported cases within Acute Pancreatitis SMQ are presented in Table 118.

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Table 118: Subject Listing of Acute Pancreatitis Standardized MedDRA Query

Study/ Subject ID	Age/ Sex	Diagnosis	Study Drug	Last Dose Study Day	AE Preferred Term	AE Onset Study Day	AE Duration (Days)	Severity	Serious	Study Drug Action Taken	AE Outcome
Eravacycline											
TP-434-P2-cIAI-1 (b) (6)	64/M	Gastric/ duodenal perforation; Peritonitis	Eravacycline 1 mg/kg q12h IV	7	Nausea	1	2	Mild	No	No change	Resolved
					Lipase increased	4	14	Moderate			
TP-434-008 (b) (6)	59/F	Complicated cholecystitis; Intra-abdominal abscess; Peritonitis	Eravacycline 1 mg/kg q12h IV	8	Pancreatitis necrotizing	21	Ongoing	Severe	**Yes**	N/A	**Death**
TP-434-008 (b) (6)	76/F	Gastric/ duodenal perforation; Intra-abdominal abscess	Eravacycline 1 mg/kg q12h IV	15	Pancreatic necrosis	4	12	Mild	No	No change	Resolved
TP-434-025 (b) (6)	59/M	Intra-abdominal abscess	Eravacycline 1 mg/kg q12h IV	3	Pancreatitis acute	3	38	Mild	**Yes**	Drug withdrawn	Resolved
TP-434-025 (b) (6)	32/M	Intra-abdominal abscess	Eravacycline 1 mg/kg q12h IV	8	Pancreatitis acute	9	6	Moderate	No	N/A	Resolved
TP-434-025 (b) (6)	31/M	Complicated appendicitis; Intra-abdominal abscess	Eravacycline 1 mg/kg q12h IV	15	Nausea	15	1	Mild	No	N/A	Resolved
					Vomiting	15	1	Mild			
					Lipase increased	15	4	Severe			
TP-434-010 (b) (6)	41/F	cUTI	Eravacycline 1.5 mg/kg q24h IV + 200 mg q12h PO	7 (4, IV)	Pancreatitis acute	7	4	Moderate	**Yes**	N/A	Resolved

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Study/ Subject ID	Age/ Sex	Diagnosis	Study Drug	Last Dose Study Day	AE Preferred Term	AE Onset Study Day	AE Duration (Days)	Severity	Serious	Study Drug Action Taken	AE Outcome
Comparator											
TP-434-P2-cIAI-1 (b) (6)	48/M	Gastric/ duodenal perforation; Peritonitis	Ertapenem	6	Nausea	2	1	Mild	No	No change	Resolved
					Lipase increased	3	15	Mild			
TP-434-P2-cIAI-1 (b) (6)	33/M	Perforation of intestine	Ertapenem	7	Nausea	1	3	Mild	No	No change	Resolved
					Amylase increased	4	16	Mild			
					Lipase increased	4	16	Mild			
TP-434-008 (b) (6)	50/M	Intra-abdominal abscess	Ertapenem	8	Pancreatitis acute	41	5	Severe	No	N/A	Resolved

Abbreviations: AE=adverse event; F=female; M=male
Source: Adapted from Integrated Analysis of Safety – Table 34

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Reviewers' Comment: *For the 6 eravacycline-treated subjects meeting the Acute Pancreatitis SMQ criteria in the Phase 2 and Phase 3 cIAI studies, alternative causes of pancreatitis were likely or the events were non-specific in nature. Two subjects (Subjects* (b) (6) *and* (b) (6) *) had elevations of lipase and amylase at baseline that improved significantly during eravacycline treatment, a third subject (Subject* (b) (6) *) had mild treatment-emergent elevations that returned to normal while still receiving the drug, and a fourth subject (Subject* (b) (6) *) was diagnosed only by elevated peritoneal fluid amylase, had normal or nearly normal serum amylase and lipase throughout the study, and may have had pancreatic injury at baseline. The remaining 2 subjects (Subjects* (b) (6) *and* (b) (6) *had elevations of pancreatic enzymes associated with nausea and/or vomiting. Nausea and vomiting are non-specific for pancreatitis and are known side-effects of tetracycline class antibiotics, including eravacycline. In both cases the nausea and/or vomiting last no more than 1 or 2 days and the laboratory abnormalities resolved.*

For the 1 eravacycline-treated subject that met the Acute Pancreatitis SMQ criteria in the Phase 3 cUTI study (Subject (b) (6) *), an alternative cause of pancreatitis was not apparent. In this case, the symptoms and laboratory abnormalities developed near the end of the planned treatment course and resolved.*

Narrative summaries for the 3 SAEs that met the Acute Pancreatitis SMQ criteria and occurred in the eravacycline-treated subjects are presented below:

- Subject (b) (6): This was a 59-year-old female with complicated cholecystitis, peritonitis, and an intra-abdominal abscess who received a 7-day course of ERV 1 mg/kg q12h. Peak lipase and amylase values were observed at the screening visit (see Table 119). Thirteen days after study drug therapy was completed, the subject was hospitalized with acute symptoms consistent with necrotizing pancreatitis and peritonitis. She underwent urgent laparotomy with debridement, necrectomy, lavage, and drainage. Aspiration and tissue cultures were positive for *Klebsiella pneumoniae*, and the postoperative diagnosis included recurrent acute necrotizing pancreatitis with hemorrhagic purulent peritonitis. Other treatments included cefoperazone + sulbactam (Day 21 – 32), metronidazole (Day 22 – 33), meropenem (Day 32 – 42), and vancomycin (Day 32 – 42). The necrotizing pancreatitis and peritonitis events were assessed as serious and were ongoing at the final study visit (Day 39).

  The SAE of necrotizing pancreatitis had a fatal outcome occur 11 days after the final study visit. Three days prior to death, she underwent a third laparotomy and required pharmacologic intervention for tachycardia and hypotension. Re-laparotomy findings revealed necrosis of the pancreas head, and a total necrosectomy was performed. Other treatments included imipenem/cilastatin (Day 47 – 50) and blood products. Urine and blood cultures were positive for *K. pneumoniae*, *Staphylococcus aureus*, and *Acinetobacter baumannii* (later revealed to be susceptible to only tobramycin). Despite resuscitation, she progressively deteriorated with tachycardia, hypotension, progressive

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anemia, leukopenia, and thrombocytopenia. On the third postoperative day, she developed hemodynamic failure and died. The investigator considered the event to be unrelated to study drug, and more likely related to an exacerbation of pancreatitis which was present at screening. Based on the baseline elevations of lipase and amylase which improved during study treatment, the investigator considered it more likely the subject had acute pancreatitis of another cause prior to starting ERV treatment.

Table 119: Subject (b) (6) Lipase and Amylase

Study Day (Visit)	Lipase (U/L)	Amylase (U/L)
Day 1 (Baseline)	624	636
Day 3	48	415
Day 4	13	159
Day 5	11	116
Day 8 (End-of-therapy)	21	111
Day 32 (Test-of-cure)	40	57
Day 39 (Follow-up)	32	62

Reference range: Lipase 7-60 U/L; Amylase 28 – 100 U/L
Source: TP-434-008 CSR Listing 16.2.8.1.1

Reviewers' Comment: *This reviewer agrees with the investigator's assessment that the necrotizing pancreatitis was not related to study drug. Consistent symptoms and laboratory abnormalities were present at screening.*

- Subject (b) (6): This was a 59-year old male with complicated appendicitis and intra-abdominal abscess (ileocecal abscess) who received a 2.5-day course of ERV 1 mg/kg q12h. Study treatment terminated prematurely on Day 3 due to the SAE of acute pancreatitis. It was reported, to the Investigator's understanding, the ileocecal abscess at presentation could have been the result of acute pancreatitis rather than appendicitis as initially diagnosed. Acute pancreatitis was only identified when amylase level from the abdominal drain discharge was noted to be 2102 U/L (reference range, 25-125 U/L). His serum amylase and lipase values were within normal limits at study entry and remained so during study treatment (see Table 120). The subject did not exhibit symptoms consistent with acute pancreatitis (i.e., nausea, vomiting, and abdominal pain) and had no evidence of ileus or ascites. He was treated with gentamycin, metronidazole, and ceftriaxone from Day 3 to Day 13. On Day 13, he was diagnosed with *Clostridium difficile* diarrhea and treated with metronidazole for 14 days. The SAE of acute pancreatitis was considered resolved on Day 40. The investigator considered the event to be unrelated to study drug.

Table 120: Subject (b) (6) Lipase and Amylase

Study Day	Lipase (U/L)	Amylase (U/L)
Day 1 (Baseline)	47	73
Day 2	47	76

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Study Day	Lipase (U/L)	Amylase (U/L)
Day 3	33	59
Day 4 (End-of-therapy)	33	52
Day 26 (Test-of-cure)	68	111
Day 40 (Follow-up)	55	48

Reference range: Lipase 6-51 U/L; Amylase 28 – 100 U/L
Source: TP-434-025 CSR Listing 16.2.8.3D

Reviewers' Comment: *This reviewer agrees with the investigator's assessment that the acute pancreatitis event was not related to study drug. The subject did not exhibit both symptoms and laboratory abnormalities consistent with acute pancreatitis.*

- Subject (b) (6): This was a 41-year-old female with cUTI with partial obstructive uropathy. Baseline lipase and amylase values were within normal limits. She received ERV 1.5 mg/kg q24h IV for 4 days, then 200 mg q12h from Day 4 to Day 7. Baseline lipase was 13 U/L (reference range, 7 - 60 U/L) and amylase was 41 U/L (reference range, 28 - 100 U/L). On Day 4, she experienced epigastric pain with complaints of nausea and abdominal cramps that radiated to the back. Treatment with pantoprazole was initiated and she continued the study treatment. She was diagnosed with acute pancreatitis 3 days later when laboratory findings revealed an elevated lipase of 775 U/L and elevated amylase level of 700 U/L. No action was taken with study drug because the planned course of treatment was completed on the day of event onset. Subsequent laboratory findings on Day 8 revealed a lipase of 387 U/L and amylase was 420 U/L. On Day 9, she no longer had any symptoms or complaints and her diet was advanced. A computed tomography scan showed a normal pancreatic size and structure with no pathological accumulation of contrast material. Laboratory findings included lipase of 111 U/L and amylase of 156 U/L. On Day 10, she was discharged from the hospital and the event was considered resolved. Her amylase and lipase normalized at the post-treatment visit on Day 15. This event was assessed as serious because it prolonged the hospitalization. The investigator also considered the event unrelated to study drug.

  Reviewers' Comment: *The symptoms and laboratory abnormalities in this subject were consistent with acute pancreatitis. Although the event was assessed by the investigator as unrelated to study drug, an alternative cause of pancreatitis was not provided.*

Narratives summaries for the non-serious, narrow term TEAEs in the eravacycline treated subjects are summarized below:

- Subject (b) (6): This was a 76-year old female with gastric/duodenal perforation and intra-abdominal abscess who received a 14-day course of ERV 1 mg/kg q12h. Her relevant medical history included hypertension, cerebrovascular disorder, and osteoporosis. Relevant prior medications included omeprazole as prophylaxis for gastro-esophageal reflux disease and transdermal demiparin as prophylaxis for thrombotic events. Baseline lipase and amylase values were within normal limits. On Day 4,

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postoperative pancreatic necrosis was diagnosed. The event was assessed by the investigator as non-serious and no changes were made to study treatment. Her lipase and amylase values initially increased while on study treatment, but resolved before study treatment was completed (see Table 121). The event of pancreatic necrosis resolved at the end of therapy visit on Day 15. The investigator considered the event unrelated to study drug.

Table 121: Subject (b) (6) Lipase and Amylase

Study Day	Lipase (U/L)	Amylase (U/L)
Day 1 (Baseline)	56	53
Day 3	62	58
Day 4	80 and 85	74 and 88
Day 8	106	105
Day 11	85	97
Day 14	52	81
Day 15 (End-of-therapy)	54	74
Day 29 (Test-of-cure)	49	72
Day 44 (Follow-up)	29	63

Reference range: Lipase 7-60 U/L; Amylase 28 – 100 U/L
Source: TP-434-008 CSR Listing 16.2.8.1.1

Reviewers' Comment: *This reviewer agrees with the investigator's assessment that the acute pancreatitis event was not related to study drug. The subject did not exhibit both symptoms and laboratory abnormalities consistent with acute pancreatitis.*

- Subject (b) (6): This was a 32-year old male with intra-abdominal abscess who received a 7-day course of ERV 1 mg/kg q12h. He was diagnosed with acute pancreatitis on Day 4. The event was assessed by the investigator as non-serious and no changes were made to study treatment. Serial lipase and amylase values are presented in Table 122. Peak lipase and amylase values were observed at the screening visit, and subsequent values decreased thereafter. Similarly, his abdominal pain, tenderness, and fever were at their worst at the initial screening visit and improved steadily thereafter. This event resolved on Day 9. The investigator considered the event unrelated to study drug.

Table 122: Subject (b) (6) Lipase and Amylase

Study Day	Lipase (U/L)	Amylase (U/L)
Day 1 (Baseline)	1515	875
Day 3	412	300
Day 4	312	208
Day 5	136	65
Day 8	217	148
Day 9 (End-of-therapy)	Not done	Not done

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Study Day	Lipase (U/L)	Amylase (U/L)
Day 25 (Test-of-cure)	21	28
Day 46 (Follow-up)	35	14

Reference range: Lipase 6-51 U/L; Amylase 28 – 100 U/L
Source: TP-434-025 CSR Listing 16.2.8.3D

Reviewers' Comment: *This reviewer agrees with the investigator's assessment that the acute pancreatitis event was not related to study drug. Consistent symptoms and laboratory abnormalities were present at screening.*

In summary, a clear associated between eravacycline treatment and clinically apparent pancreatitis was not identified. Although there were more events meeting the acute pancreatitis SMQ criteria among eravacycline-treated subjects than among comparator-treated subjects, all but 1 subject (cUTI subject (b) (6)) had alternative causes of pancreatitis present or the events were non-specific in nature.

9.5.2 Acute Renal Failure

Acute renal failure was of special interest because it has been reported with other classes of broad-spectrum antibiotics such as aminoglycosides and vancomycin. As mentioned in Section 9.3.2, the MedDRA-specified Acute Renal Failure SMQ was used to identify events that might represent episodes of acute renal failure.

There were no events meeting the Acute Renal Failure SMQ criteria in the Phase 1 IV Pool, Phase 2 cIAI study, or among the eravacycline-treated subjects in the Phase 3 cIAI studies. Three comparator-treated subjects (0.6%) in the Phase 3 cIAI studies experienced events that met the Acute Renal Failure SMQ criteria. These events included renal failure (n=1, ertapenem group; n=1, meropenem group) and oliguria (n=1, ertapenem group).

Reviewers' Comment: *In Study TP-434-025, this reviewer identified 2 additional subjects with adverse events related to acute renal failure (both in the eravacycline group). These eravacycline-treated subjects (Subject (b) (6) and Subject (b) (6)) had non-serious creatinine renal clearance decreased. The event in Subject (b) (6) was likely misclassified because their creatinine clearance was >90 mL/min throughout the study (at baseline and on Days 2, 3, 4, 7, 8, 29, and 45). In contrast, Subject (b) (6) was noted to have an abnormal creatinine clearance that worsened after starting study drug. The subject's creatinine clearance according to the Cockcroft-Gault equation was 51 mL/min at baseline, 33 mL/min on Day 2, and 23 mL/min on Days 3 and 4. The same subject also experienced the SAE of respiratory failure on Day 3 which resulted in discontinuation of study drug and death (on Days 4 and 16, respectively). Please see Section 9.4.1 for additional information with respect to the fatal SAE in Subject (b) (6). The event of creatinine renal clearance decreased in this subject was ongoing at the time of death and considered unrelated to study drug by the investigator. This explanation is reasonable given the subject's pre-existing conditions of cachexia and malnutrition as well as decreased creatinine clearance at baseline.*

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The Phase 3 cUTI study that evaluated an IV-to-PO regimen had 1 eravacycline-treated subject (0.2%) and 1 levofloxacin-treated subject (0.2%) experience TEAEs within the Acute Renal Failure SMQ. A brief narrative of the TEAE in the eravacycline-treated subject is presented below:

- Subject (b) (6): This was a 65-year old male with cUTI and associated with urinary retention and indwelling urinary catheter. At screening, he had an elevated serum creatinine of 131 µmol/L (reference range, 62 to 106 µmol/L) and a creatinine clearance of 57 mL/min. He received ERV 1.5 mg/kg q24h for 7 days and did not receive oral study drug. On Day 3, the subject experienced the non-serious adverse event of renal impairment. That day his serum creatinine increased to 187 µmol/L and his creatinine clearance decreased to 40 mL/min. He had no related symptoms and no action was taken with study drug. The event was reported as resolved on Day 8. On that day, his serum creatinine and creatinine clearance values returned to baseline (130 µmol/L and 57 mL/min, respectively). Both laboratory findings were normal by Day 15. Although the investigator considered the event as possibly related to study drug, the Applicant considered it unlikely that eravacycline contributed to the impaired renal function based upon the time course of the changes in CrCl. According to the Applicant, it is more likely that the underlying infection was the primary cause.

  Reviewers' Comment: *This reviewer considered the Applicant's alternative explanation for the event of elevated serum creatinine in Subject (b) (6) to be reasonable given the elevated serum creatinine and low normal creatinine clearance at baseline.*

  In Study TP-434-010, this reviewer identified 3 additional subjects with adverse events related to acute renal failure (1 in the eravacycline group and 2 in the levofloxacin group). The eravacycline-treated subject (Subject (b) (6) had non-serious creatinine renal clearance decreased and the 2 levofloxacin-treated subjects had non-serious blood creatinine increased. Subject (b) (6) was noted to have an abnormal creatinine clearance that transiently worsened the same day study treatment was completed (Day 7). The subject's creatinine clearance according to the Cockcroft-Gault equation was 38 mL/min at baseline, 37 mL/min on Day 3, 33 mL/min on Day 7, 55 mL/min on Day 13, and 68 mL/min on Day 25. Although the event was considered possibly related to study drug by the investigator, the decline was transient and resolved by study completion. In addition, the subject already had decreased creatinine at baseline that could have been associated with the underlying infection.

In summary, the risk of acute renal failure due to treatment with eravacycline appears to be low, and comparable to the compartor groups (i.e., ertapenem, meropenem, and levofloxacin).

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9.5.3 Hypersensitivity

Hypersensitivity was of special interest because it has been reported in patients treated with tetracycline class antibiotics as well as other broad-spectrum antibiotics. As mentioned in Section 9.3.2, the MedDRA-specified Hypersensitivity SMQ was used to identify events that might represent episodes of Hypersensitivity.

There were no events meeting the Hypersensitivity SMQ criteria in the Phase 1 Single Dose IV Pool. Three subjects (4.4%) in the Phase 1 Multiple Dose IV Pool had TEAEs that met the Hypersensitivity SMQ criteria. The events, all from Study TP-434-016, included rash (n=2) and rash maculo-papular (n=1). All the TEAEs were non-serious, did not lead to study drug discontinuation, and resolved within 2 weeks.

The Phase 2 cIAI study had 1 eravacycline-treated subject (1.5 mg/kg dose group, 1.9%) and 2 ertapenem-treated subjects (6.7%) experience TEAEs that met the Hypersensitivity SMQ criteria. The eravacycline-treated subject experienced contact dermatitis on Day 3 and no changes were made to the study drug treatment. The event was non-serious and was recovering/resolving by the final study visit (Day 38). The hypersensitivity events in the 2 ertapenem-treated subjects (application site hypersensitivity; hypersensitivity) were non-serious and resulted in study drug discontinuation.

Subjects in the Phase 3 cIAI studies that met the Hypersensitivity SMQ criteria are summarized in Table 123. There were 6 eravacycline-treated subjects (1.2%), 2 ertapenem-treated subject (0.7%), and 1 meropenem-treated subject (0.4%) experience TEAEs that met the Hypersensitivity SMQ. All the TEAEs in Hypersensitivity SMQ were non-serious. One event of hypersensitivity in the eravacycline group and one event of infusion site urticaria in the meropenem group resulted in discontinuation of study drug. The eravacycline-treated subject (Subject (b) (6)) experienced non-serious hypersensitivity (allergic reaction) and non-serious nausea on Day 2. The investigator assessed both the allergic reaction and nausea to be related to study drug. Both events resolved the following day. Most of the other eravacycline-treated subjects identified in the Hypersensitivity SMQ had transient events that resolved within 1 or 2 days.

Table 123: Hypersensitivity SMQ - Phase 3 cIAI studies (Safety Population)

Preferred Term	Studies TP-434-008 and TP-434-025		
	Eravacycline 1 mg/kg q12h N=520 n (%)	Ertapenem N=268 n (%)	Meropenem N=249 n (%)
Hypersensitivity SMQ[1]	**6 (1.2)**	**2 (0.7)**	**1 (0.4)**
Rash	3 (0.6)	1 (0.4)	–
Hypersensitivity	2 (0.4)	–	–
Scrotal edema	1 (0.2)	–	–

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Preferred Term	Studies TP-434-008 and TP-434-025		
	Eravacycline 1 mg/kg q12h N=520 n (%)	Ertapenem N=268 n (%)	Meropenem N=249 n (%)
Rash erythematous	–	1 (0.4)	–
Infusion site urticaria	–	–	1 (0.4)

Source: Adapted from Pooled analysis tables – Integrated safety, Table 1.17.4; Clinical Reviewer's Analysis

The Phase 3 cUTI study that evaluated an IV-to-PO regimen had 2 eravacycline-treated subjects (0.4%) and 3 levofloxacin-treated subjects (0.6%) experience TEAEs that met the Hypersensitivity SMQ criteria. The TEAEs in the eravacycline group included 1 case of rash (0.2%) and 1 case of allergic dermatitis (0.2%], while the TEAEs in the levofloxacin-group included 1 case each of hypersensitivity (0.2%), toxic skin eruption (0.2%), and urticaria (0.2%). All the TEAEs in Hypersensitivity SMQ were non-serious and resolved within 4 days.
One event (rash) in the eravacycline group and two events (hypersensitivity and toxic skin eruption) in the levofloxacin group resulted in discontinuation of study drug.

In summary, the risk of hypersensitivity reactions due to treatment with eravacycline appears to be low, and comparable to other broad-spectrum antibiotics.

9.5.4 Anaphylactic reaction

Anaphylactic reactions were of special interest because it has been reported in patients treated with tetracycline class antibiotics as well as other broad-spectrum antibiotics. As mentioned in Section 9.3.2, the MedDRA-specified Anaphylactic Reaction SMQ was used to identify events that might represent episodes of Hypersensitivity. In addition, all subjects treated with eravacycline who were identified by the Hypersensitivity SMQ were also evaluated for the possibility of anaphylaxis. Available data was reviewed that documented involvement of the skin and mucosal tissue, potential respiratory compromise, reduction of systolic blood pressure (<90 mmHg or a >30% reduction from baseline), and/or presence of persistent gastrointestinal symptoms.

None of the subjects in the Phase 1 IV Pool, the Phase 2 cIAI study, the Phase 3 cIAI studies, or the Phase 3 cUTI study that evaluated an IV-to-PO regimen experienced TEAEs that met the Anaphylactic Reaction SMQ criteria. None of the cases identified using the Hypersensitivity SMQ exhibited signs and/or symptoms that fulfilled criteria for anaphylaxis.

The second Phase 3 cUTI study (Study TP-434-021) had at least 1 eravacycline-treated subject experience a SAE that may have fulfilled criteria for anaphylactic reaction. A brief narrative of the event is summarized below:

- Subject (b) (6): This was a 34-year old male with cUTI with indwelling urinary catheter and partial obstructive uropathy. His relevant medical history included

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hypertension, and COPD. At screening, his blood pressure was 145/100 mm Hg, heart rate was 89 beats per minute (bpm), and respiratory rate was 15/minute (min). He received his first and only dose of IV eravacycline (1.5 mg/kg) on Day 1 and that same day experienced an allergic reaction (systemic reaction to the study drug), which was life-threatening. The subject became nervous and reported a heating sensation on his torso and neck within 10 minutes of his first infusion of study drug. Five minutes later, he also developed difficulty breathing and a pressure sensation in his chest. He was relatively hypotensive with blood pressure of 105/70 mm Hg, heart rate 98 bpm, and respiratory rate 27/min. His oxygen saturation was reduced to 85%. Study drug infusion was interrupted and the subject received supplemental oxygen, methylprednisolone, chloropyramine, aminophylline, and a bolus of glucose. The subject gradually stabilized and normal breathing, pulse, and blood pressure were restored. No urticaria, pruritus, flushing, tongue or throat swelling, or any gastrointestinal symptoms were reported during the event. Treatment was permanently discontinued due to the SAE. The Sponsor assessed the event as related to study drug.

Reviewers' Comment: *The 120-day safety update report included subject narratives for the SAEs reported during Study TP-434-021. Final datasets were not available for review of other potential subjects with hypersensitivity reactions, anaphylactic reactions, or other adverse events of special interest.*

9.5.5 Hepatic Disorders

Drug-induced liver injury (DILI) was of special interest because it has been reported by subjects treated with other classes of broad spectrum antibiotics. Evaluation of hepatic function in the setting of eravacycline treatment included the review of TEAEs terms meeting the treatment-related Hepatic Disorders SMQ. In addition, subjects who fulfilled Hy's Law laboratory criteria for potential drug-induced liver injury were also reviewed.

None of the subjects in the Phase 1 IV Pool experienced TEAEs that met the Hepatic Disorders SMQ criteria. However, in Study TP-434-013 (a single-dose PK study of eravacycline conducted in healthy subjects and subjects with hepatic impairment), 1 subject with severe hepatic impairment experienced a SAE that met the Hepatic Disorder SMQ criteria. A brief narrative for the event is summarized below:

- Subject (b) (6): This was a 55-year old male who enrolled in Study TP-434-013 with severe hepatic impairment. Relevant medical included hepatic encephalopathy, cirrhosis, esophageal varices, cholethiasis, hypertension, asthma, and diabetes mellitus type 2. Single dose IV eravacycline (1.5 mg/kg) was administered on Day 1 and 12 days later he experienced the SAE of hepatic encephalopathy (worsening hepatic encephalopathy), which required hospitalization. He was admitted to the intensive care unit with altered mental status and an elevated ammonia level. The subject's ammonia level eventually decreased with pharmacologic treatment, and his mental status

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improved. The event lasted 6 days, and was considered resolved on the day of hospital discharge (Day 18). The investigator considered the event unrelated to study drug. According to the investigator, the SAE was related to the pre-existing condition of worsening of hepatic encephalopathy secondary to hyperammonemia.

Reviewers' Comment: *This reviewer agrees with the investigator's assessment that the non-fatal SAE experienced in this subject was not related to study drug.*

The subjects who met the Hepatic Disorders SMQ criteria in the Phase 2 cIAI study are summarized in Table 124. None of the events were reported as serious or resulted in discontinuation of study drug.

Table 124: Hepatic Disorders SMQ - Phase 2 cIAI Study (Safety Population)

System Organ Class Preferred Term	Study TP-434-P2-cIAI-1		
	Eravacycline 1 mg/kg q12h N=56 n (%)	Eravacycline 1.5 mg/kg q24h N=53 n (%)	Ertapenem N=30 n (%)
Hepatic Disorders SMQ	**1 (1.8)**	**2 (3.8)**	**1 (3.3)**
Prothrombin time prolonged	1 (1.8)	1 (1.9)	1 (3.3)
Hypoalbuminemia	–	1 (1.9)	–

Source: Adapted from Pooled analysis tables – Integrated safety, Table 1.17.4; Clinical Reviewer's Analysis

The subjects who met the Hepatic Disorders SMQ criteria in the Phase 3 cIAI studies are summarized in Table 125. None of the events were reported as serious or resulted in discontinuation of study drug.

Table 125: Hepatic Disorder SMQ - Phase 3 cIAI Studies (Safety Population)

Preferred Term	Studies TP-434-008 and TP-434-025		
	Eravacycline 1 mg/kg q12h N=520 n (%)	Ertapenem N=268 n (%)	Meropenem N=249 n (%)
Hepatic Disorders SMQ	**9 (1.7)**	**3 (1.1)**	**5 (2.0)**
ALT increased	3 (0.6)	–	1 (0.4)
AST increased	2 (0.4)	2 (0.7)	–
GGT increased	2 (0.4)	–	1 (0.4)
Hypoalbuminemia	1 (0.2)	–	1 (0.4)
Hypercoagulable state	1 (0.2)	–	–
Hepatic enzyme increased	1 (0.2)	1 (0.4)	–
Transaminases increased	–	–	1 (0.4)
Blood fibrinogen decreased	–	–	1 (0.4)

Source: Adapted from Pooled analysis tables – Integrated safety, Table 1.17.4; Clinical Reviewer's Analysis

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The Phase 3 cUTI study that evaluated an IV-to-PO regimen had 3 eravacycline-treated subjects (0.5%) and 5 levofloxacin-treated subjects (1.0%) experience TEAEs that met the Hepatic Disorders SMQ criteria. The TEAEs in the eravacycline group included 1 case of drug-induced liver injury (0.2%), 1 case of blood bilirubin unconjugated increased (0.2%), and 1 case of transaminases increased (0.2%). All of the TEAEs in Hepatic Disorders SMQ were non-serious and did not lead to discontinuation of study drug. A brief narrative for the event of drug induced liver injury is presented below:

- Subject (b) (6): This was a 41-year old male with cUTI. Relevant medical history included sarcoidosis and chronic pyelonephritis. He also reported use of an NSAID (nimesulide) prior to enrollment. The NSAID was taken for 3 days and last administered 2 days prior to starting study treatment. At screening (1 day prior to starting study drug), the subject had elevated ALT of 132 U/L (reference range, 0 to 45 U/L) and elevated AST of 104 U/L (reference range, 0-41). The non-serious adverse event of drug-induced liver injury was reported on Day 1 based on the laboratory abnormalities at screening. He received ERV 1.5 mg/kg q24h for 7 days and his ALT and AST levels consistently improved after starting the study drug. No concomitant elevations in total bilirubin or alkaline phosphatase were observed at any time point. By the final study visit (Day 21), ALT was 67 U/L and AST was normal. The investigator considered the event unrelated to study drug and probably due to NSAID use.

  Reviewers' Comment: *This reviewer agrees with the investigator's assessment that the drug-induced liver injury was not related to study drug. The abnormal liver function results associated with the event were already present at screening.*

Subjects meeting Hy's Law Laboratory Criteria

Four eravacycline-treated subjects and 2 comparator-treated subjects satisfied Hy's Law laboratory criteria for potential drug-induced liver injury: ALT or AST ≥3×ULN, alkaline phosphatase ≤2×ULN, and total bilirubin ≥2×ULN. Three of the eravacycline-treated subjects were from the Phase 3 cIAI studies and the fourth was from the Phase 3 cUTI study that utilized a IV-to-PO regimen. The two comparator-treated subjects were from the Phase 3 cIAI studies (1 treated with ertapenem and 1 treated with meropenem).

None of the potential cases identified by Hy's Law laboratory criteria were likely to represent true cases of drug-induced liver injury caused by eravacycline. Of the 4 eravacycline-treated subjects who met Hy's Law laboratory criteria, 1 subject had asymptomatic elevations of AST and total bilirubin that may have been attributed to concomitant medications and resolved following planned completion of study drug. The remaining subjects had time courses of liver function abnormalities that were not suggestive of drug induced liver injury and/or likely alternative causes for the abnormalities were present. Brief narratives for the eravacycline-treated subjects are presented below:

- (b) (6): This was a 68-year-old female who enrolled in Study TP-434-008 with peritonitis. He received ERV 1 mg/kg q12h from Day 1 to Day 8. Her course was notable for a pleural effusion on Day 1 (resolved on Day 8) requiring placement of a

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drain, as well as anemia on Day 1 and leukopenia on Day 12 (both ongoing at the time of study completion). The investigator considered these TEAEs unrelated to study drug.

As shown in Table 126, her baseline AST and alkaline phosphatase were mildly elevated at baseline. On Day 7, she had increases in AST and total bilirubin which met Hy's Law criteria. By Day 30, her liver functions tests had normalized. No action was taken with study drug treatment as it had been completed per protocol on Day 8. No TEAEs suggestive of hepatic injury were reported in this subject. Concomitant medications administered during study participation included omeprazole and tramadol, both of which have been implicated in drug induced hepatic injury.

Table 126: Subject (b) (6) Liver Tests

Study Day	ALT (U/L) (×ULN)	AST (U/L) (×ULN)	ALP (U/L) (×ULN)	Total Bilirubin (µmol/L) (×ULN)	Met Hy's Law Criteria
Day 1 (Baseline)	12 (0.3)	62 (1.5)	148 (1.4)	22 (1.0)	N
Day 3	10 (0.2)	49 (1.2)	120 (1.2)	25 (1.2)	N
Day 4	11 (0.2)	55 (1.3)	135 (1.3)	24 (1.1)	N
Day 5	10 (0.2)	51 (1.2)	125 (1.2)	21 (1.0)	N
Day 7	**20 (0.4)**	**148 (3.6)**	**165 (1.6)**	**57 (2.7)**	**Y**
Day 8 (End-of-therapy)	**24 (0.5)**	**150 (3.7)**	**165 (1.6)**	**57 (2.7)**	**Y**
Day 30 (Test-of-cure)	17 (0.4)	33 (0.8)	42 (0.4)	9 (0.4)	N
Day 42 (Follow-up)	21 (0.5)	20 (0.5)	73 (0.7)	6 (0.3)	N

Note: Hy's law laboratory criteria is defined as Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) ≥3 × ULN, Alkaline phosphatase (ALP) ≤2 × ULN and Total Bilirubin ≥2 × ULN
Reference range: ALT: 0 - 45 U/L; AST: 0 - 41 U/L; ALP: 35 - 104 U/L; Total Bilirubin: 2 - 21 µmol/L
Source: Pooled analysis tables – Integrated safety, Table 1.27.6

Reviewers' Comment: *The investigator's assessment that the liver function abnormalities may have been attributable to concomitant medications is reasonable.*

- Subject (b) (6) This was a 54-year-old female who enrolled in Study TP-434-025 with gastric/duodenal perforation and peritonitis. She received ERV 1 mg/kg q12h from Day 1 to Day 7. Study drug was discontinued on Day 7 when the subject was considered a treatment failure and linezolid, moxifloxacin, and ornidazole were started. Her course was notable for TEAEs of toxic encephalopathy starting on Day 4 and COPD exacerbation starting on Day 6, which resulted in respiratory insufficiency, and death on Day 7. She was also diagnosed with sepsis on Day 7 which was ongoing at the time of death.

  As shown in Table 127, her baseline liver function tests were notable for a transaminitis and on Day 7 she had concomitant elevations in AST and total bilirubin that fulfilled Hy's Law laboratory criteria of drug-induced liver injury. Given the baseline transaminitis and the timecourse of worsening AST and total bilirubin relative to the adverse events, the

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investigator considered the liver function abnormalities to be related to the worsening underlying infection rather than to drug-induced liver injury. The subject was also receiving a proton-pump inhibitor (pantoprazole) which has been rarely associated with liver injury. According to the investigator, the toxic encephalopathy adverse event was unlikely hepatic in origin because the adverse event preceded the more significant elevations of AST and total bilirubin.

Table 127: Subject (b) (6) Liver Tests

Study Day	ALT (U/L) (×ULN)	AST (U/L) (×ULN)	ALP (U/L) (×ULN)	Total Bilirubin (µmol/L) (×ULN)	Met Hy's Law Criteria
Day 1 (Baseline)	51 (1.5)	82 (2.4)	49 (0.5)	11.7 (0.6)	N
Day 3	46 (1.4)	83 (2.4)	65 (0.7)	12.8 (0.6)	N
Day 4	44 (1.3)	96 (2.8)	66 (0.7)	17.2 (0.8)	N
Day 5	35 (1.1)	76 (2.2)	63 (0.6)	19.2 (0.9)	N
Day 7 (End-of-therapy)	**46 (1.4)**	**130 (3.8)**	**85 (0.9)**	**42.6 (2.1)**	**Y**

Note: Hy's law laboratory criteria is defined as Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) ≥3 × ULN, Alkaline phosphatase (ALP) ≤2 × ULN and Total Bilirubin ≥2 × ULN
Reference range: ALT: 0 - 33 U/L; AST: 14 - 34 U/L; ALP: 42 - 98 U/L; Total Bilirubin: 5.1 - 20.5 µmol/L
Source: Pooled analysis tables – Integrated safety, Table 1.27.6

Reviewers' Comment: *The investigator's assessment that the liver function abnormalities may have been attributable to the underlying infection and/or concomitant medications is reasonable.*

- Subject (b) (6): This was a 25-year-old male who enrolled in Study TP-434-025 with complicated appendicitis with intra-abdominal abscesses. He received ERV 1 mg/kg q12h from Day 1 to Day 5. His course was notable for non-serious adverse events of cold and earache. No adverse events suggestive of hepatic injury were reported in this subject

  As shown in Table 128, her baseline liver function tests were notable for a transaminitis and increased total bilirubin that fulfilled Hy's Law laboratory criteria. Transaminitis initially worsened during study treatment and peaked on Day 2. All three abnormalities improved by Day 5 and normalized by Day 31. Given the baseline transaminitis and the timecourse of worsening AST and total bilirubin relative to the adverse events, the investigator considered the liver function abnormalities unlikely due to drug-induced liver injury. Although the subject did receive pantoprazole, diclofenac, piroxicam, sevoflurane, tramadol, and metoclopramide which have been rarely associated with liver injury, the timing of the first doses of these medication also make them unlikely causes of the liver function test abnormalities.

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Table 128: Subject (b) (6) Liver Tests

Study Day	ALT (U/L) (×ULN)	AST (U/L) (×ULN)	ALP (U/L) (×ULN)	Total Bilirubin (µmol/L) (×ULN)	Met Hy's Law Criteria
Day 1 (Baseline)	**104 (2.4)**	**127 (3.3)**	**91 (0.7)**	**64.2 (3.1)**	**Y**
Day 2	**268 (6.1)**	**286 (7.3)**	**153 (1.2)**	**41.4 (2.0)**	**Y**
Day 3	308 (7.0)	205 (5.3)	166 (1.3)	19.5 (1.0)	N
Day 4	248 (5.6)	92 (2.4)	168 (1.3)	15.3 (0.7)	N
Day 5 (End-of-therapy)	177 (4.0)	54 (1.4)	174 (1.3)	12.6 (0.6)	N
Day 31 (Test-of-cure)	42 (1.0)	24 (0.6)	66 (0.5)	8.9 (0.4)	N
Day 43 (Follow-up)	51 (1.2)	32 (0.8)	60 (0.5)	11.9 (0.6)	N

Note: Hy's law laboratory criteria is defined as Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) ≥3 × ULN, Alkaline phosphatase (ALP) ≤2 × ULN and Total Bilirubin ≥2 × ULN
Reference range: ALT: 0 - 44 U/L; AST: 14 - 39 U/L; ALP: 53 - 129 U/L; Total Bilirubin: 5.1 - 20.5 µmol/L
Source: Pooled analysis tables – Integrated safety, Table 1.27.6

Reviewers' Comment: *The investigator's assessment that the liver test abnormalities may have been attributable to the underlying infection is reasonable given the baseline abnormalities noted at screening.*

- Subject (b) (6): This was a 57-year-old female who enrolled in Study TP-434-010 with a diagnosis of cUTI with partial obstructive uropathy that failed prior antibiotic treatment. Her relevant past medical history was significant for hepatitis C infection, hypothyroidism, urinary stones, and obesity. She received a 4-day course of ERV 1.5 mg/kg q24h IV and transition then transitioned to 200 mg q12h PO. Study drug was discontinued on Day 6 due to the SAE of disseminated intravascular coagulation, which resulted in multiple organ failure and death on Day 13. The investigator concluded that failure of treatment resulted in sepsis and disseminated intravascular coagulation in the setting of underlying hepatitis C infection.

  As shown in Table 129, her baseline and Day 3 liver function tests were notable for a transaminitis and increased total bilirubin that fulfilled Hy's Law laboratory criteria. The criteria for Hy's Law was not met at the EOT visit (Day 7).

Table 129: Subject (b) (6) Liver Tests

Study Day	ALT (U/L) (×ULN)	AST (U/L) (×ULN)	ALP (U/L) (×ULN)	Total Bilirubin (µmol/L) (×ULN)	Met Hy's Law Criteria
Day 1 (Baseline)	**43 (1.0)**	**141 (3.4)**	**125 (1.2)**	**48 (2.3)**	**Y**
Day 3	**41 (0.9)**	**123 (3.0)**	**110 (1.1)**	**66 (3.1)**	**Y**
Day 7 (End-of-therapy)	36 (0.8)	113 (2.8)	93 (0.9)	155 (7.4)	N

Note: Hy's law laboratory criteria is defined as Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST)

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>3 × ULN, Alkaline phosphatase (ALP) ≤2 × ULN and Total Bilirubin >2 × ULN
Reference range: ALT: 0 - 45 U/L; AST: 0 - 41 U/L; ALP: 35 - 104 U/L; Total Bilirubin: 2 - 21 µmol/L
Source: Pooled analysis tables – Integrated safety, Table 1.27.6

> ***Reviewers' Comment:*** *The investigator's assessment that the liver function abnormalities may have been attributable to the pre-existing condition of hepatitis C is reasonable given the baseline abnormalities noted at screening.*

Based on the evaluation of the Hepatic Disorders SMQ, examination of clinical chemistry assessments of liver function and detailed review of potential drug-induced liver injury cases identified by Hy's Law laboratory criteria, there is no clear evidence of drug induced liver injury associated with eravacycline.

9.5.6 Pseudomembranous colitis

C. difficile-associated diarrhea was of special interest because it has been reported with the use of nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis. As mentioned in Section 9.3.2, the MedDRA-specified Pseudomembranous colitis SMQ was used to identify events that might represent episodes of *C. difficile*-associated diarrhea.

None of the subjects in the Phase 1 IV Pool (N=181) or the Phase 2 cIAI study (N=139) reported *C. difficile*-associated diarrhea. The TEAE of diarrhea was reported in 10 subjects (5.5%) from the Phase 1 IV Pool and one eravacycline-treated subject (1 mg/kg group) from the Phase 2 cIAI study. These events were non-serious, did not lead to study drug discontinuation, and resolved.

In the Phase 3 cIAI studies, 1 subject experienced *C. difficile*-associated diarrhea. This subject (Subject (b) (6)) received eravacycline treatment and experienced non-serious *C. difficile* colitis on Days 13 to 16. The event occurred after the subject experienced the non-fatal SAE of pancreatitis acute on Day 3, which led to study drug discontinuation and additional antibiotic treatment with gentamycin, ceftriaxone, and metronidazole (Days 3 to Day 13). The *C. difficile* colitis was not considered related to study drug. The TEAE of diarrhea was reported in 12 (2.3%) eravacycline-treated subjects and 8 (1.5%) comparator-treated subjects in the Phase 3 cIAI studies. These events were non-serious, did not lead to study drug discontinuation, and resolved.

In the Phase 3 cUTI study that evaluated an IV-to-PO regimen, 1 subject experienced *C. difficile*-associated diarrhea. This subject received levofloxacin treatment and experienced non-serious C. difficile colitis, which led to discontinuation of study drug. The TEAE of diarrhea was reported in 14 subjects (3%) in each treatment group. The eravacycline and levofloxacin treatment groups had 3 subjects each develop diarrhea which led to discontinuation of study drug. These events were all assessed as non-serious and resolved.

In summary, the similar incidences of *C. difficile* colitis and diarrhea suggest that eravacycline treatment does not increase the risk relative to alternative antibiotics. The single case of *C.*

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difficile colitis in the eravacycline-treated subjects was confounded by exposure to other broad-spectrum antibiotics prior to the onset of the event.

9.5.7 Infusion-site Complication

Infusion site complications were of special interest because it has been reported in patients treated with eravacycline and other broad-spectrum antibiotics. As mentioned in Section 9.3.2, the Infusion site Complications CMQ was used to identify events that might represent episodes of infusion reactions.

The subjects who met the Infusion Site Complication CMQ criteria in the Phase 1 IV Pool are summarized in Table 130. Most of the TEAEs that met the Infusion-Site Complication CMQ began within the first week of study treatment and resolved within 1 week. None of the cases were serious. Four subjects in the Phase 1 Multiple Dose IV Pool experienced TEAEs (phlebitis superficial) that led to discontinuation of study drug.

Table 130: Infusion Site Complication CMQ – Phase 1 IV Pool (Safety Population)

System Organ Class Preferred Term	Phase 1 IV Pool	
	Eravacycline Single Dose IV N=113 n (%)	Eravacycline Multiple Dose IV N=68 n (%)
Infusion Site Complications CMQ	**5 (4.4)**	**34 (50)**
General disorders and administration site conditions	**4 (3.5)**	**18 (26.5)**
Infusion/Vessel puncture site pain	2 (1.8)	11 (16.2)
Infusion site erythema	1 (0.9)	8 (11.8)
Infusion site discomfort	–	7 (10.3)
Infusion site extravasation	1 (0.9)	3 (4.4)
Infusion site swelling	1 (0.9)	1 (1.5)
Vascular disorders	**1 (0.9)**	**27 (39.7)**
Phlebitis superficial	1 (0.9)	14 (20.6)
Phlebitis	–	13 (19.1)

Source: Adapted from Pooled analysis tables – Integrated safety, Table 1.17.1; Clinical Reviewer's Analysis

The subjects who met the Infusion Site Complication CMQ criteria in the Phase 2 cIAI study are summarized in Table 131. There were 3 subjects (5.4%) in the eravacycline 1 mg/kg dose group and 1 subject (1.9%) in the eravacycline 1.5 mg/kg dose group experience TEAEs that met the Infusion Site Complication CMQ criteria. These TEAEs began within the first week after starting study drug and resolved within 5 days. None of the events were serious or led to premature discontinuation of study drug.

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Table 131: Infusion Site Complication CMQ - Phase 2 cIAI Study (Safety Population)

System Organ Class Preferred Term	Study TP-434-P2-cIAI-1		
	Eravacycline 1 mg/kg q12h N=56 n (%)	Eravacycline 1.5 mg/kg q24h N=53 n (%)	Ertapenem N=30 n (%)
Infusion Site Complication CMQ	**3 (5.4)**	**1 (1.9)**	**0**
General disorders and administration site conditions	**1 (1.8)**	**0**	**0**
Catheter site pain	1 (1.8)	–	–
Vascular disorders	**2 (3.6)**	**1 (1.9)**	**0**
Thrombophlebitis	2 (3.6)	1 (1.9)	–

Source: Adapted from Pooled analysis tables – Integrated safety, Table 1.17.4; Clinical Reviewer's Analysis

Subjects in the Phase 3 cIAI studies who had TEAEs that met the Infusion Site Complication CMQ criteria or had the event of vessel puncture site erythema, vessel puncture site swelling, or injection site hypoesthesia are summarized in Table 132. There were 40 eravacycline-treated subjects (7.7%), 5 ertapenem-treated subject (1.9%), and 5 meropenem-treated subjects (2.0%) experience TEAEs that met the Infusion Site Complication CMQ. Most of the cases began within the first week after starting study drug and resolved within 7 days. All were assessed as non-serious. None of the events in the eravacycline group led to premature discontinuation of study drug. Four of the eravacycline-treated subjects with infusion site phlebitis or phlebitis had the adverse event mitigated by reducing the rate and/or concentration of the eravacycline infusion.

Table 132: Infusion Site Complication CMQ - Phase 3 cIAI Studies (Safety Population)

System Organ Class Preferred Term	Studies TP-434-008 and TP-434-025		
	Eravacycline 1 mg/kg q12h N=520 n (%)	Ertapenem N=268 n (%)	Meropenem N=249 n (%)
Infusion Site Complication CMQ[1]	**40 (7.7)**	**5 (1.9)**	**5 (2.0)**
General disorders and administration site conditions	**28 (5.4)**	**3 (1.1)**	**4 (1.6)**
Catheter/Infusion/Injection site phlebitis	14 (2.7)	–	2 (0.8)
Infusion site thrombosis	6 (1.2)	–	1 (0.4)
Injection/Vessel puncture site erythema[1]	4 (0.8)	1 (0.4)	–
Catheter/Infusion/Vessel puncture site pain	2 (0.4)	1 (0.4)	–
Infusion site hypoaesthesia[1]	2 (0.4)	–	–
Infusion site extravasation	1 (0.2)	1 (0.4)	–
Vessel puncture site swelling[1]	1 (0.2)	–	–
Infusion site urticaria	–	–	1 (0.4)
Vascular disorders	**12 (2.3)**	**2 (0.7)**	**1 (0.4)**
Phlebitis	10 (1.9)	1 (0.4)	–
Phlebitis superficial	1 (0.2)	–	–

System Organ Class Preferred Term	Studies TP-434-008 and TP-434-025		
	Eravacycline 1 mg/kg q12h N=520 n (%)	Ertapenem N=268 n (%)	Meropenem N=249 n (%)
Thrombophlebitis	1 (0.2)	1 (0.4)	1 (0.4)

[1] The events of vessel puncture site erythema, infusion site hypoaesthesia, and vessel puncture site swelling were not included in the Applicant's CMQ events terms for Infusion Site Complications.
Source: Adapted from Pooled analysis tables – Integrated safety, Table 1.17.4; Clinical Reviewer's Analysis

Reviewers' Comment: *Overall, the incidence of infusion site complications among eravacycline-treated subjects was higher than in comparator-treated subjects. The increased incidence was primarily due to phlebitis at the infusion site. This reviewer identified 4 subjects, all from the eravacycline treatment group, who experienced either vessel puncture site erythema (Subjects (b) (6)), infusion site hypoaesthesia (Subject (b) (6)), or vessel puncture site swelling (Subject (b) (6)) as the only event term related to an infusion site complication. These 4 subjects are included in Table 132.*

In the Phase 3 cUTI study that evaluated an IV-to-PO regimen, 26 eravacycline-treated subjects (4.8%) and 6 levofloxacin-treated subjects (1.2%) met the Infusion Site Complication CMQ criteria. Infusion site reactions in the eravacycline group included 7 cases of catheter/infusion site erythema, 5 cases of infusion site phlebitis, 4 cases of infusion site thrombosis, 4 cases of thrombophlebitis/thrombophlebitis superficial, 2 cases of infusion site pain, 2 cases of infusion site reaction, 2 cases of infusion site irritation, and 1 case of catheter site inflammation. Two of these cases (thrombophlebitis superficial and catheter site inflammation) occurred in the same subject. No cases in either treatment group were assessed as serious or led to premature discontinuation of study treatment.

In summary, the infusion site complication did not appear to constitute a significant tolerability concern. Although more infusion site reactions occurred in the eravacycline-treated subjects than among comparator-treated subjects, these events were all mild or moderate and none of the events in the Phase 2/Phase 3 study led to study drug discontinuation. Most cases resolved spontaneously and a few were mitigated by reducing the eravacycline infusion concentration or infusion rate.

9.5.8 Thrombophlebitis

Thrombophlebitis was of special interest because it has been reported by subjects treated with eravacycline and other broad-spectrum antibiotics. As mentioned in Section 9.3.2, the MedDRA-specified Thrombophlebitis SMQ was used for this analysis. Many of the preferred terms overlapped within those included in the Infusion site Complications CMQ.

None of the subjects in the Phase 1 Single Dose IV Pool (N=113) experienced TEAEs that met the Thrombophlebitis SMQ criteria. The Phase 1 Multiple Dose IV Pool had 13 subjects (19.1%)

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experience TEAEs that met the Thrombophlebitis SMQ criteria (phlebitis). The events began within the first week of starting study treatment and resolved within 4 weeks. None of the cases were serious or led to premature discontinuation of study drug.

Reviewers' Comment: *The phlebitis events occurred early during study treatment (by Day 4). Most of these subjects (7 of 13) had a single brief episode that lasted 1 day.*

The Phase 2 cIAI study had 2 subjects (3.6%) in the eravacycline 1 mg/kg dose group, 1 subject (1.9%) in the eravacycline 1.5 mg/kg dose group, and zero subjects in the ertapenem group experience TEAEs that met the Thrombophlebitis SMQ criteria. The events began within the first week of starting study treatment and resolved within 5 days.

Reviewers' Comment: *The thrombophlebitis events reported in the Phase 2 study occurred only in the eravacycline treatment groups. These events were reported early during study treatment (by Day 5). Most of these subjects (2 of 3) had a single brief episode that lasted 1 day.*

Subjects in the Phase 3 cIAI studies that met the Thrombophlebitis SMQ criteria are summarized in Table 133. The Phase 3 cIAI studies had 27 eravacycline-treated subjects (5.2%), 1 ertapenem-treated subject (0.7%), and 3 meropenem-treated subjects (1.2%) experience TEAEs that met the Thrombophlebitis SMQ. Most of the events began within the first week of starting study treatment and resolved within 7 days. All the TEAEs, with one exception, were assessed as non-serious. None of the events in either treatment group resulted in premature discontinuation of study drug. A single eravacycline-treated subject from Study TP-434-008 (Subject (b) (6)) experienced the SAE of deep vein thrombosis that met the Thrombophlebitis SMQ. The event of deep vein thrombosis developed 3 weeks after study treatment was completed, required hospitalization, and resolved within 2 weeks. A brief narrative for the event is presented below.

- Subjects (b) (6): This was a 76-year old female who enrolled in Study TP-434-0008 with complicated cholecystitis and intra-abdominal abscesses who received a 6-day course of ERV 1 mg/kg q12h. Her past medical history was significant for diabetes mellitus, cerebrovascular disease, and obesity. She underwent a laparotomy to treat the cIAI and experienced the following non-serious TEAEs during study treatment: post-operative wound infection (from Day 5 through Day 28) and blood pressure increased (from Day 5 through Day 7). The final dose of study drug was administered on Day 7 and she was discharged from the hospital. Three weeks after the final dose of study drug, the subject developed non-serious pain and edema of the right calf, diagnosed as deep vein thrombosis (DVT). She was hospitalized on Day 32 due to worsening of the lower extremity symptoms, upgrading the event to serious. The diagnosis was confirmed on Doppler ultrasound. She received anticoagulation therapy for the event and was discharged from the hospital 1 week later. The event was considered resolved at the time of discharge (Day 39). The investigator considered the event unrelated to study drug. According to the investigator, DVT was related to postoperative thrombophlebitis.

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Table 133: Thrombophlebitis SMQ - Phase 3 cIAI studies (Safety Population)

System Organ Class Preferred Term	Studies TP-434-008 and TP-434-025		
	Eravacycline 1 mg/kg q12h N=520 n (%)	Ertapenem N=268 n (%)	Meropenem N=249 n (%)
Thrombophlebitis SMQ[1]	**27 (5.2)**	**2 (0.7)**	**3 (1.2)**
General disorders and administration site conditions	**14 (2.7)**	**0**	**2 (0.8)**
Infusion site phlebitis	13 (2.5)	–	1 (0.4)
Injection site phlebitis	1 (0.2)	–	–
Catheter site phlebitis	–	–	1 (0.4)
Vascular disorders	**13 (2.5)**	**2 (0.7)**	**1 (0.4)**
Phlebitis	10 (1.9)	1 (0.4)	–
Deep vein thrombosis	2 (0.4)	–	–
Thrombophlebitis	1 (0.2)	1 (0.4)	1 (0.4)

Source: Adapted from Pooled analysis tables – Integrated safety, Table 1.17.4; Clinical Reviewer's Analysis

Reviewers' Comment: *The incidence of thrombophlebitis events among eravacycline-treated subjects was higher than in comparator-treated subjects. The increased incidence was primarily due to phlebitis at the infusion site. Most of these events were reported early during study treatment (by Day 7) and resolved within 1 week.*

In the Phase 3 cUTI study that evaluated an IV-to-PO regimen, 10 eravacycline-treated subjects (1.8%) and 2 levofloxacin-treated subjects (0.4%) met the Thrombophlebitis SMQ criteria. The events reported in the eravacycline group included 5 cases of infusion site phlebitis and 2 cases each of thrombophlebitis, thrombophlebitis superficial, and deep vein thrombosis. Besides infusion site phlebitis, there were no other TEAEs from the levofloxacin group that met the Thrombophlebitis SMQ criteria. One eravacycline-treated subject experienced a SAE of deep vein thrombosis, which required hospitalization. This event occurred 2 days after the last dose of study drug and resolved with anticoagulation therapy. Another eravacycline-treated subject had a non-serious case of both deep vein thrombosis and thrombophlebitis superficial. These events occurred 1 week after the last dose of study drug and resolved with anticoagulation therapy. The remaining events reported in both treatment groups were non-serious and did not lead to premature discontinuation of study drug.

In summary, the incidence of thrombophlebitis events among eravacycline-treated subjects was higher than in comparator-treated subjects. The increased incidence was primarily due to phlebitis at the infusion site. Although there were more events of deep venous thrombosis among eravacycline-treated subjects, the event was uncommon and consistent with the background rate of this complication in hospitalized subjects. The other events identified in the thrombophlebitis SMQ were contained in the infusion-site complications CMQ analysis.

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9.5.9 Nausea and Vomiting

Gastrointestinal side effects including nausea and vomiting have been reported for all tetracycline class antibiotics. These TEAEs were also observed throughout the clinical development program for eravacycline. As mentioned in Section 9.3.2, the nausea and vomiting CMQ was used to identify events that might represent episodes of either nausea and/or vomiting.

Subjects in the Phase 1 IV Pool that met the Nausea and Vomiting CMQ criteria are summarized in Table 134. There were 9 subjects (8.0%) in the Phase 1 Single Dose IV Pool and 10 subjects (14.7%) in the Phase 1 Multiple Dose IV Pool who reported both nausea and vomiting/retching. All the TEAEs that met the Nausea and Vomiting CMQ were non-serious and did not lead to study drug discontinuation. Most of the events began within the first few days of starting study treatment and resolved within 1 or 2 days.

Table 134: Nausea and Vomiting CMQ - Phase 1 IV Pool (Safety Population)

Preferred Term	Phase 1 IV Pool	
	Eravacycline Single Dose IV N=113 n (%)	Eravacycline Multiple Dose IV N=68 n (%)
Nausea and Vomiting CMQ	**23 (20.4)**	**31 (45.6)**
Nausea	22 (19.5)	31 (19.1)
Vomiting	9 (8.0)	9 (13.2)
Retching	–	1 (1.5)

Source: Pooled analysis tables – Integrated safety, Table 1.17.1; Clinical Reviewer's Analysis

Subjects in the Phase 2 cIAI study that met the Nausea and Vomiting CMQ criteria are summarized in Table 135. One subject from the eravacycline 1 mg/kg dose group (1.8%) reported both nausea and vomiting. All the TEAEs that met the Nausea and Vomiting CMQ began within the first week after starting study drug and were assessed as non-serious. Most of the events did not lead to study drug discontinuation and resolved within 1 or 2 days. One notable exception was the previously mentioned subject in the eravacycline 1.5 mg/kg dose group who experienced the fatal SAE of atrial fibrillation associated vomiting, abdominal pain, and ileus (Subject (b) (6)). Additional information pertaining to this subject can be found in the Summary of Deaths.

Table 135: Nausea and Vomiting CMQ - Phase 2 cIAI Study (Safety Population)

Preferred Term	Study TP-434-P2-cIAI-1		
	Eravacycline 1 mg/kg q12h N=56 n (%)	Eravacycline 1.5 mg/kg q24h N=53 n (%)	Ertapenem N=30 n (%)

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Preferred Term	Study TP-434-P2-cIAI-1		
	Eravacycline 1 mg/kg q12h N=56 n (%)	Eravacycline 1.5 mg/kg q24h N=53 n (%)	Ertapenem N=30 n (%)
Nausea and Vomiting CMQ	**6 (10.7)**	**4 (7.5)**	**2 (6.7)**
Nausea	6 (10.7)	1 (1.9)	2 (6.7)
Vomiting	1 (1.8)	3 (5.7)	–

Source: Adapted from Pooled analysis tables – Integrated safety, Table 1.17.4; Clinical Reviewer's Analysis

Subjects in the Phase 3 cIAI studies that met the Nausea and Vomiting CMQ criteria are summarized in Table 136. There were 11 eravacycline-treated subjects (2.1%), 1 ertapenem-treated subject (0.4%), and zero meropenem-treated subjects who reported both nausea and vomiting. All the TEAEs that met the Nausea and Vomiting CMQ were assessed as non-serious. Most of the events began within the first week after starting study drug and resolved within 7 days. In the eravacycline group, one case of nausea and zero cases of vomiting resulted in premature discontinuation of study drug.

Table 136: Nausea and Vomiting CMQ - Phase 3 cIAI Studies (Safety Population)

Preferred Term	Studies TP-434-008 and TP-434-025		
	Eravacycline 1 mg/kg q12h N=520 n (%)	Ertapenem N=268 n (%)	Meropenem N=249 n (%)
Nausea and Vomiting CMQ	**42 (8.1)**	**9 (3.4)**	**6 (2.4)**
Nausea	34 (6.5)	2 (0.7)	1 (0.4)
Vomiting	19 (3.7)	8 (3.0)	5 (2.0)

Source: Adapted from Pooled analysis tables – Integrated safety, Table 1.17.4; Clinical Reviewer's Analysis

In the Phase 3 cUTI study that evaluated an IV-to-PO regimen, 108 eravacycline-treated subjects (19.7%) and 18 levofloxacin-treated subjects (3.6%) met the Nausea and Vomiting CMQ criteria. None were assessed as serious. In the eravacycline group, 8 cases (1.5%) of nausea and/or vomiting resulted in discontinuation of study drug.

In summary, nausea and vomiting occurred more frequently in subjects treated with eravacycline than subjects treated with comparator. This is consistent with other tetracycline-class antibiotics. Most events in both treatment groups were mild or moderate and few led to study drug discontinuation, indicating that nausea and vomiting may not constitute a major tolerability concern.

9.5.10 Pseudotumor cerebri / Elevated intracranial pressure

Pseudotumor cerebri/elevated intracranial pressure was of special interest because it has been reported by subjects treated with tetracycline class antibiotics. As mentioned in Section 9.3.2,

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the pseudotumor cerebri/elevated intracranial pressure CMQ was used for this analysis.

None of the subjects in the Phase 1 IV Pool, the Phase 2 cIAI study, the Phase 3 cIAI studies, or the Phase 3 cUTI study that evaluated an IV-to-PO regimen experienced TEAEs that met the Pseudotumor cerebri/Elevated intracranial pressure CMQ criteria.

9.5.11 Photosensitivity

Photosensitivity was of special interest because it has been reported by subjects treated with tetracycline class antibiotics. As mentioned in Section 9.3.2, the photosensitivity CMQ was used for this analysis.

None of the subjects in the Phase 1 IV Pool, the Phase 2 cIAI study, the Phase 3 cIAI studies, or the Phase 3 cUTI study that evaluated an IV-to-PO regimen experienced TEAEs that met the Photosensitivity CMQ criteria.

9.6 Safety Analyses by Demographic Subgroups

The safety of eravacycline was examined by pre-defined subgroups using the pooled Phase 3 cIAI studies. The intrinsic factors of age, gender, race, ethnicity, BMI, APACHE II score, renal and hepatic function were investigated, as was the extrinsic factor of geography.

The incidence of any TEAE by age, gender, race, ethnicity, geographic region, BMI, APACHE II score, creatinine clearance, and hepatic function (Child-Pugh Class) is presented in Table 137. Rates of any SAE, TEAE leading to discontinuation of study drug, and death in selected subgroups is presented in Table 138. Overall, the evaluation of the influence of baseline characteristics on the safety of eravacycline did not reveal any meaningful differences between treatment groups. For each treatment group, TEAEs were more common in older subjects (≥65 years old) as well as in subjects with either higher BMI (≥30 kg/m^2), higher APACHE II score (≥10), moderate/severe renal impairment (creatinine clearance <60 mL/min), or moderate hepatic impairment (Child-Pugh Class B). These subjects also had higher rates of serious TEAEs, which is consistent with the expected increased morbidity associated with these risk factors. In addition, subjects in North America treated with either eravacycline or comparator had higher rates of TEAEs, SAEs, and TEAEs leading to study drug discontinuation than the subjects in Europe. However, the small sample size for these relavent subgroups may confound findings from the sub-group analysis.

Table 137: Adverse Event Rate by Baseline Characteristic - Phase 3 cIAI Studies (Safety Pop.)

TEAE Category	Baseline Characteristic	Studies TP-434-008 and TP-434-025	
		Eravacycline 1 mg/kg q12h n/N (%)	Comparator n/N (%)
	Overall	201/520 (38.7)	144/517 (27.9)

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TEAE Category	Baseline Characteristic	Studies TP-434-008 and TP-434-025	
		Eravacycline 1 mg/kg q12h n/N (%)	Comparator n/N (%)
Any TEAE	**Age categories**		
	17 – 64 years	136/362 (37.6)	90/366 (24.6)
	≥65 years	65/158 (41.1)	54/151 (35.8)
	≥75 years	23/59 (39.0)	26/69 (37.7)
	Gender		
	Male	105/295 (35.6)	81/292 (27.7)
	Female	96/225 (42.7)	63/225 (28.0)
	Race		
	White	198/512 (38.7)	137/506 (27.1)
	Black/African American	2/2 (100)	2/3 (66.7)
	Asian	0/1 (0)	2/3 (66.7)
	Other	0/4 (0)	3/5 (60)
	Missing	1/1 (100)	–
	Ethnicity		
	Hispanic or Latino	6/12 (50)	3/8 (37.5)
	Not Hispanic or Latino	193/500 (38.6)	138/498 (27.7)
	Unknown/Not Reported	2/8 (25.0)	3/11 (27.3)
	Region		
	Europe	182/494 (36.8)	130/493 (26.4)
	North America	19/26 (73.1)	14/23 (60.9)
	South Africa	0/0 (0)	0/1 (0)
	Body Mass Index		
	<25 kg/m^2	58/179 (32.4)	42/196 (21.4)
	25 - <30 kg/m^2	70/180 (38.9)	55/176 (31.3)
	≥30 kg/m^2	73/161 (45.3)	47/145 (32.4)
	APACHE II Score		
	<10	155/419 (37.0)	102/406 (25.1)
	≥10	44/99 (44.4)	41/108 (38.0)
	Missing	2/2 (100)	1/3 (33.3)
	Creatinine Clearance		
	<15 ml/min	0/1 (0)	–
	15 - <60 ml/min	22/41 (53.7)	14/33 (42.4)
	≥60 ml/min	177/471 (37.6)	124/471 (26.3)
	Missing	2/7 (28.6)	6/13 (46.2)
	Child-Pugh Class		
	Class A	139/381 (36.5)	84/361 (23.3)
	Class B	36/66 (54.5)	33/78 (42.3)
	Missing	26/73 (35.6)	27/78 (34.6)

Source: Clinical Reviewer's Analysis

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Table 138: Adverse Event Rate for Selected TEAE Categories by Baseline Characteristics - Phase 3 cIAI Studies (Safety Population)

TEAE Category	Demographic Group	Studies TP-434-008 and TP-434-025	
		Eravacycline 1 mg/kg q12h n/N (%)	Comparator n/N (%)
Any SAE	**Overall**	**32/520 (6.2)**	**32/517 (6.2)**
	Age Groups		
	17 – 64 years	18/362 (5.0)	17/366 (4.6)
	≥65 years	14/158 (8.9)	15/151 (9.9)
	≥75 years	4/59 (6.8)	8/69 (11.6)
	Gender		
	Male	18/295 (6.1)	15/292 (5.1)
	Female	14/225 (6.2)	17/225 (7.6)
	Region		
	Europe	28/494 (5.7)	27/493 (5.5)
	North America	4/26 (15.4)	5/23 (21.7)
	Body Mass Index		
	<25 kg/m^2	8/179 (4.5)	8/196 (4.1)
	25 - <30 kg/m^2	11/180 (6.1)	10/176 (5.7)
	≥30 kg/m^2	13/161 (8.1)	14/145 (9.7)
	APACHE II Score		
	<10	25/419 (6.0)	19/406 (4.7)
	≥10	7/99 (7.1)	12/108 (11.1)
	Missing	0/2 (0)	1/3 (33.3)
	Creatinine Clearance		
	15 - <60 ml/min	5/41 (12.2)	5/33 (15.2)
	≥60 ml/min	27/471 (5.7)	24/471 (5.1)
	Missing	0/7 (0)	3/13 (23.1)
	Child-Pugh Class		
	Class A	15/381 (3.9)	14/361 (3.9)
	Class B	11/66 (16.7)	8/78 (10.3)
	Missing	6/73 (8.2)	10/78 (12.8)

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TEAE Category	Demographic Group	Studies TP-434-008 and TP-434-025	
		Eravacycline 1 mg/kg q12h n/N (%)	Comparator n/N (%)
Any TEAE leading to discontinuation of study drug	**Overall**	**11/520 (2.1)**	**11/517 (2.1)**
	Age Groups		
	17 – 64 years	6/362 (1.7)	6/366 (1.6)
	≥65 years	5/158 (3.2)	5/151 (3.3)
	≥75 years	2/59 (3.4)	0/69 (0)
	Gender		
	Male	8/295 (2.7)	6/292 (2.1)
	Female	3/225 (1.3)	5/225 (2.2)
	Region		
	Europe	10/494 (2.0)	10/493 (2.0)
	North America	1/26 (3.8)	1/23 (4.3)
	Body Mass Index		
	<25 kg/m^2	3/179 (1.7)	2/196 (1.0)
	25 - <30 kg/m^2	3/180 (1.7)	2/176 (1.1)
	≥30 kg/m^2	5/161 (3.1)	7/145 (4.8)
	APACHE II Score		
	<10	7/419 (1.7)	7/406 (1.7)
	≥10	4/99 (4.0)	4/108 (3.7)
	Creatinine Clearance		
	15 - <60 ml/min	1/41 (2.4)	2/33 (6.1)
	≥60 ml/min	10/471 (2.1)	9/471 (1.9)
	Child-Pugh Class		
	Class A	8/381 (2.1)	8/361 (2.2)
	Class B	2/66 (3.0)	1/78 (1.3)
	Missing	1/73 (1.4)	2/78 (2.6)

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TEAE Category	Demographic Group	Studies TP-434-008 and TP-434-025	
		Eravacycline 1 mg/kg q12h n/N (%)	Comparator n/N (%)
Any TEAE resulting in Death	**Overall**	**8/520 (1.5)**	**7/517 (1.4)**
	Age Groups		
	17 – 64 years	3/362 (0.8)	3/366 (0.8)
	≥65 years	5/158 (3.2)	4/151 (2.6)
	≥75 years	2/59 (3.4)	3/69 (4.3)
	Gender		
	Male	4/295 (1.4)	2/292 (0.7)
	Female	4/225 (1.8)	5/225 (2.2)
	Region		
	Europe	8/494 (1.6)	5/493 (1.0)
	North America	0/26 (0)	2/23 (8.7)
	Body Mass Index		
	<25 kg/m^2	3/179 (1.7)	0/196 (0)
	25 - <30 kg/m^2	4/180 (2.2)	2/176 (1.1)
	≥30 kg/m^2	1/161 (0.6)	5/145 (3.4)
	APACHE II Score		
	<10	3/419 (0.7)	3/406 (0.7)
	≥10	5/99 (5.1)	4/108 (3.7)
	Creatinine Clearance		
	15 - <60 ml/min	3/41 (7.3)	3/33 (9.1)
	≥60 ml/min	5/471 (1.1)	3/471 (0.6)
	Missing	0/7 (0)	1/13 (7.7)
	Child-Pugh Class		
	Class A	2/381 (0.5)	2/361 (0.6)
	Class B	3/66 (4.5)	3/78 (3.8)
	Missing	3/73 (4.1)	2/78 (2.6)

Source: Clinical Reviewer's Analysis

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9.7 Specific Safety Studies/Clinical Trials

There were no specific studies for review.

9.8 Additional Safety Explorations

9.8.1 Human Carcinogenicity or Tumor Development

There have been no formal studies in humans to assess human carcinogenicity development with eravacycline. Carcinogenicity studies were not conducted because of the short-term, intermittent use of eravacycline and no findings in the eravacycline toxicology program suggested a cause for concern.

In the overall safety population, 7 subjects experienced adverse events within the SOC of Neoplasms benign, malignant, and unspecified. These subjects included 4 eravacycline-treated subjects (all from Study TP-434-025) and 3 comparator-treated subjects (1 subject each in Studies TP-434-025, TP-434-010, and TP-434-021). In the eravacycline group, 1 subject each had adenocarcinoma of appendix (Subject (b) (6)), adenocarcinoma of colon (Subject (b) (6)), adenocarcinoma of gallbladder (Subject (b) (6)), and neuroendocrine tumor (Subject (b) (6)). The events in the comparator group were gallbladder cancer in a meropenem-treated subject (Subject (b) (6)), recurrent endometrial cancer in a levofloxacin-treated subject (Subject (b) (6)), and meningioma in a ertapenem-treated subject (Subject (b) (6)). None of the events in the eravacycline or comparator groups were related to study drug.

Reviewers' Comment: *Based on the available data from the clinical trial, there is no clinical evidence of carcinogenicity for the eravacycline regimen intended for cIAI. In addition, the proposed recommended duration of therapy is for a short duration (4 to 14 days).*

9.8.2 Human Reproduction and Pregnancy

Eravacycline, like other tetracycline class antibacterials, may cause discoloration of deciduous teeth and reversible inhibition of bone growth when administered during the second and third trimester of pregnancy. Animal studies have shown that eravacycline crosses the placenta and is found in fetal plasma; doses greater than 3- and 2.8-fold the clinical exposure, based on AUC in rats and rabbits, respectively, administered during the period of organogenesis were associated with decreased ossification, decreased fetal body weight, and/or increased post-implantation loss.

Reviewers' Comment: *In the clinical studies, two pregnancies were reported among eravacycline-treated subjects (both from Study TP-434-010). Both subjects completed study treatment prior to confirmation of pregnancy. One pregnancy was electively terminated and the*

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other pregnancy resulted in a healthy child. The limited data with eravacycline use in pregnant women are insufficient to inform drug-associated risk of major birth defects and miscarriages.

It is not known whether eravacycline is excreted in human breast milk. Eravacycline (and its metabolites) is excreted in milk of lactating rats. Other tetracycline class antibacterials are excreted in human milk. There are no data on the effects of eravacycline on the breast-fed infant, or the effects on milk production.

Reviewers' Comment: *Eravacycline is not recommended for lactating women because of* the potential for serious adverse reactions *associated with tetracycline class antibiotics (i.e., tooth discoloration and inhibition of bone growth) and other antibacterial drug options are available for cIAI. The XERAVA label will recommend not breast feed during treatment and for 4 days (based on half-life) after the last dose.*

Based on animal studies, eravacycline can lead to impaired spermiation and sperm maturation, resulting in abnormal sperm morphology and poor motility. The effect is reversible in rats. The long-term effects of eravacycline on male fertility have not been studied.

Reviewers' Comment: *No adverse events related to infertility were reported in the clinical studies.*

9.8.3 Pediatrics and Assessment of Effects on Growth

The Applicant submitted an initial Pediatric Study Plan (iPSP) for the development of eravacycline for treatment of cIAI (b) (4) The proposed plan includes documentation in support of a waiver request for the pediatric population less than 8 years of age, and a deferral request for the pediatric population aged 8 to 17 years of age. Non-clinical studies with eravacycline have shown the potential for permanent staining of developing bone and teeth. These observation are similar across tetracycline-class antibacterial drugs. The PeRC agreed with the plan for a waiver in pediatric patients less than 8 years of age based on these safety concerns and for deferral in pediatric patients aged 8 to 17 years of age until safety and efficacy data were obtained in the adult population. The planned pediatric studies in the agreed iPSP are listed in Table 139.

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Table 139: Planned Pediatric Studies

Source: iPSP

9.8.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No reports of overdose were reported in the clinical studies. Intravenous administration of single doses of eravacycline in healthy volunteers in Study TP-434-P1-SAD-1 up to a maximum dose of 3 mg/kg showed that nausea and vomiting were more prevalent at the higher doses.

9.9 Safety in the Postmarket Setting

9.9.1 Safety Concerns Identified Through Postmarket Experience

Not Applicable – no postmarket experience.

9.9.2 Expectations on Safety in the Postmarket Setting

No other potential safety concerns expected beyond the risks conveyed in the proposed labeling.

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9.10 Integrated Assessment of Safety

Overview of TEAEs in the Applicant's Integrated Analysis Pools are summarized in Table 141. Across the multiple analyses, rates of TEAEs leading to discontinuation of study drug, serious TEAEs, and death were low and similar between treatment groups. None of the SAEs (including fatal events) were considered related to eravacycline treatment. The majority of SAEs in both treatment groups were primarily indicative of disease related processes or comorbidities. There were no safety signals of treatment related increase in morbidity. Subgroup analysis in the pooled Phase 3 cIAI studies did not reveal a significant, specific influence with respect to age, gender, race, ethnicity, BMI, APACHE II score, renal function, hepatic function or geography on the safety of eravacycline. However, the race, ethnicity, and geography analyses should be interpreted with caution given the few subjects who were either non-white, hispanic/latino, or from North America. There were also few subjects with severe renal impairment (CrCl: <15 mL/min) and none with severe hepatic impairment (Child Pugh Class C).

Table 140: Overview of TEAEs in the Integrated Analysis Pools (Safety Population)

TEAE Category (n, %)	Phase 1 IV	cIAI Only Phase 2/Phase 3			All Phase 2/Phase 3	
	All ERV N=181	ERV 1 mg/kg q12h N=576	ERV 1.5 mg/kg q24h N=53	Comparator N=547	All ERV N=1176	All Comparators N=1045
No. of studies	**9**	**3**			**4**	
Any TEAE	93 (51.4)	217 (37.7)	19 (35.8)	152 (27.8)	447 (38.0)	265 (25.4)
Any severe TEAE[1]	0	28 (4.9)	4 (7.5)	31 (5.7)	51 (4.3)	37 (3.5)
Any SAE	0	33 (5.7)	6 (11.3)	33 (6.0)	48 (4.1)	40 (3.8)
Any TEAE leading to discontinuation of study drug	2 (1.1)	11 (1.9)	2 (3.8)	13 (2.5)	32 (2.7)	24 (2.3)
Any TEAE resulting in Death	0	8 (1.4)	3 (5.7)	7 (1.3)	12 (1.0)	7 (0.7)

Abbreviations: All ERV=any dose of IV eravacycline (ERV); Comparator=ertapenem or meropenem; All Comparators = ertapenem, meropenem, or levofloxacin;

[1] Severe is defined as severe, life-threatening, or fatal. TEAEs with missing severity are included as severe.

Source: Adapted from Pooled analysis tables – Integrated safety, Tables 1.3.1 and 1.3.4; Clinical Reviewer's Analysis.

In the completed Phase 2 and Phase 3 cIAI and cUTI studies, TEAEs generally occurred at a higher rate in subjects who received eravacycline compared to those who received comparator. The increase was driven primarily by increased rates of gastrointestinal events (i.e., nausea and vomiting) and localized infusion site reactions (i.e., phlebitis, phlebitis superficial, thrombophlebitis, and/or pain, erythema, swelling, hypoaesthesia, extravasation, phlebitis, or thrombosis at the catheter/infusion/injection/vessel puncture site). These events were not a

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tolerability issue because the majority were mild or moderate in severity and infrequently led to discontinuation of study drug.

No new safety signals with eravacycline were observed in the clinical development program that would not be expected for a tetracycline class antibacterial drug. Pancreatitis and increased lipase and/or amylase were reported at a frequency similar to that reported for comparators. The reported TEAEs in the controlled studies may have been the result of confounding due to peritoneal inflammation associated with the underlying disease process. An evaluation of TEAE and laboratory data consistent with pancreatitis did not provide conclusive evidence of an increased risk of pancreatitis associated with eravacycline treatment. Evaluation of clinical chemistry and TEAEs suggestive of drug related hepatic disorders did not suggest an increased risk of hepatic injury associated with eravacycline treatment. There were no likely cases of drug-induced liver injury caused by eravacycline. Increases in ALT, AST, and bilirubin were reported in subjects treated with eravacycline at frequencies similar to those reported for comparators. Events identified by the hypersensitivity SMQ were uncommon in the clinical studies with IV eravacycline. For the cases identified in the eravacycline-treated subjects in either the Phase 1 IV Pool or All Phase 2/Phase 3 Pool, none had signs and/or symptoms consistent with criteria for anaphylaxis. Unexpected or clinically meaningful safety signals were not found in the other SMQ and CMQ analyses (i.e., acute renal failure, pseudomembranous colitis, pseudotumor cerebri/ elevated intracranial pressure, and photosensitivity).

During the individual Phase 2 and Phase 3 cIAI studies, the mean changes from baseline for clinical chemistry, hematology, and coagulation parameters at each study visit were generally small and did not appear clinically significant. Similarlly, evaluation of vital signs and ECG data from each of these studies did no reveal remarkable trends. There was also no clinically significant prolongation of QTcF noted in the thorough QT study (Study TP-434-004) conducted in healthy volunteers.

A second Phase 3 cUTI study (TP-434-021) evaluating IV eravacycline compared to ertapenem was recently completed, but the final datasets were not available for inclusion in the integrated Analysis Pools. Top-line safety data was presented in the 120-day Safety Update to this NDA. Results were similar to the observations from the other clinical studies. However, a single life-threatening hypersensitivity (anaphylactic) reaction was reported in a eravacycline-treated subject in this study and was considered related to study drug by the investigator. The other clinical studies with IV eravacycline had no serious TEAE considered related to study drug or potential anaphylactic reactions reported.

10 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not convened for this NDA.

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11 Pediatrics

There were no pediatric studies included in the NDA. To establish XERAVA dosing in pediatric patients and address PREA obligations, there are 2 required post-marketing studies in pediatric patients aged 8 to 17 years old (see Section 9.8.3 of this review). Children less than 8 years of age will not be studied due to the risks tetracycline-associated bone and tooth staining.

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12 Labeling Recommendations

12.1 Prescribing Information

Draft prescribing information was provided within the application, and the following significant changes were made during the course of the review:

Labeling Section	Modifications
INDICATIONS AND USAGE	• A Limitation of Use statement for complicated urinary tract infections (cUTI) added (Section 1) due to the results of two clinical trials conducted by the Applicant (Section 14).
DOSAGE AND ADMINISTRATION	• Added XERAVA dosage adjustment in patients with severe hepatic impairment (b) (4) Supporting information referenced in Section 12.3 • Added XERAVA dosage adjustment for patients with concomitant use of a strong cytochrome CYP 3A inducer (b) (4) Supporting information referenced in Section 12.3
WARNINGS AND PRECAUTIONS	• Added tetracycline-class drug warnings for tooth discoloration and enamel hypoplasia based upon non-clinical study data.
DRUG INTERACTIONS	• Added XERAVA dosage adjustment for patients with concomitant use of a strong cytochrome CYP 3A inducer (b) (4). Supporting information referenced in Section 12.3
USE IN SPECIFIC POPULATIONS	• Added XERAVA dosage adjustment in patients with severe hepatic impairment (b) (4). Supporting information referenced in Section 12.3
CLINICAL STUDIES	• Added clinical trial information to support limitation of use statement for the treatment of cUTI.

12.2 Patient Labeling

The Applicant did not propose patient labeling for XERAVA.

Reviewer Comment: This is acceptable. XERAVA is anticipated to be administered parenterally in a healthcare setting.

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13 Risk Evaluation and Mitigation Strategies (REMS)

13.1 Safety Issue(s) that Warrant Consideration of a REMS

The main serious risks associated with eravacycline are similar to the other tetracycline-class antibacterial drugs and include life-threatening hypersensitivity (anaphylactic) reactions, tooth discoloration and enamel hypoplasia, inhibition of bone growth, *C. difficile*-associated diarrhea, tetracycline class adverse reactions (i.e., photosensitivity, pseudotumor cerebri, and anti-anabolic action which has led to increased BUN, azotemia, acidosis, hyperphosphatemia, pancreatitis, and abnormal liver function tests), potential for microbial overgrowth, and development of drug-resistant bacteria. The safety issues will be included in labeling and there are no specific risks that warrant consideration of a REMS.

13.2 Conditions of Use to Address Safety Issue(s)

The Applicant's proposal to not include any risk management activities for eravacycline beyond routine pharmacovigilance and labeling is reasonable.

13.3 Recommendations on REMS

No REMS are recommended. At this time, there is no data to indicate the risks associated with eravacycline are more concerning than the other tetracycline-class antibacterials. These risks can be communicated in the labeling for eravacycline, as is the case for other tetracyclines.

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14 Postmarketing Requirements and Commitments

The following postmarketing studies are required:

1. Conduct a study to evaluate the pharmacokinetics, safety and tolerability of a single-dose of intravenous XERAVA (eravacycline) in children from 8 years to less than 18 years of age with suspected or confirmed bacterial infection.

2. Conduct a randomized, multicenter, active-controlled trial to evaluate the safety and tolerability of intravenous XERAVA (eravacycline) in children from 8 years to less than 18 years of age with cIAI.

3. Conduct a US surveillance study for five years from the date of marketing to determine if resistance to XERAVA (eravacycline) has developed in those organisms specific to the indication in the label.

Please see the approval letter for the milestone dates for the postmarketing requirements.

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15 Appendices

15.1 References

FDA Guidance for Industry Complicated Intra-Abdominal Infections: Developing Drugs for Treatment (2015).

Miettinen O, Nurminen M, 1985, Comparative analysis of two rates, Statistics in Medicine, 4(2):213-226.

Clopper CJ, Pearson ES, 1934, The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika, 26:404-413.

Chan I, Zhang Z, 1999, Test-based exact confidence intervals for the difference of two binomial proportions, Biometrics, 55:1202-1209.

15.2 Financial Disclosure

Financial disclosure information was provided for the investigators who conducted the Phase 2 and Phase 3 clinical studies evaluating IV administration of eravacycline in cIAI (Studies TP-434-P2-cIAI-1, TP-434-008, and TP-434-025). The Applicant determined there were no financial interests or arrangements to disclose for the investigators in these studies.

Covered Clinical Study (Name and/or Number): TP-434-P2-cIAI-1, TP-434-008, and TP-434-025

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: Study TP-434-P2-cIAI-1: 19 investigators Study TP-434-008: 69 investigators Study TP-434-025: 65 investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR		

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54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from Applicant)

Financial disclosure information was also provided for the Phase 3 clinical study evaluating IV ± PO administration of eravacycline in cUTI (Study TP-434-010), the Phase 1 thorough QT study (Study TP-434-004), and 3 Phase 1 drug interaction studies (TP-434-015, TP-434-016, and TP-434-020). The Applicant determined there were no financial interests or arrangements to disclose for the investigators in these additional studies.

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15.3 Technical documents supporting OCP recommendations

15.3.1 Summary of Bioanalytical Method Validation and Performance

Multiple validated LC-MS/MS assays were used for quantification of eravacycline, TP-498, TP-6208, and TP-034 in the plasma and urine as shown in Table 141 and Table 142, respectively.

When concentrations exceeded the standard curve range, samples were diluted, then reassayed. Dilution integrity was verified within each clinical pharmacology study when dilution was performed. The sample preparation, stability, analysis accuracy, and precision in each clinical pharmacology study were reported in the corresponding bioanalytical reports and reviewed by the Clinical Pharmacology reviewer. Please refer to Section 0 Individual Study Reviews for further details.

Table 141. Validation Reports of Quantification of Eravacycline, TP-498, TP-6208, and TP-034 in Plasma.

Validation Parameter	Plasma Validation Reports Laboratory				
	(b) (4) R09-137 (b) (4)	4171120001[a] (4171100001**) (4171100005***) (4171110002, (b) (4) (b) (4)	(b) (4) -12262 (b) (4)	(b) (4) 113360QB02 (b) (4)	(b) (4) 274745QB02 (b) (4)
Analytes measured	TP-434, TP-498	TP-434, TP-498, TP-6208	TP-434, TP-498, TP-6208	TP-434, TP-498, TP-6208	TP-034
Range and LLOQ (ng/mL)	5.00 - 1,000 (434) 4.43 - 886 (498)	5.00 - 500 (all)	5 - 500 (all)	5.0 - 500 (all)	5.00 - 500
R^2 or r (mean) $1/x^2$ weighted	0.9963 (434) 0.9966 (498)	*0.9978 (434*) **0.9982 (498*) ***0.9980 (6208*)	0.9991 (434) 0.9983 (498) 0.9971 (6208)	0.9983 (434) 0.9989 (498) 0.9972 (6208)	0.9934 (034)
Batch size	220	not specified	102	not specified	96
Stability (temperature)					
Whole blood	ND	ND	ND	2 h (wet ice)	1 h (wet ice)
Plasma: benchtop RT	ND	1 day (**,***)	6 h		ND
Plasma: (wet ice)	6 h (covered)	1 day (refrid, **,***)	ND	24 h 4°C	24 h 4°C
Plasma: F/T	4 cycles -70°C	3 cycles -80°C (*)	3 cycles -70°C	4 cycles -80°C	6 cycles
Plasma: long-term	32 days -20°C 124 days -70°C	12 months -80°C (LTS) 3.5 months -20°C (LTS)	54 days -20°C and -70°C	49 days -80°C (434 and 498) 14 days -80°C (6208)	93 days -80°C 103 days -80°C (alone)
Stock solutions	6 h 1-8°C covered 41 days -20°C covered	37 days -20°C (434, 498**)	6 h RT 60 days -20°C	42 days 4°C (434) 42 days -20°C (498, 6208)	48 days -20°C
Working solutions	ND	4 days refrigerated (434, 498**)	ND	38 days -20°C	42 days -20°C
Injector storage	ND	ND	63 h -5°C	ND	ND
Reinjection reproducibility	137 h 1-8°C covered	ND	ND	48 h 4°C	ND
Processed samples	ND	1 day RT (434, 498**) 3-4 days refrigerated (**,***)	27 h 4°C	24 h 4°C	5 days 4°C
Interference (plasma)					
Haemolysed or lipaemic	ND	ND	ND	none	none
Dilution factor	10-fold	10-fold (**,***)	10-fold	10-fold	50-fold

F/T = freeze/thaw; LLOQ = lower limit of quantitation; ND: not determined; RT = room temperature.
[a] validation data reported in table from revalidation of new method MS0181(*) or from original validation reports as noted by **, ***

Source: Adapted from Table 19 in the Summary of Biopharmaceutic Studies and Associated Analytical Methods.

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Table 142. Validation Reports of Quantification of Eravacycline, TP-498, TP-6208, and TP-034 in Urine.

Validation Parameter	Urine Validation Reports Laboratory			
	(b) (4) R09-136 (b) (4)	4171100003 (b) (4)	(b) (4) 256064QB01[a] (b) (4)	(b) (4) 266344QB02 (b) (4)
Analytes measured	TP-434, TP-498	TP-434, TP-498, TP-6208	TP-434 only	TP-434, TP-498, TP-6208
Internal Standard (Deuterated)	D8-434 and D8-498	D8-434 and D8-498	D8-434	D8-434 and D8-498
Range and LLOQ (ng/mL)	5.00 - 1,000 (434, 498)	5.00 -1,000	100 - 20,000 ng/mL	50 - 10,000 ng/mL (434) 50 - 1,000 ng/mL (498) 20 - 1,000 ng/mL (6208)
R^2 or r^2 (mean) $1/x^2$ weighted	0.9960 (434) 0.9977 (498)	0.9975# (434) 0.9986# (498) 0.9977# (6208)	0.9992	0.9985 (434) 0.9981 (498) 0.9941 (6208)
Batch size	220	not specified	not specified	120
Stability (temperature)				
urine: benchtop (RT)	ND	4 day ambient	ND	ND
urine: (wet ice) 4°C	24 h (protected from light)	7 day refrigerated	6 h without (-) acid 24 h with (+) acid	6 h without acid 49 h with acid
urine: F/T	4 cycles -70°C	3 cycles -70°C	4 cycles -80°C (+ acid)	4 cycles +/- acid
urine: long-term	11 days -70°C	13 weeks -70°C (434, 498 only)	14 days -20°C (-) acid 4 months -80°C (-) acid 182 days -80°C (+) acid	83 days +/- acid -80°C
stock solutions	6 h (1-8°C protected from light) 41 days (-20°C protected from light)	19 days -20°C	42 days 4°C	ND
working solutions	ND	17 days refrigerated	22 days 4°C	14 days -20°C
injector storage	ND	13 h	5 days 4°C	6 days 4°C
reinjection reproducibility	104 h (1-8°C protected from light)	ND	ND	ND
processed samples	ND	1 day ambient 3 days refrigerated	22 days 4°C	ND
Dilution factor	10 fold	10 fold	ND	100 fold

ND=not determined #mean of n=5 curves.
[a] method qualification, not validation, report. No claim to GLP compliance.

Source: Adapted from Table 19 in the Summary of Biopharmaceutic Studies and Associated Analytical Methods.

15.3.2 Population PK Analysis

The Applicant formulated two major population PK (PPK) analyses: TETR-PCS-100 and ICPD-0380-1 with Table 143 and Table 144 showing the studies from which the data was generated, respectively.

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Table 143. Studies Included in TETR-PCS-100.

Study No.	Enrollment	Study title
TP-434-P1-SAD-1	56	Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Pharmacokinetics of Single Ascending Doses of TP-434
TP-434-P1-MAD-1	32	Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Pharmacokinetics of Multiple Ascending Dose Regimens of TP-434
TP-434-Oral-P1-SAD-1[a]	32	A Phase 1 Single-Center, Double-Blind, Randomized, Placebo-Controlled Clinical Trial to Investigate the Safety, Tolerability and Pharmacokinetics of TP-434 Administered as a Single Ascending Oral Dose to Healthy Male and Female Subjects
TP-434-002-P1-MAD-Oral	58	Phase 1 Single-Center, Double-Blind, Randomized, Placebo-Controlled Clinical Trial to Investigate the Safety, Tolerability and PK of TP-434 Administered as Multiple-Ascending Oral Doses to Healthy Male and Female Subjects
TP-434-004	54	A Randomized, Placebo- and Positive Controlled, Three-Way, Crossover Study to Evaluate the Effects of an Intravenous Infusion of Eravacycline (TP-434) on Cardiac Repolarization in Healthy Male and Female Subjects: A Thorough QT/QTc Study
TP-434-006	20	Phase 1, Open-Label, Safety and PK Study to Assess Bronchopulmonary Disposition of Intravenous TP-434 in Healthy Men and Women
TP-434-007	47	A Randomised, Placebo-Controlled, Double-Blind Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Ascending Doses of Oral Eravacycline (TP-434) Administered Multiple Times Daily for Seven Days
TP-434-009[b]	12	A Two Part Study to Investigate the Pharmacokinetic Profile of Different Oral Formulations of Eravacycline Administered as Single and Multiple Daily Doses (Part 2, MAD, of this study was not initiated)
TP-434-013	24	A Phase 1, Open-Label Study to Assess the Single-Dose Pharmacokinetics of Eravacycline in Subjects with Impaired Hepatic Function and Healthy Subjects
TP-434-014	12	A Phase 1, Open-Label Study to Assess the Single-Dose PK of Eravacycline in Subjects with ESRD and Healthy Subjects
TP-434-001	143	A Phase 2, Randomized, Double-Blind, Double-Dummy, Multicenter, Prospective Study to Assess the Efficacy, Safety and Pharmacokinetics of 2 Dose Regimens of TP-434 Compared with Ertapenem in Adult Community-Acquired Complicated Intra-abdominal Infections
TP-434-008	536	A Phase 3, Randomized, Double-Blind, Double-Dummy, Multicenter, Prospective Study to Assess the Efficacy and Safety of Eravacycline Compared with Ertapenem in Complicated Intra-abdominal Infections (cIAI)
TP-434-010	840	A Phase 3, Randomized, Double-Blind, Double-Dummy, Multicenter, Prospective Study to Assess the Efficacy and Safety of Eravacycline Compared with Levofloxacin in cUTI

[a]: Not used; [b]: Data for manufactured IR capsules were not used

Source: Adapted from Table 7.1 in Report TETR-PCS-100.

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Table 144. Studies Included in ICPD-0380-1

Protocol number	Study design	Dose regimens	Scheduled plasma PK samples collection time
TP-434-P2-cIAI-1	Phase 2, randomized, double-blind, double-dummy study in patients with community-acquired complicated intra-abdominal infections	1.5 mg/kg q24h or 1.0 mg/kg q12h intravenously administered for 4-14 days	Day 1: pre-infusion, at the end of the first infusion, 3 and 7 hr after the start of the first infusion Days 2, 5, and 10: pre-infusion
TP-434-008	Phase 3, randomized, double-blind, double-dummy study in patients with complicated intra-abdominal infections	1.0 mg/kg q12h intravenously administered for 4-14 days	Day 1: pre-infusion, at the end of the first infusion, 3 and 7 hr after the start of the first infusion, prior to the start of second infusion

Source: Adapted from Table 2 in the Report ICPD 0380-1.

The Applicant found that the model ICPD-0380-1 adequately described the PK data in Phase 3 study TP-434-025 in a Bayesian post-hoc approach. It should also be noted that TETR-PCS-100 includes data that was generated from subjects administered oral eravacycline and in patients that were treated for complicated urinary tract infection (cUTI).

Reviewer Comment: The FDA reviewer updated the population PK model based on TETR-PCS-100 by combining the datasets used with TETR-PCS-100 and ICPD-0380-1. The updated model was then compared to the original 2 PPK models. The PPK model with pooled data was selected for covariate analysis. As the exposure-response analysis was performed based on the Applicant's the population PK model predicted eravacycline exposure, the FDA reviewer assessed the potential discrepancy of model predicted eravacycline exposure between the Applicant's final PPK model and the FDA reviewer's PPK model. The eravacycline concentration-time profiles from the Applicant's final PPK model and the FDA reviewer's PPK model were highly correlated. Thus, the Applicant's PPK model is acceptable to interpolate eravacycline exposure for the exposure-response analysis. The details of the model are stated in the Reviewer's Analysis section.

The final model of TETR-PCS-100 was a 3-compartment model with allometric scaling on parameters of volume and clearance. The final PK parameters are shown in Table 145.

Reference ID: 4312284

Table 145. Population PK Parameters of Eravacycline in TETR-PCS-100.

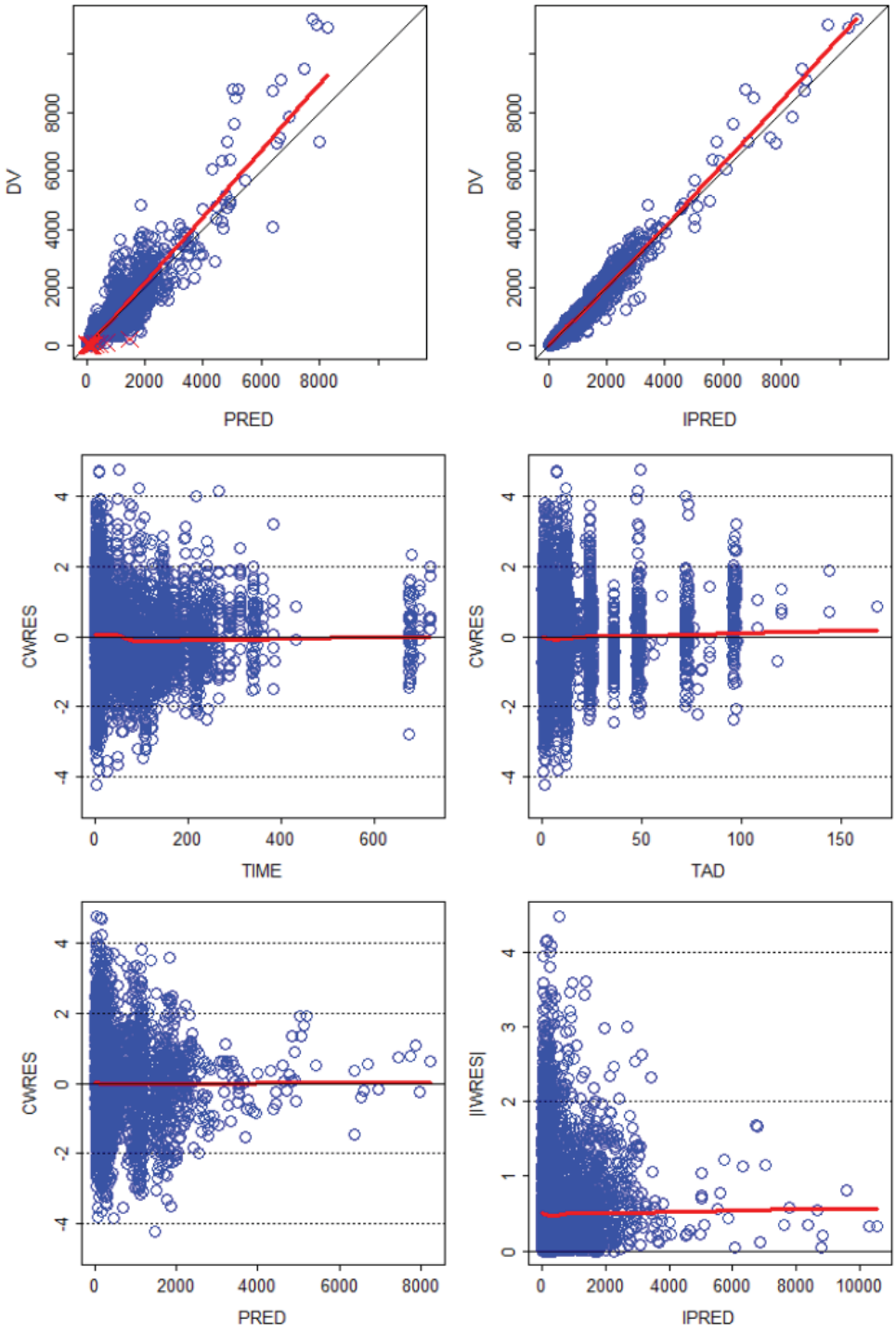
Parameter	Estimate (RSE)	Covariate Effects	BSV (%)
CL (L/hr)	10.1 (3.6%)	× $(Weight/70)^{0.75}$ × $(Age/45)^{-0.335}$ × 0.756 if Mild HI[a] × 0.777 if Moderate HI[a] × 0.529 if Severe HI[a] × 1.07 if RI[b] × 1.22 if TP-434-008 (cIAI) × 1.12 if TP-434-010 (cUTI)	32.6
V_2 (L)	15.5 (7.0%)	× $(Weight/70)^{1.0}$ × 1.20 if Female × 0.444 if TP-434-008 (cIAI) × 1.50 if TP-434-010 (cUTI)	32.4
Q_3 (L/hr)	33.1 (8.5%)	× $(Weight/70)^{0.75}$ × 1.63 if TP-434-008 (cIAI) × 6.75 if p.o. with food × exp (-0.274 × [Dose/Weight - 1.0]) if i.v. infusion	59.6
V_3 (L)	58.9 (3.3%)	× $(Weight/70)^{1.0}$	32.4
Q_4 (L/hr)	13.3 (7.0%)	× $(Weight/70)^{0.75}$ × 1.93 if TP-434-008 (cIAI) × 1.99 if p.o. with food × exp(-0.240 × (Dose/Weight - 1.0)) if i.v. infusion	73.9
V_4 (L)	179 (2.3%)	× $(Weight/70)^{1.0}$	32.4
F	0.119 (5.9%)	× $(Dose/200)^{-0.554}$ if p.o. × 0.390 if p.o. with food × 1.23 if tablets × 0.310 if TP-434-010 (cUTI)	36.9
K_a (1/hr)	0.386 (5.6%)	× 1.28 if with food	10.0
T_{lag} (hr)	0.807 (1.8%)	× 1.10 if with food × 1.09 if tablets	7.1
Proportional Error	18.0%	NA	NA
Additive Error (ng/mL)	1.24	NA	NA

Source: Adapted from Table 9.5.1 of Report TETR-PCS-100.

Goodness-of-fit plots are shown in Figure 6.

Reference ID: 4312284

Figure 6. Goodness-of-fit Plots for TETR-PCS-100.

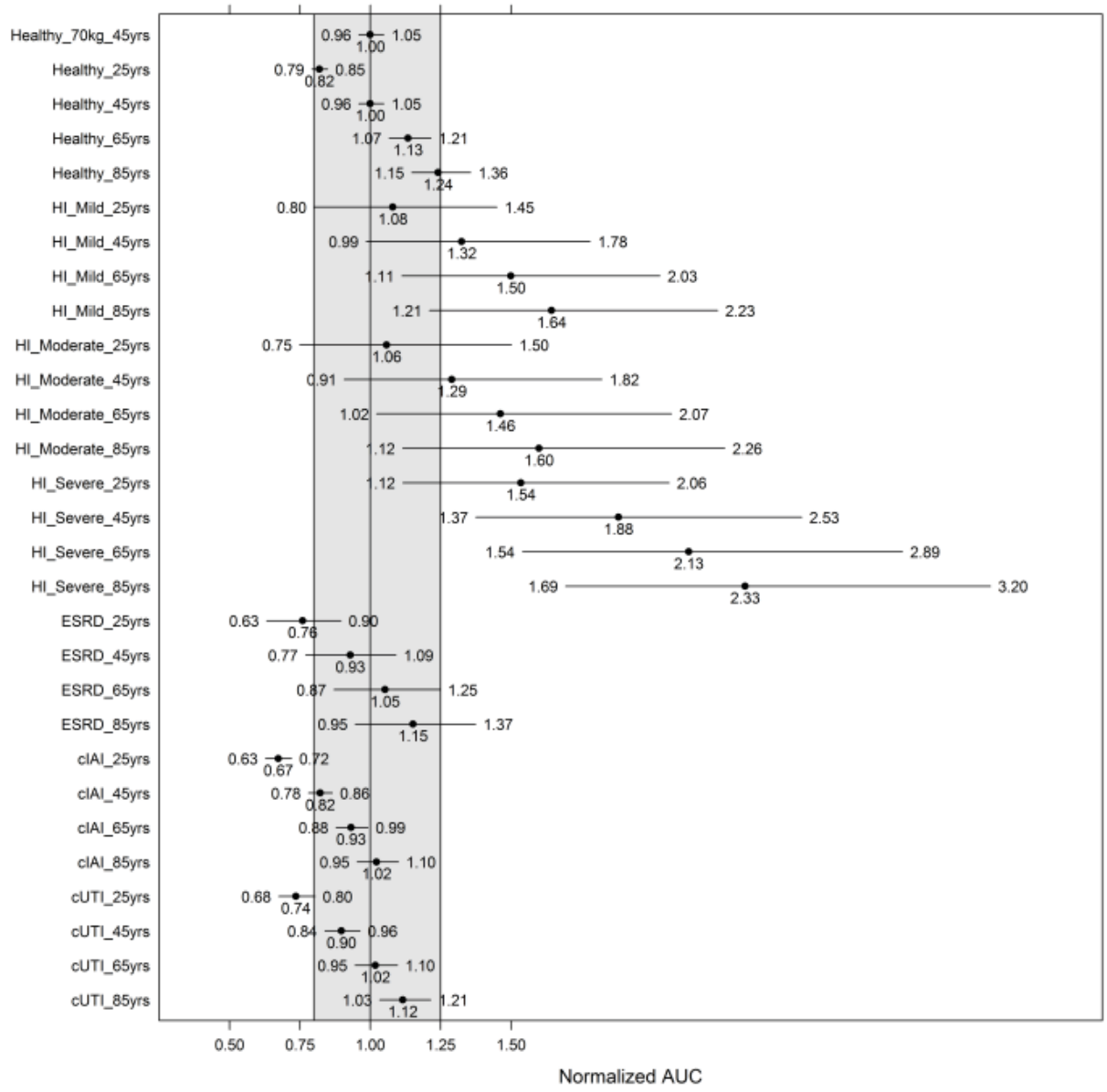


Source: Adapted from Figures 9.5.1 and 9.5.2 in Report TETR-PCS-100

The Sponsor generated the forest plot shown in Figure 7 to assess the effects of covariates on the AUC.

Reference ID: 4312284

Figure 7. Mean Ratios and 95% CI of Covariate Effects on AUC of Eravacycline



Source: Adapted from Figure 9.5.4 in Report TETR-PCS-100.

Intrinsic Factors:

Age

Age was found to be a significant covariate on CL. However, changes in age do not affect the AUC by more than 25% from the reference age of 45 years as shown in Figure 7. In addition, a wide age range of patients was enrolled in the Phase 2 and 3 studies: mean of 53 years, standard deviation of 18 years. There did not appear to be a significant change in exposure or efficacy based on age. Thus, age does not appear to be a clinically significant covariate.

Reference ID: 4312284

Sex
Sex was found to be a significant covariate on V2. However, since there is no effect of sex on CL, there is no expected change on AUC.

Race
Race was not found to be a significant covariate in the PPK model. No changes in PK are expected based on race.

Renal Impairment
Presence of ESRD was found to be a significant covariate on CL. However, the change in AUC is less than 10% in patients with ESRD relative to patients with normal renal function of the same age. Thus, there is no clinically significant difference.

Hepatic Impairment
The Applicant analyzed the effect of hepatic impairment on CL as shown in Table 145. In the Applicant's analysis, the hepatic impairment covariate effect was only based on PK data from the dedicated hepatic impairment study. Relative to healthy volunteers, there was a decrease in CL in patients with hepatic impairment with larger decreases in CL for more severe hepatic impairment. Because patients with hepatic impairment were also included in Phase 2 and 3 studies as shown Table 146, this reviewer analyzed the effect of hepatic impairment on CL in those patients.

Table 146. Baseline Liver Function in Patients in the cIAI Phase 2 and Phase 3 Trials.

Parameter	Eravacycline 1.0 mg/kg q12h IV N=576	Eravacycline 1.5 mg/kg q24h IV N=53	Comparators[a] N=547
Hepatic Impairment, n (%)			
Child-Pugh Class A	418 (72.6)	33 (62.3)	382 (69.8)
Child-Pugh Class B	77 (13.4)	12 (22.6)	84 (15.4)
Child-Pugh Class C	0	0	0
Missing	81 (14.1)	8 (15.1)	81 (14.8)
AST and/or ALT > 2xULN	56 (9.7)	3 (5.7)	55 (10.1)
AST and ALT ≤ 2xULN	483 (83.9)	42 (79.2)	457 (83.5)
Missing	37 (6.4)	8 (15.1)	35 (6.4)

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CrCl=creatinine clearance; ESRD=end-stage renal disease; max=maximum; min=minimum; q12h=every 12 hours; q24h=every 24 hours; SD=standard deviation; ULN=upper limit of normal.

a Comparators include Ertapenem and Meropenem

Source: Adapted from Table 6 in the Summary of Clinical Safety.

Reviewer's Analysis

Reference ID: 4312284

As discussed previously, the objectives of this analysis were to update the model with the combined datasets from TETR-PCS-100 and ICPD-0380-1 and to incorporate the effect of hepatic impairment on PK for subjects outside of the dedicate hepatic impairment study to form a "Uni" model.

Hepatic impairment was assessed using the Child-Pugh classification. The covariate effect was modeled as a parameter on CL. This parameter represented the CL of patients with moderate hepatic impairment relative to patients with normal liver function or mild hepatic impairment that were not in the dedicated hepatic impairment study. NONMEM and R were used primarily for this analysis.

Table 147 shows the results of estimation of the reviewer's model compared to the Applicant's model.

Table 147: Comparison of PPK Parameter Estimates in the Applicant's Model and the Reviewer's Uni Model.

	TETR-PCS-100 Model (as run by Reviewer)			Reviewer Updated Model		
Parameter	**Theta**	**Theta RSE**	**CV (%)**	**Theta**	**Theta RSE**	**CV (%)**
CL (L/hr)	10.1	3.50%	31.8	9.83	6.30%	46.9
V2 (L)	15.5	7%	31.6	15.8	7.20%	31.6
Q3 (L/hr)	33.1	8.50%	55.1	32.9	10.60%	64.7
V3 (L)	58.9	3.30%	31.6	52.4	3.20%	31.6
Q4 (L/hr)	13.3	7%	66	14.1	8.50%	74.1
V4 (L)	179	2.30%	31.6	172	2.20%	31.6
Ka (1/hr)	0.386	5.60%	10	0.397	6.50%	10
Tlag (hr)	0.807	1.80%	7.1	0.794	1.80%	7.1
F1	0.119	5.90%	35.6	0.11	6%	35.2
Food_F1	-0.942	3.20%		-0.935	3.50%	
Food_Tlag	0.095	0%		0.095	0%	
Food_Ka	0.249	38.80%		0.188	59%	
Tabl_F1	0.206	5.70%		0.2	7%	
Tabl_Tlag	0.085	0%		0.085	0%	
Tabl_Ka	0			0		
Dose_F1	-0.554	24%		-0.578	23.20%	
cUTI_F1	-1.17	10.10%		-1.05	12.10%	
STUDHI_REF_CL	1.02	18.80%		1.03	39.60%	
HEP_GR1_CL	-0.28	88.60%		-0.276	192.40%	
HEP_GR2_CL	-0.252	88.50%		-0.254	190.20%	
HEP_GR3_CL	-0.637	37.70%		-0.673	80.10%	
STUDHI_REF_V2	0.907	17.30%		0.832	26.40%	
STUDRI_REF_CL	0.829	39.80%		0.849	81.20%	
REN_GR1_CL	0.0707	640.70%		0.0622	1640%	
STUDRI_REF_V2	0.791	26.40%		0.744	31.70%	
cIAI_CL	0.199	20.50%		0.193	35.70%	
cIAI_V2	-0.812	16.70%		-1.34	8.10%	
cUTI_CL	0.11	55.50%		0.152	76.30%	
cUTI_V2	0.404	24.80%		0.407	25.80%	

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DoseIV_Q3	-0.274	51.50%		-0.278	65.10%	
DoseIV_Q4	-0.24	53.80%		-0.239	65.30%	
Age_CL	-0.335	11.10%		-0.347	13.50%	
Sex_V2	0.184	42.70%		0.13	58.50%	
clAI_Q3	0.491	18.10%		0.453	24.50%	
clAI_Q4	0.659	12%		0.733	12.70%	
Food_Q3	1.91	15.80%		1.95	15.80%	
Food_Q4	0.686	33.20%		0.634	36.80%	
HEP_MOD_CL				-0.098	59.30%	
Proportional Error	0.0325			0.0395		
Additive Error	1.53			0.813		
Objective Function Value	57829.124			68658.443		
Individuals	736			979		
Observations	6775			7627		

X_Y: effect of covariate X on PK parameter Y, STUDHI/STUDRI: describe unique study effects on PK in the hepatic impairment and renal impairment studies.
Source: Reviewer's Table.

Reviewer Comment: The objection function value is higher in the reviewer's model compared to the Applicant's model. However, they are not directly comparable because the reviewer's model includes more individuals and observations.

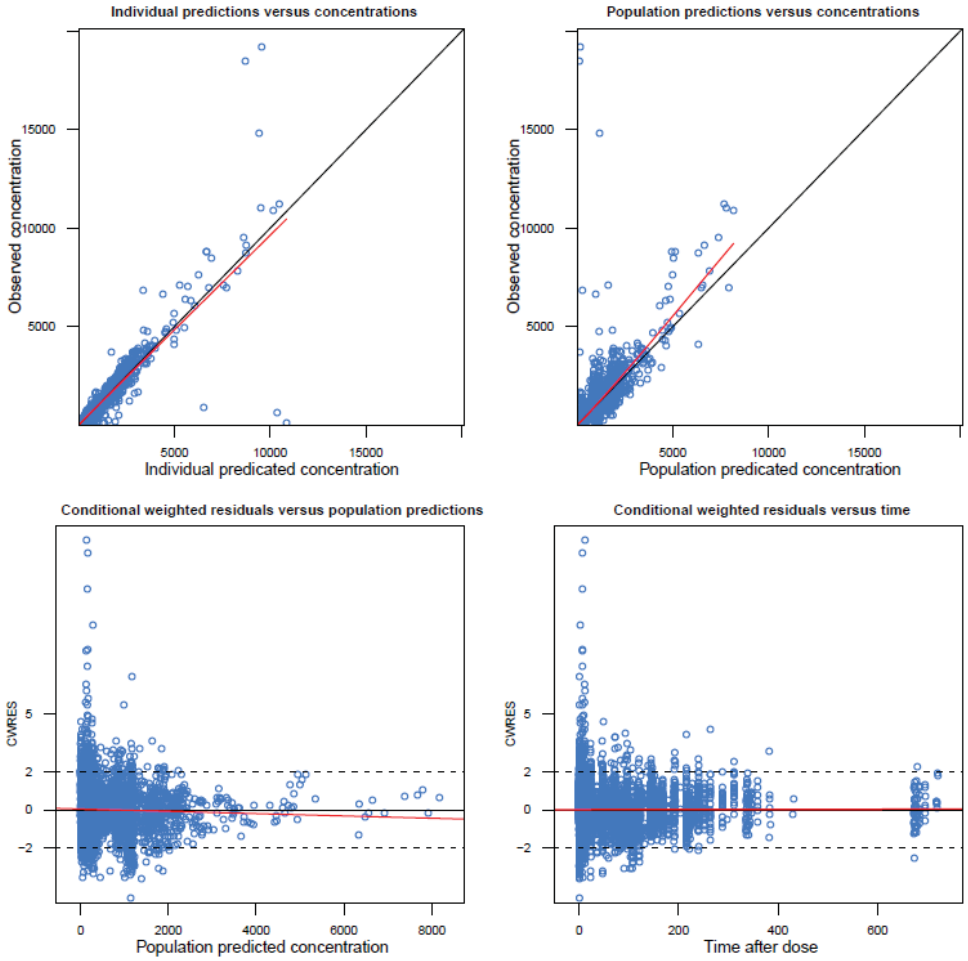
The reviewer's model used the same structure as TETR-PCS-100 with three compartments and allometric scaling on volume and clearance parameters. Most parameter values are not significantly different from the parameter values in TETR-PCS-100 as shown in Table 147. The major difference is the presence of the covariate effect of moderate hepatic impairment on CL relative to normal liver function or mild hepatic impairment on CL. After estimation, this covariate effect was equal a 9.3% decrease in CL in patients with moderate renal impairment.

Reviewer Comment: The effect of hepatic impairment on CL in this reviewer's analysis for the Phase 2 and 3 studies is lower than the value estimated in PPK model TETR-PCS100, 22.3% lower CL, from the dedicated hepatic impairment study. However, the data for patients that were not in the dedicated HI trial did not separate patients with normal hepatic function and patients with mild hepatic function. This could dilute the covariate effect of hepatic impairment. An additional limitation of this analysis is that no patients with severe hepatic impairment were included in the Phase 2 or 3 studies. As such, the PPK analysis provides limited extra supportive PK information on these subpopulations.

The goodness of fit of the reviewer's updated model is shown in Figure 8.

Reference ID: 4312284

Figure 8. Goodness-of-fit Plots for the Uni Model.

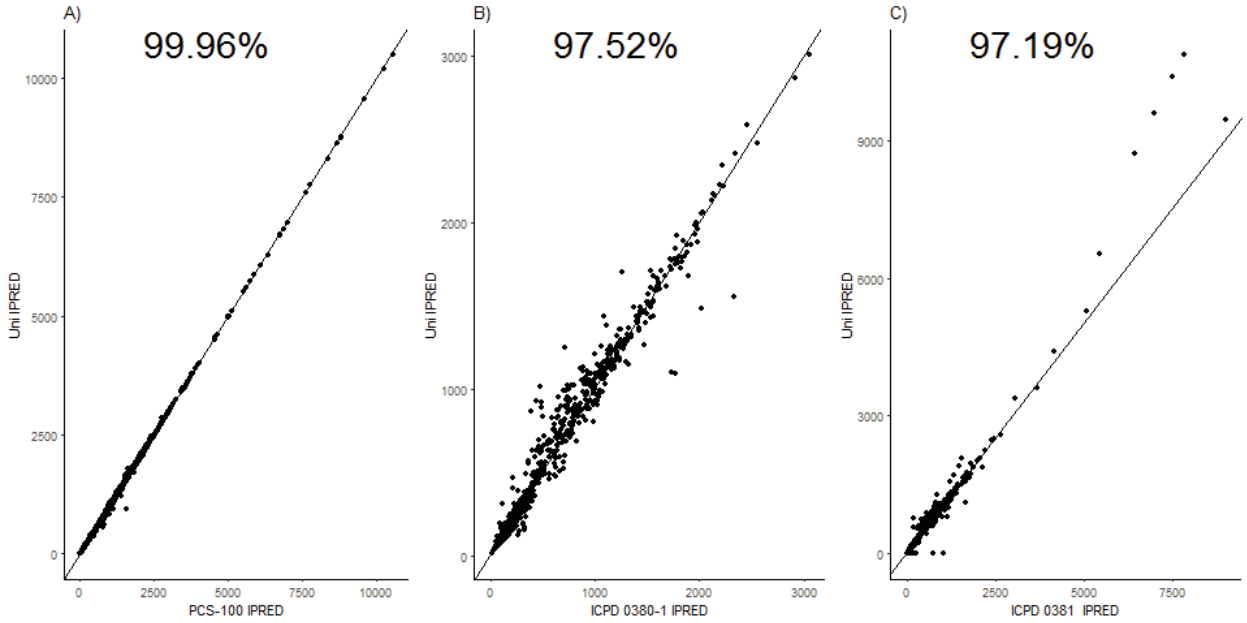


Source: Reviewer's Figure.

The correlation between the IPREDs of the updated model and the Applicant's models are shown in Figure 9. For the purposes of this graphic, "ICPD 0381" refers to the application of model ICPD 0380-1 to fit the data generated in Phase 3 Study TP-434-025.

Reference ID: 4312284

Figure 9: Comparison of IPRED Estimates Between Reviewer's Uni Model (Uni) Vs A) TETR-PCS-100 (PCS-100), B) ICPD 00380-1, and C) ICPD 0381 with Corresponding Values of R^2.



Source: Reviewer's Figure.

Reviewer Comment: Due to the similarity between the models, the Applicant's PPK model is acceptable for interpolation of eravacycline exposure for the exposure-response analysis.

Addendum:
After the late-cycle meeting, the Applicant submitted an additional PK model and associated dataset in order to support a proposed dose adjustment in patients receiving concomitantly a strong CYP 3A inducer. The dataset included data from 2 drug-drug interaction studies: TP-434-016 and TP-434-020 in which itraconzole and rifampin, respectively, were concomitantly administered with eravacycline in healthy volunteers.

This reviewer found that the Applicant's population PK model misspecified the parameter representing CYP 3A4 induction of CL on patients administered oral ERV and IV ERV. This parameter did not account for the inducible first-pass effect that oral ERV undergoes but IV ERV does not. Consequently, this reviewer updated the model to include parameter effects of the CYP inducer on both bioavailability and clearance. The Applicant originally estimated that a strong CYP3A inducer increases ERV CL by 93% while model 9a estimated the same effect to have a value of 74%. Model 9a also estimated that a strong CYP3A inducer decreases oral bioavailability of eravacycline by 42.3% while the Applicant did not originally estimate this parameter.

15.3.3 Exposure-Response Analysis

Reference ID: 4312284

Efficacy – Clinical or Microbiological Response

The Applicant assessed the PK-PD relationship for efficacy as measured by clinical or microbiological response in a logistic regression. Efficacy was greater than 90% at the End-of-Therapy (EOT), Test-of-Cure (TOC), and Follow-Up (FU) visits in patients in the Microbiologically Evaluable (ME) subpopulations of the Phase 2 and 3 trials as displayed in Table 148.

Table 148. Response Rate for Efficacy Endpoints in the Phase 2 and 3 Studies.

Analysis population	Assessment visit	Percent success (n/N) by analysis population					
		Phase 3			Phase 2 and 3 pooled		
		Investigator-defined clinical response	Sponsor-defined clinical response	Microbiological response	Investigator-defined clinical response[a]	Sponsor-defined clinical response[a]	Microbiological response[a]
All patients	EOT	96.0 (358/373)	96.0 (358/373)	96.0 (360/375)	96.5 (436/452)	96.2 (435/452)	96.3 (437/454)
	TOC	94.9 (333/351)	94.9 (333/351)	95.2 (336/353)	95.5 (405/424)	95.1 (405/426)	95.3 (410/430)
	FU	93.7 (326/348)	93.7 (326/348)	–	–	–	–
Patients with Enterobacteriaceae	EOT	94.9 (263/277)	94.9 (263/277)	95.3 (265/278)	95.6 (325/340)	95.3 (324/340)	95.6 (326/341)
	TOC	93.8 (241/257)	93.8 (241/257)	94.6 (244/258)	94.6 (298/315)	94.0 (298/317)	94.7 (303/320)
	FU	92.1 (234/254)	92.1 (234/254)	–	–	–	–

Source: Adapted from Table 7 in Report ICPD 0381.

A summary of PK parameters for patients in the Phase 2 and 3 trials is shown in Table 149.

Table 149. Summary Statistics for PK for ME-Patients in the Phase 2 and 3 Trials.

Variable	Analysis population							
	Phase 3				Phase 2 and 3 pooled			
	All patients (n = 375)		Patients with Enterobacteriaceae (n = 278)		All patients (n = 454)		Patients with Enterobacteriaceae (n = 341)	
	Median or $MIC_{50/90}$	Min, Max	Median or $MIC_{50/90}$	Min, Max	Median or $MIC_{50/90}$	Min, Max	Median or $MIC_{50/90}$	Min, Max
Day 1 free-drug AUC (mg•h/L)	1.165	0.51, 3.424	1.168	0.51, 3.424	1.131	0.272, 3.424	1.132	0.272, 3.424
MIC (µg/mL)	0.12/0.5	0.002, 8	0.25/1	0.06, 2	0.25/0.5	0.002, 8	0.25/0.5	0.06, 2
Day 1 free-drug AUC:MIC ratio	7.441	0.148, 634.4	5.47	0.469, 38.56	6.533	0.148, 634.4	4.975	0.279, 38.56

Note: For Day 1 free-drug AUC or AUC:MIC ratio, median values are reported. For MIC, MIC_{50} and MIC_{90} values are reported.

Reference ID: 4312284

Source: Adapted from Table 8 in Report ICPD 0381.

Table 150 shows the results of the statistical analyses of clinical and microbiological response against free-drug AUC:MIC (FAUC:MIC), which was analyzed as a continuous covariate and analyzed as 2, 3, and 4 quantiles. The calculation of free drug was based on Study (b) (4) -001 as described in the Appendix.

Table 150. Summary of Relationships Between the Probability of Achieving Efficacy Endpoints and Free-drug AUC:MIC Ratio in Patients in the Phase 2 and 3 Trials.

Assessment visit	Efficacy endpoint	P-values by form of the Day 1 free-drug AUC:MIC ratio[a]							
		All patients				Patients with Enterobacteriaceae			
		Continuous	Quartiles	Three-group	Two-group	Continuous	Quartiles	Three-group	Two-group
EOT	Investigator-defined clinical response	0.26	0.68	0.016 (V)	0.26	0.96	0.94	0.027 (V)	0.28
	Sponsor-defined clinical response	0.2	0.64	0.017 (V)	0.18	0.78	0.98	0.04 (V)	0.37
	Microbiological response	0.53	0.55	0.017 (V)	0.18	0.3	>0.99	0.018 (V)	0.21
TOC	Investigator-defined clinical response[b]	0.35	0.95	0.014 (V)	0.14	0.52	0.79	0.017 (V)	0.13
	Sponsor-defined clinical response[b]	0.26	0.91	0.024 (V)	0.28	0.78	0.9	0.043 (V)	0.27
	Microbiological response[b]	0.56	0.81	0.006 (V)	0.28	0.74	0.95	0.011 (V)	0.26

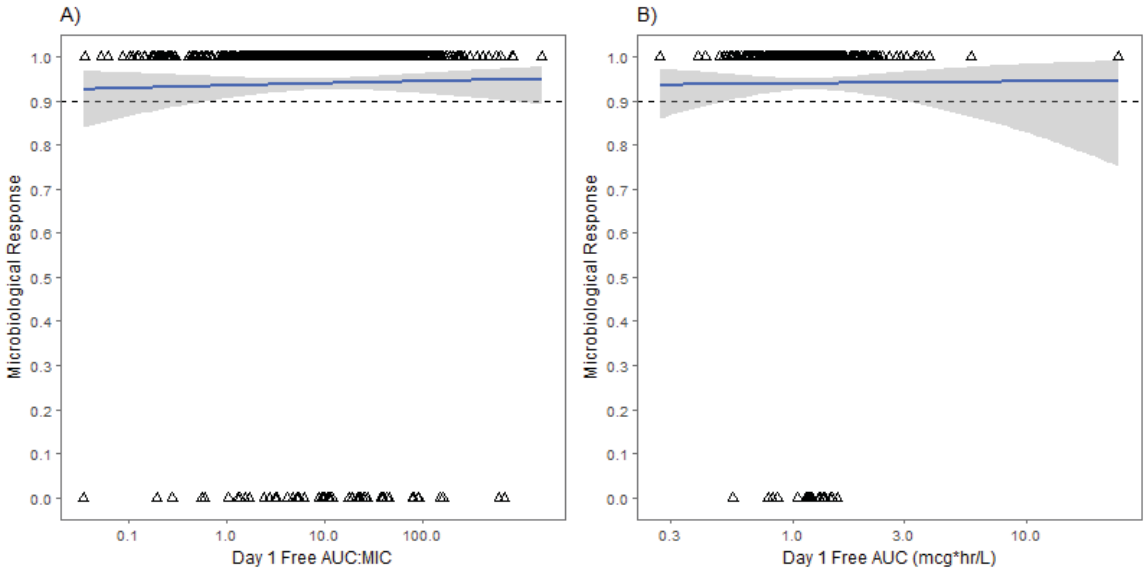
Source: Adapted from Table 10 in Report ICPD 0381.

In all patients and patients with Enterobacteriaceae, all metrics of clinical response were only significant when FAUC:MIC was analyzed as a three-group (three-quantile) variable. The "V" signifies that efficacy is highest in the lowest and highest groups of FAUC:MIC.

Figure 10 displays the relationship between exposure and microbiological response when analyzed as single variables.

Reference ID: 4312284

Figure 10. Relationship between Exposure as A) Day 1 FAUC:MIC and B) Day 1 Free AUC and Microbiological Response at the Test-of-Cure Visit.

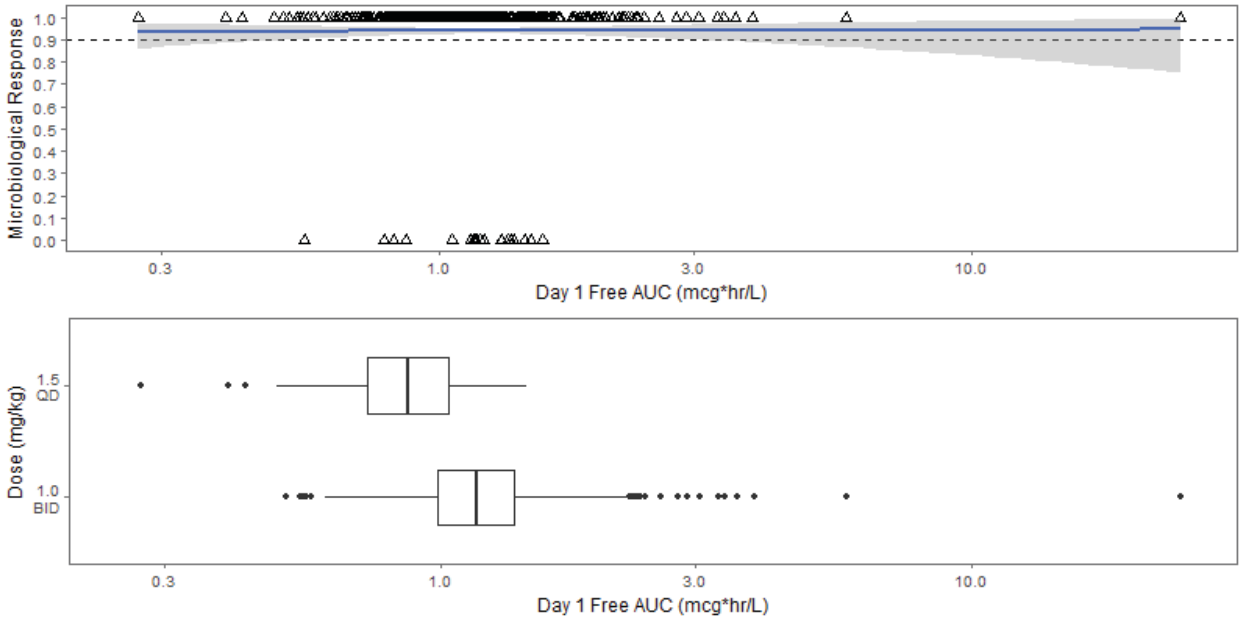


Source: Reviewer's Figure.

Reviewer Comment: This reviewer analyzed the data of clinical and microbiological response in the Phase 2 and 3 studies using a logistic regression model with a full covariate approach of clinically relevant covariates including age, infection type, albumin, Acute Physiology and Chronic Health Evaluation (APACHE) score, BMI, ethnicity, pathogen group, and sex. Neither Free Day 1 AUC/MIC nor Free Day 1 AUC as continous variables were significant predictors of microbiological response. In addition, there was a high correlation between microbiological response and clinical response at each visit. Overall, there does not appear to be a significant relationship between exposure and efficacy at the 1 mg/kg BID and the 1.5 mg/kg QD doses. As shown in Figure 11, both doses are on the flat part of the exposure-response relationship.

Reference ID: 4312284

Figure 11. Comparison of Exposure-Response Relationship for Efficacy and Dose.



Source: Reviewer's Figure.

Efficacy – Time to Fever Resolution

The Applicant assessed the PK-PD relationship for efficacy as measured by time to fever resolution. The patients that were evaluable for this analysis are shown in Table 151.

Table 151. Patients Evaluable in the PK-PD Analysis of Fever Resolution.

Population	Number of patients evaluable for PK-PD analyses[a]			
	Study TP-434-P2-cIAI-1	Study TP-434-008	Study TP-434-025	Total
Patients who received eravacycline in the CE-EOT population	96	252	239	587
Patients who received eravacycline in the analysis population of interest with PK data	94[b]	250[c]	233[d]	565
Patients who received eravacycline in the analysis population of interest with PK data and had a temperature >38°C at baseline	51	86	82	219

a. Patients in the ITT population who received eravacycline in Studies TP-434-P2-cIAI-1, TP-434-008, and TP-434-025 are 109, 270, and 250, respectively.
b. Patients TP-434-P2-cIAI-1-030-2059 and TP-434-P2-cIAI-1-030-2067 were in the CE-EOT population but did not have PK data.
c. Patients TP-434-008/008-094-0002 and TP-434-008/008-102-0015 were in the CE-EOT population but did not have PK data.
d. Six patients (TP-434-025/025-336-0008, TP-434-025/025-344-0007, TP-434-025/025-344-0008, TP-434-025/025-347-0009, TP-434-025/025-347-0010, TP-434-025/025-347-0014) were in the CE-EOT population but did not have PK data.

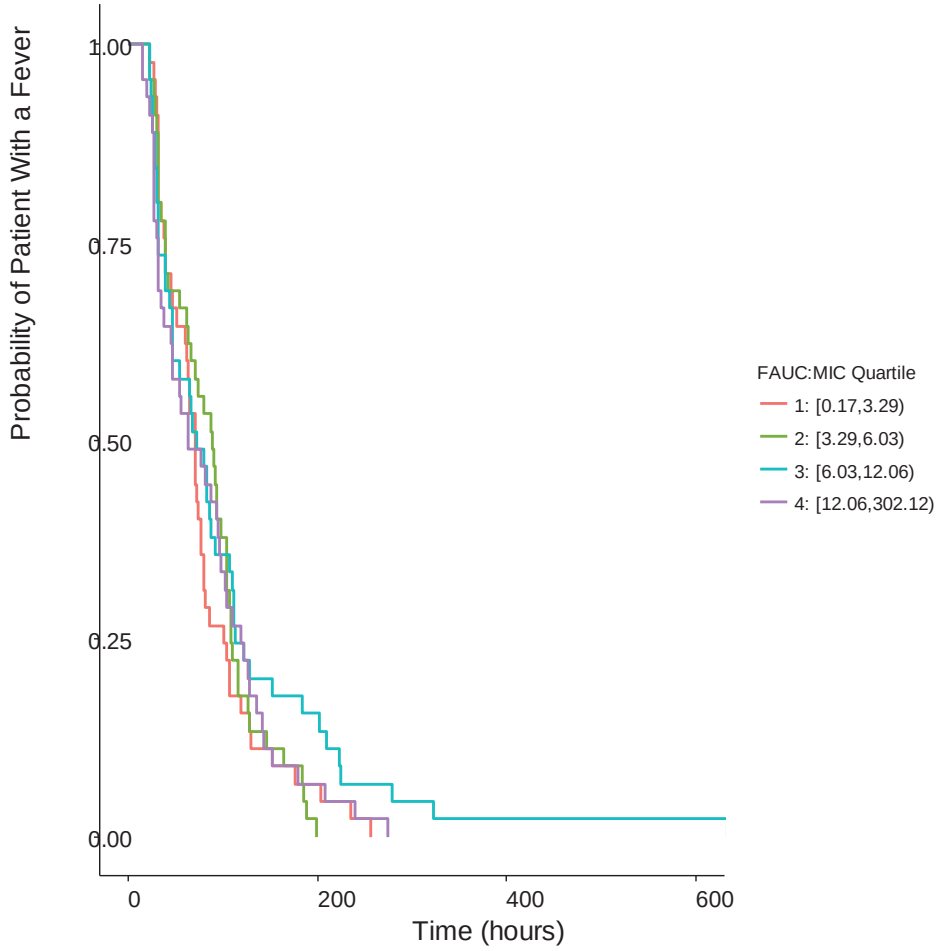
Source: Adapted from Table 11 of Report ICPD 0381.

Reference ID: 4312284

The Applicant did not find a consistent trend in exposure and time to fever resolution among their Phase 2 and 3 studies.

Reviewer Comment: This reviewer analyzed the relationship between exposure as Day 1 FAUC:MIC or Day 1 FAUC and time to fever resolution. Figure 12 shows a Kaplan-Meier plot of time to fever resolution grouped by quartiles of Day 1 FAUC:MIC. There appears to be no difference between each AUC:MIC quartile. In addition, this reviewer analyzed the data using a Cox proportional hazards model with a full covariate approach using clinically relevant covariates such as age, albumin, Apache score, BMI, ethnicity, sex, and ideal body weight. Neither Day 1 FAUC:MIC nor Day 1 FAUC was a significant predictor of time to fever resolution. Furthermore, the analysis appears to be confounded by the administration of antipyretic medication to approximately 50% of patients.

Figure 12. Relationship between Day 1 FAUC:MIC and Time to Fever Resolution.



Source: Reviewer's Figure.

Safety – Nausea and Vomiting

Reference ID: 4312284

The Applicant investigated whether there was an exposure- response relationship for nausea and vomiting. Table 152 shows the results of univariate analyses between total-drug exposure (C_{min}, C_{max}, or AUC) and nausea/vomiting.

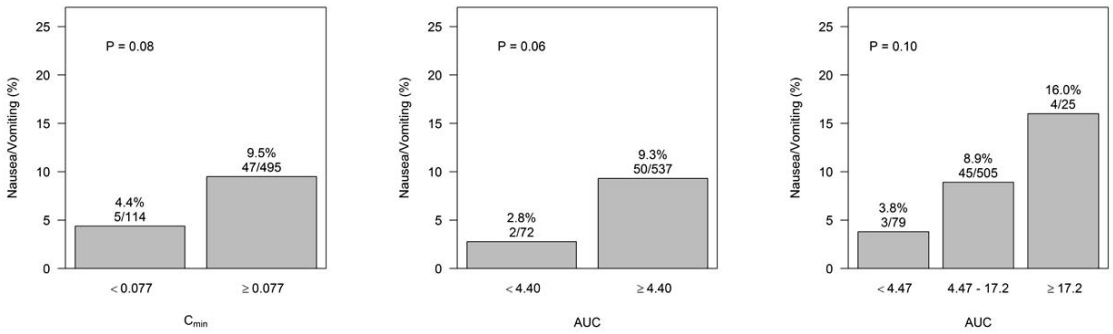
Table 152. Univariate analyses of Total-drug Exposure (C_{min}, C_{max}, or AUC) and Nausea/Vomiting.

Total-drug exposure	P-values by form of the total-drug eravacycline exposures[a]							
	Nausea/vomiting				Moderate nausea/vomiting			
	Continuous	Quartiles	Three-group	Two-group	Continuous	Quartiles	Three-group	Two-group
C_{min}	0.88	0.71	0.30	0.08 (/)	0.85	0.82	0.21	0.23
C_{max}	0.95	0.67	0.12	0.21	0.63	0.24	0.028 (∩)	0.13
AUC	0.95	0.53	0.10 (/)	0.06 (/)	0.76	0.64	0.13	0.36

The "/" symbol signifies that the incidence of nausea and vomiting increased with increasing exposure. The inverted U symbol signifies that the incidence of nausea and vomiting was highest in the middle tertile of exposure relative to the upper and lower tertiles of exposure.
Source: Adapted from Table 17 of ICPD 0381.

C_{min} and AUC were significant predictors of nausea/vomiting when analyzed as a two-group variable (C_{min} and AUC) and as a three-group variable (AUC). In both cases, increased exposure was predictive of a higher incidence of nausea and vomiting. This is visualized in the Figure 13.

Figure 13. Relationships Between Nausea/Vomiting and C_{min} as a 2-group Variable, AUC as a 2-group Variable, and AUC as a 3-group Variable.



Source: Adapted from Figures 7 and 8 in ICPD 0381.

In a multivariate analysis, height, albumin, BMI, and age were significant predictors of nausea/vomiting as shown in Table 153.

Reference ID: 4312284

Table 153. Multivariate Analysis of the Relationship Between Nausea/Vomiting and AUC as a 2-group Variable.

Independent variable	Parameter estimate (SE)	Odds ratio (95% CI)	Likelihood ratio P-value
Height (per 1 m increase)	-0.0419 (0.0177)	0.959 (0.926, 0.993)	0.016
Albumin (per of 1 g/dL increase)	-0.7336 (0.2325)	0.480 (0.304, 0.758)	0.002
BMI (per 1 kg/m^2 increase)	0.0632 (0.0265)	1.065 (1.011, 1.122)	0.016
Age (per year increase)	-0.0202 (0.0093)	0.980 (0.962, 0.998)	0.03
AUC ≥ 4.40 mg•h/L	0.9581 (0.7510)	2.607 (0.596, 11.393)	0.15

Number of patients=594; number of events=50.

Source: Adapted from Table 19 of ICPD 0381 Report.

Reviewer Comment: The results of the model in Table 153 demonstrate that there is a non-statistically significant trend of increased AUC causing increase incidence of nausea/vomiting. Increases in BMI also predicted a higher incidence of nausea/vomiting while increases in height, albumin, and age predicted a lower incidence of nausea/vomiting.

Although the relationship does not reach statistical significance in the univariate or multivariate analyses, there does appear to be a clear relationship between AUC and incidence of nausea/vomiting. Total-drug AUC is the most predictive exposure metric for nausea/vomiting because there were trends towards significance both as a 2-group and as a 3-group variable.

Safety – Laboratory Values: Amylase, aPTT, INR, Lipase

The Applicant investigated whether there were exposure-response relationships for the laboratory values of amylase, aPTT, INR, and lipase. These relationships were assessed using repeated measures multiple linear regression analyses. Exposure was measured as 24-hour prior C_{max}, C_{min}, or AUC untransformed or square-root transformed. Models were selected based on the AIC. The multivariate models with the best fit are shown in the tables below. C_{max} was a significant predictor of amylase values as shown in Table 154. C_{min} was a significant predictor of lipase, aPTT, and INR values as shown in Table 155, Table 156, and Table 157, respectively.

Reference ID: 4312284

Table 154. Final Repeated Measures Multiple Linear Regression Model for Amylase.

Variable	Estimate[a]	SE	Means ratio (95% CI)[a]	P-value
Intercept	7.0005	0.3360	-	-
Race (white)	-0.5059	0.1496	0.704 (0.575, 0.863)	<0.001
CLcr (per 1 mL/min/1.75 m^2 increase)	-0.0056	0.0012	0.996 (0.995, 0.998)	<0.001
Albumin (per 1 g/dL increase)	0.0281	0.0601	1.02 (0.940, 1.11)	0.64
SQRT (Time in days)	0.0951	0.0372	1.07 (1.02, 1.12)	0.011
SQRT (Prior 24-hour C_{max})	0.4492	0.1370	1.37 (1.13, 1.64)	0.001
Age (per year increase)	-0.0074	0.0027	0.995 (0.991, 0.998)	0.006
BMI (per 1 unit increase)	-0.0131	0.0060	0.991 (0.983, 0.999)	0.03
Race and SQRT (24-hour prior C_{max}) interaction	-0.2411	0.0751	0.846 (0.764, 0.937)	0.001
CLcr and SQRT (24-hour prior C_{max}) interaction	0.0020	0.0005	1.00 (1.00, 1.00)	<0.001
Albumin and SQRT (24-hour prior C_{max}) interaction	-0.2037	0.0306	0.868 (0.833, 0.905)	<0.001
SQRT (Time in days) and SQRT (24-hour prior C_{max}) interaction	0.1525	0.0331	1.11 (1.06, 1.16)	<0.001

a. All parameter estimates and means ratios for continuous independent variables are with respect to 1 unit increases in the respective variables and should not be compared for relative magnitudes

Source: Adapted from Table 25 of ICPD 0381 Report.

Reviewer Comment: The race variable is calculated as the probability of laboratory value increase in white patients relative to non-white patients. Other than the demographic factors, both C_{max} and time in days appear to result in increased amylase. There is also an interaction term between time and C_{max} that signified a synergistic increase in amylase with increased time and C_{max}.

Reference ID: 4312284

Table 155. Final Repeated Measures Multiple Linear Regression Model for Lipase.

Variable	Estimate[a]	SE	Means ratio (95%CI)[a]	P-value
Intercept	4.2845	0.3808	-	-
Study TP-434-008	0.1407	0.1226	1.10 (0.933, 1.30)	0.25
Study TP-434-025	0.4375	0.1251	1.35 (1.14, 1.61)	<0.001
Age (per year increase)	-0.00002	0.0032	1.00 (0.996, 1.00)	0.99
Race (white)	-0.2254	0.1718	0.855 (0.677, 1.08)	0.19
CLcr (per 1 mL/min/1.75 m^2 increase)	-0.0005	0.0013	1.00 (0.998, 1.00)	0.69
Albumin (per 1 g/dL increase)	-0.0169	0.0647	0.988 (0.905, 1.08)	0.79
SQRT (Time in days)	0.1242	0.0336	1.09 (1.04, 1.14)	<0.001
SQRT (Prior 24-hour C_{min})	6.3614	0.5434	82.2 (39.3, 172)	<0.001
BMI (per 1 unit increase)	0.0139	0.0066	1.01 (1.00, 1.02)	0.037
Study TP-434-008 and SQRT (24-hour prior C_{min}) interaction	-0.7376	0.2082	0.600 (0.452, 0.796)	<0.001
Study TP-434-025 and SQRT (24-hour prior C_{min}) interaction	-1.1074	0.2143	0.464 (0.347, 0.621)	<0.001
Age and SQRT (24-hour prior C_{min}) interaction	-0.0199	0.0044	0.986 (0.980, 0.992)	<0.001
Race and SQRT (24-hour prior C_{min}) interaction	-1.4967	0.2801	0.354 (0.242, 0.518)	<0.001
CLcr and SQRT (24-hour prior C_{min}) interaction	-0.0066	0.0018	0.995 (0.993, 0.998)	<0.001
Albumin and SQRT(24-hour prior C_{min}) interaction	-0.6866	0.0895	0.621 (0.550, 0.702)	<0.001
SQRT (Time in days) and SQRT (24-hour prior C_{min}) interaction	0.5116	0.0756	1.43 (1.29, 1.58)	<0.001

a. All parameter estimates and means ratios for continuous independent variables are with respect to 1 unit increases in the respective variables and should not be compared for relative magnitudes

Source: Adapted from Table 26 of ICPD 0381 Report.

Reviewer Comment: This model had separate variables for the Phase 3 studies with the Phase 2 study as the reference. The positive regression of lipase on C_{min} appears to be smaller in the Phase 3 trials. There is also an interaction term between time and C_{min} that signified a synergistic increase in lipase with increased time and C_{min}. Lastly, in non-white patients, the

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relationship between C_{min} and lipase appears to have a higher magnitude than in white patients. Thus, elevations in C_{min} in non-white patients are predicted to lead to higher values of lipase than in white patients. However, this may be due to the small sample size of non-white patients (39) relative to white patients (566) administered eravacycline in the Phase 2 and 3 studies included in the dataset.

Table 156. Final Repeated Measures Multiple Linear Regression Model for aPTT.

Variable	Estimate[a]	SE	Means ratio (95%CI)[a]	P-value
Intercept	5.5541	0.0693	-	-
Study TP-434-008	-0.1586	0.0351	0.896 (0.854, 0.940)	<0.001
Study TP-434-025	0.0260	0.0365	1.02 (0.969, 1.07)	0.48
Race (white)	-0.2733	0.0491	0.827 (0.774, 0.885)	<0.001
SQRT (Time in days)	0.0323	0.0104	1.02 (1.01, 1.04)	0.002
Prior 24- hour C_{min}	-0.5604	0.2658	0.678 (0.473, 0.973)	0.035
Sex (male)	0.0459	0.0222	1.03 (1.00, 1.06)	0.0396
Albumin (per 1 g/dL increase)	-0.0961	0.0169	0.936 (0.914, 0.957)	<0.001
Study TP-434-008 and SQRT (24-hour prior C_{min}) interaction	0.5117	0.2003	1.43 (1.09, 1.87)	0.011
Study TP-434-025 and SQRT (24-hour prior C_{min}) interaction	0.4433	0.2031	1.36 (1.03, 1.79)	0.029
Race and SQRT (24-hour prior C_{min}) interaction	-0.6545	0.2523	0.635 (0.451, 0.895)	0.010
SQRT (Time in days) and SQRT (24-hour prior C_{min}) interaction	0.3653	0.0998	1.29 (1.12, 1.48)	0.0003

a. All parameter estimates and means ratios for continuous independent variables are with respect to 1 unit increases in the respective variables and should not be compared for relative magnitudes

Source: Adapted from Table 27 of ICPD 0381 Report.

Reviewer Comment: C_{min} has a negative relationship with aPTT on Day 1. However, the interaction term signifies that the relationship between C_{min} and aPTT shifts to become positive with increasing time. There was also a higher chance of increased aPTT with increased C_{min} in the Phase 3 studies.

Reference ID: 4312284

Table 157. Final Repeated Measures Multiple Linear Regression Model for INR.

Variable	Estimate[a]	SE	Means ratio (95%CI)[a]	P-value
Intercept	1.2387	0.1101	-	<0.001
Race (white)	-0.2023	0.0451	0.869 (0.818, 0.924)	<0.001
Albumin (per 1 g/dL increase)	-0.1780	0.0203	0.884 (0.860, 0.909)	<0.001
SQRT (time in days)	-0.0283	0.0173	0.981 (0.958, 1.00)	0.10
SQRT (Prior 24-hour C_{min})	-1.1081	0.2116	0.464 (0.348, 0.618)	<0.001
Age (per year increase)	-0.0022	0.0008	0.998 (0.997, 1.00)	0.01
Sex (male)	0.0510	0.0209	1.04 (1.01, 1.07)	0.015
CLcr (per 1 mL/min/1.75m^2 increase)	-0.0008	0.0003	0.999 (0.999, 1.00)	0.030
Race and SQRT (24-hour prior C_{min}) interaction	-0.2922	0.1068	0.817 (0.706, 0.944)	0.01
Albumin and SQRT (24-hour prior C_{min}) interaction	0.1658	0.0484	1.12 (1.05, 1.20)	<0.001
SQRT(time in days) and SQRT (24-hour prior C_{min}) interaction	0.4155	0.0542	1.33 (1.24, 1.44)	<0.001

a. All parameter estimates and means ratios for continuous independent variables are with respect to 1 unit increases in the respective variables and should not be compared for relative magnitudes

Source: Adapted from Table 28 of ICPD 0381 Report.

Reviewer Comment: INR appeared to decrease with increasing C_{min} on Day 1. However, the interaction term signifies that the relationship between C_{min} and INR shifts to become positive with increasing time.

Laboratory values were simulated based on the PPK model, linear regression models, and demographic information from the Phase 2 and Phase 3 cIAI trials. This was then used to calculate the probability of patients reaching laboratory values above the upper limit of normal (ULN) or 3 times the ULN as shown in Table 158.

Reference ID: 4312284

Table 158. Percent Probabilities of Laboratory Values > 1x ULN and > 3x ULN among Observed and Simulated Patients

Laboratory variable	Days since start of treatment	Percent probabilities >1x ULN			Percent probabilities > 3x ULN		
		Observed	Simulated		Observed	Simulated	
			Phase 2	Phase 3		Phase 2	Phase 3
Amylase	Baseline	5.85	9.11	9.11	1.03	0.72	0.72
	4	7.82	9.65	9.65	0.21	0.30	0.30
	6	13.02	12.41	12.41	1.30	0.40	0.40
	8	12.23	14.26	14.26	0.72	0.54	0.54
	12	24.60	18.86	18.86	0.79	1.03	1.03
Lipase	Baseline	7.23	8.13	9.24	1.61	1.64	1.84
	4	22.06	32.92	24.57	3.09	4.40	2.87
	6	29.07	41.99	33.51	6.40	5.95	4.20
	8	25.90	41.77	32.48	6.47	6.02	3.83
	12	48.41	47.03	37.93	7.94	7.49	5.01
aPTT	Baseline	19.23	30.24	13.94	0.14	0.00	0.00
	4	16.74	17.43	14.02	0.00	0.00	0.00
	6	26.67	25.62	23.78	0.33	0.02	0.02
	8	25.00	31.43	29.45	0.00	0.00	0.00
	12	29.63	44.42	43.64	0.00	0.00	0.02
INR	Baseline	22.24	29.39	29.39	0.55	0.10	0.10
	4	16.20	23.49	23.49	0.00	0.00	0.00
	6	26.58	35.98	35.98	1.33	0.26	0.26
	8	21.43	45.56	45.56	0.00	0.02	0.02
	12	39.62	67.08	67.08	0.00	0.00	0.00

Source: . Adapted from Table 29 of ICPD 0381 Report.

Reviewer Comment: There was a slight trend toward over-prediction of laboratory values. Only lipase appears to have a significant probability of values above three times the ULN. aPTT and INR showed a trend towards a decrease followed by an increase as was described in the model. The trends in aPTT and INR are difficult to interpret without more information on the patients' medical history and concomitant medications. Many of these patients were above 65 years of age, which increases the likelihood that they were prescribed anticoagulants targeted to increase INR or aPTT. Surgical intervention, which may require discontinuation of anticoagulants, also confounds the results of this analysis of changes in INR and aPTT.

15.3.4 Individual Study Reviews

The following clinical pharmacology related individual studies were reviewed. For clarity and simplicity, only selected data tables and figures from these sub-reviews are indexed in the table of contents.

Study No.	Study Title
TET-R2645	In vitro investigation of eravacycline metabolism and formation of TP-6208
TET-R4680	In vitro investigation of eravacycline and TP-6208 metabolism
8TETRPI	Bidirectional Permeability of TP-434 in MDR1-MDCK Cells

Reference ID: 4312284

Tetraphase-02-12Jun2013	In vitro Interaction Studies of Eravacycline and TP-6208 with human transporters MDR1, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 and MATE2-K
Tetraphase-03-14Jul2014	In vitro Interaction studies of TP-498 with the human transporters MDR1, BCRP, BSEP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 and MATE2-K
(b) (4) **158063**	In vitro Evaluation of TP 034 as an Inhibitor and a Substrate of Human P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1 and MATE2-K transporters
AD09-06	The in vitro Protein Binding of TP-434 and the Blood:Plasma Distribution of TP-434 in Human Blood
(b) (4) **-001**	Protein binding of eravacycline in determined by in vitro microdialysis
TET-R4384	In vitro Protein Binding of Eravacycline in Human Plasma, Serum Albumin and α1-Acid Glycoprotein
(b) (4) **085084**	In vitro Evaluation of TP-434 as an Inhibitor of Human Cytochrome P450 Enzymes
(b) (4) **145065**	In vitro Evaluation of TP-498 as an Inhibitor of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes
(b) (4) **135050**	In vitro Evaluation of TP-6208 as an Inhibitor of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes
(b) (4) **155034**	In vitro Evaluation of TP-034 as an Inhibitor of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes
10TETPP2	Induction of CYP1A2, 2B6, and 3A4 Enzyme Activities in Fresh Human Hepatocytes
(b) (4) **153026**	In vitro Evaluation of TP-034 as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes
(b) (4) **133065**	In Vitro Evaluation of TP-6208 as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes
(b) (4) **143046**	In Vitro Evaluation of Eravacycline and TP-498 as Inducers of Cytochrome P450 Expression in Cultured Human Hepatocytes
TP-434-016	A Phase 1 Open-Label Clinical Study to Assess the Impact of Itraconazole on Eravacycline PK in Healthy Subjects
TP-434-020	A Phase 1, Open-Label Clinical Study to Assess the Impact of Rifampin on Eravacycline PK in Healthy Subjects
TP-434-P1-SAD-1	Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Pharmacokinetics of Single Ascending Doses of TP-434

Reference ID: 4312284

TP-434-P1-MAD-1	Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Pharmacokinetics of Multiple Ascending Dose Regimens of TP-434
TP-434-013	TP-434-013: A Phase 1, Open-Label Study to Assess the Single-Dose Pharmacokinetics of Eravacycline in Subjects with Impaired Hepatic Function and Healthy Subjects
TP-434-014	A Phase 1, Open-Label Study to Assess the Single-Dose Pharmacokinetics of Eravacycline in Subjects with End Stage Renal Disease and Healthy Subjects
TP-434-012 / TETP2989	An Open-Label, Single Dose Study Designed to Assess the Mass Balance Recovery, Metabolite Profile and Identification of Metabolite Structure for [14C]-Eravacycline in Healthy Male Subjects after Oral and Intravenous Dosing

Study No.: TET-R2645

Title: Metabolism of Eravacycline (TP-434) and Formation of TP-6208 by Recombinant Human CYP450 Enzymes and Flavin-Containing Monooxygenases (FMO), and by Liver Microsomes and Hepatocytes from Sprague Dawley Rats, Cynomolgus Monkeys and Humans

Date(s): August 29, 2013 to February 27, 2014
Sponsor: TetraPhase Pharmaceuticals, Inc. Watertown, MA
Testing Facility: (b) (4)

METHODS

The metabolism of eravacycline to the major human metabolite TP-6208 was studied with recombinant human CYP450, Flavin-containing monooxygenase (FMO), liver microsomes, cytosol, mitochondria and hepatocytes from Sprague-Dawley rats, cynomolgus monkeys and humans to identify the enzymes responsible for the production of TP-6208. The chemical inhibitors and their respective concentrations used for CYP reaction phenotyping studies are shown in Table 1. Testosterone was incubated under similar conditions for all three species to demonstrate the metabolic activities of liver microsomes. Known substrates were used as positive controls to demonstrate enzyme activity.

Table 1. Inhibitors Used for CYP450 Reaction Phenotyping Studies

Inhibitor (Concentration)	Supplier	Enzyme inhibited
α-Naphthoflavone (2 µM)	(b) (4)	CYP1A2
Orphenadrine (750 µM)		CYP2B6
Monteleukast (2 µM)		CYP2C8
Sulphaphenazole (10 µM)		CYP2C9
Modafinil (250 µM)		CYP2C19
Quinidine (10 µM)		CYP2D6
Diethyldithiocarbamate (50 µM)		CYP2E1
Ketoconazole (1 µM)		CYP3A4

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RESULTS

Eravacycline was stable in the presence of liver microsomes and hepatocyctes from rats, monkeys and humans. CYP3A4 was the only human CYP450 enzyme capable of forming TP-6208 from eravacycline, with no formation by other CYP isoenzymes. TP-6208 was also formed by FMO-1, FMO-3 and FMO-5. Human liver microsomes showed a higher Km and Vmax than rat liver microsomes for the formation of TP-6208 (Table 2).

Studies with human liver microsomes in the presence and absence of specific CYP450 enzyme inhibitors demonstrated that eravacycline was a substrate of CYP3A4. Formation of TP-6208 was reduced significantly (>85% inhibition) when eravacycline and ketoconazole were used together. The role of CYP3A4 in metabolizing eravacycline was further confirmed by studies conducted with the recombinant CYP3A4 enzyme, where the formation of TP-6208 was much greater after incubation of eravacycline with CYP3A4 and only trace quantities produced by other CYP isoforms. These results were reinforced by another experiment, where TP-6208 formation increased after induction with rifampin, a prototypical inducer of CYP3A4.

The mechanism proposed for the formation of TP-6208 involves an initial N-oxidation of the pyrrolidine nitrogen, mediated by either FMO or CYP3A4, and the formation of an N-oxide metabolite which quickly decomposes to an iminium intermediate capable of an intra-molecular cyclization leading to a stable fused bicyclic ring system (Figure 1).

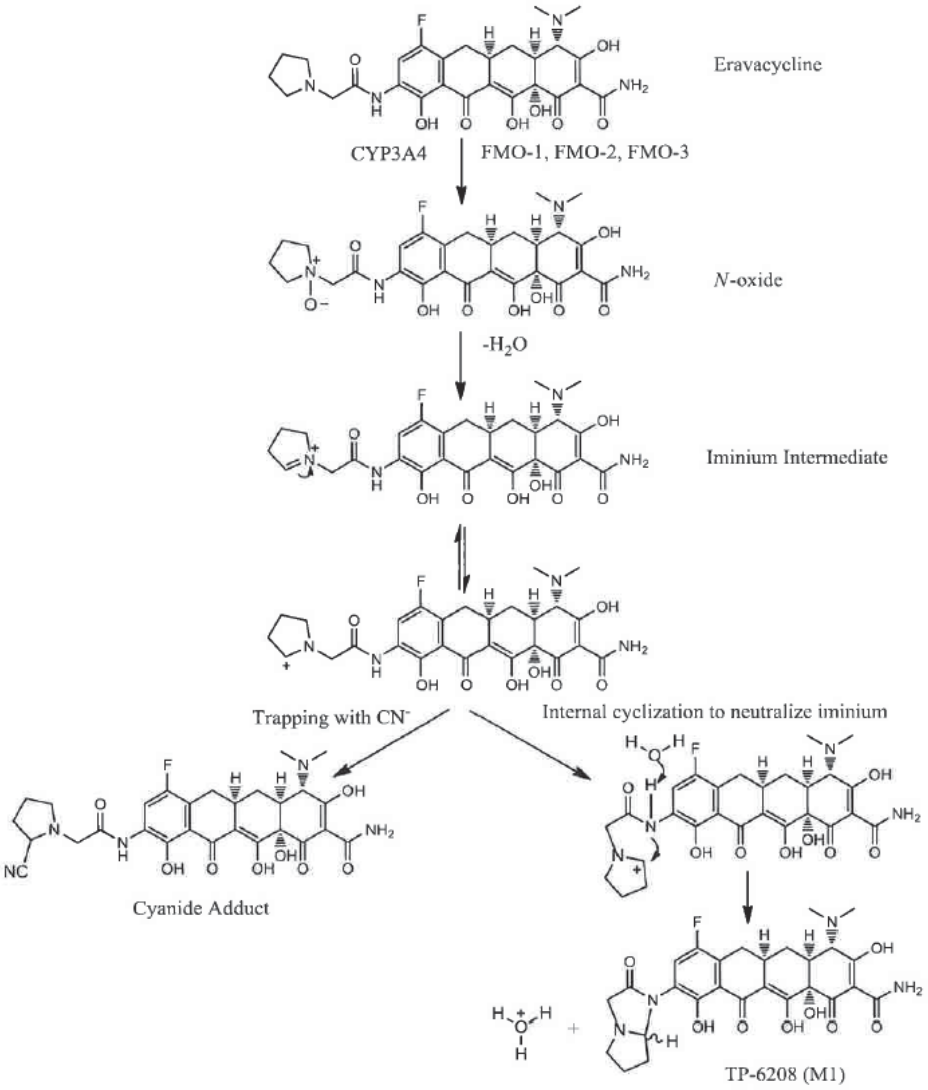
Table 2. Summary of Km and Vmax for the Formation of TP-6208 from Eravacycline Following Incubations in Human and Rat Liver Microsomes

Species	Enzyme kinetic parameters	
Human	K_m (μM)	365.20
	V_{max} (nmol/min/mg)	0.48
Rat	K_m (μM)	92.66
	V_{max} (nmol/min/mg)	0.10

Data are mean of duplicate sample analyses

Figure 1. Proposed Mechanism for the Formation of TP-6208 from Eravacycline

Reference ID: 4312284



Study No.: TET-R4680

TET-R4680: Metabolism of Eravacycline (TP-434) and TP-6208 by In Vitro Metabolizing Systems including Microsomes, S9 Fractions and Recombinant Enzymes: Characterization of the Metabolite TP-034

Date(s): October 13, 2015 to January 19, 2016
Sponsor: TetraPhase Pharmaceuticals, Inc. Watertown, MA
Testing Facility: (b) (4)

METHODS

TP-434 and TP-6208 (both at 1 and 10 µM) were incubated separately with human liver microsomes (1 mg/mL), or microsomes recombinantly enriched with CYP3A4 (100 pmol/mL) or

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CYP3A5 (100 pmol/mL), NADPH (2 mM), and MgCl2 (3 mM) in 0.1 M phosphate buffer (pH 7.4) at 37 °C. Incubations were also carried out in phosphate buffer to investigate the formation of TP-034 and TP-6208 non-enzymatically. Experiments to study the metabolism of eravacycline by human and dog intestinal microsomes and S9 were also conducted similar to those stated above.
In addition, TP-434 (10 uM) was incubated in phosphate buffer (pH 7.4), human whole blood and plasma for 4 hours. Urine samples were also analyzed from two human subjects after eravacycline dosing, treated with potassium cyanide (KCN) and analyzed by MRM to investigate the potential formation of a TP-6208 cyanide adduct.

RESULTS

Incubations with Eravacycline: The only in vitro system that clearly formed TP-034 was human liver microsomes in the presence of NADPH. The amount of TP-034 at the 60 min time point was approximately 10 to 15-fold higher (at the two concentrations tested) than what was observed at the zero time point. TP-6208 was also formed in an NADPH-dependent manner, through metabolism by CYP3A4 and CYP3A5, confirming earlier studies.

Incubations with TP-6208: The increases in the level of TP-034 over the 60 min incubation period were <3-fold in any of the incubations. There was no difference in formation of TP-034 by buffer and enzymatic incubations, indicating this small amount of TP-034 formation did not require the presence of an enzyme or NADPH.

Metabolism of Eravacycline in the Presence of Intestinal Microsomes and S9 from Humans: The concentrations of TP-034 and TP-6208 obtained in human intestinal microsomal and S9 incubation of eravacycline were below quantitation limit of the assay at 1 uM. At 10 uM, both human intestinal microsomes and S9 formed TP-034, with concentrations ranging from 0.0108 to 0.0201 µM. The maximum formation of TP-034 was 0.0443 µM with an S9 incubation of 4 hr. Similarly, TP-6208 was formed in both intestinal microsomal and S9 incubations. The highest concentrations attained were 0.05675 and 0.04285 µM in intestinal microsomes and S9, respectively.

Potential Metabolism and/or Degradation of Eravacycline in Human Whole Blood, Plasma and Phosphate Buffer: There was little/no formation of these metabolites by human whole blood, plasma or in phosphate buffer incubations.

Characterization of the Iminium Intermediate of TP-6208 from Human Urine: MS data identified a cyanide adduct of TP-6208 in the urine of subjects that had been dose with eravacycline and treated with KCN and heat.

REVIEWER ASSESSMENT: The two major metabolites of eravacycline, TP-034 and TP-6208, were formed directly from TP-434 in an enzymatic- and NADPH-dependent manner. While liver microsomal enzymes catalyzed the formation of TP-034 from TP-434 in an NADPH-dependent manner, there was no clear formation of TP-034 by recombinant CYP3A4 or CYP3A5. CYP3A4

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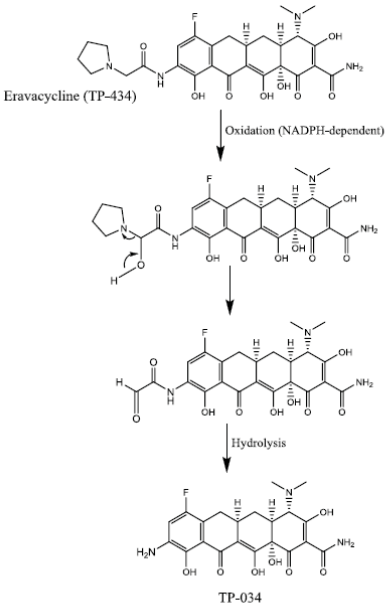
and CYP3A5 catalyzed the formation of TP-6208 from TP- 434 and the extent of formation of TP-6208 via chemical degradation or non-CYP pathways was insignificant in comparison to its NADPH-dependent generation by HLM, CYP3A4 and CYP3A5.

Based on this experiment, the proposed pathway of TP-034 formation is an oxidation reaction involving hydroxylation of the methylene carbon adjacent to the nitrogen of the pyrrolidine ring to yield the carbinol amine. This would then prompt rearrangement to the oxo-aldehyde derivative, which would go through a hydrolysis step to give TP-034 (**Figure 1**). Formation of TP-034 or TP-6208 from TP-434 by blood and plasma, or by chemical degradation, is negligible.

Figure 1. Proposed Mechanism for the NADPH-dependent Liver Microsomal Formation of TP-034 from Eravacycline



Study No.: 8TETRPI

MDR1-MDCK Permeability

Date(s): May 4, 2015
Sponsor: TetraPhase Pharmaceuticals, Inc. Watertown, MA
Testing Facility: (b) (4)

METHODS
The bidirectional permeability of test TP-434 (eravacycline; 1µM) was examined in an MDR1-MDCK cell system.

Reference ID: 4312284

The lucifer yellow flux was also measured for each monolayer after being subjected to the test compound to ensure no damage was inflicted to the cell monolayers during the flux period. Permeability through a cell-free membrane was also studied to assess the free diffusion of the test compound. The apparent permeability, Papp, and percent recovery were calculated. All samples were assayed by LC-MS/MS using electrospray ionization.

RESULTS
All cell monolayers passed the post-experiment lucifer yellow monolayer integrity test. Results for recovery and permeability are outlined in **Table 1** below.

Table 1. Recovery and Apparent Permeability (10-6 cm/s) of Test Compound

Test Compound Identification	Direction	Recovery (%)	P_{app} (10^{-6} cm/s)				Efflux Ratio	Brain Penetration Potential(A)
			R1	R2	R3	Avg.		
TP-434	A-to-B	65	0.52	0.36	0.43	0.44	3.6	Low
	B-to-A	77	1.55	1.60	1.55	1.57		
	Cell-Free	76	25.2	21.2	22.3	22.9		

(A) Brain Penetration Potential Classification:
A-to-B P_{app} < 3.0: **Low**
A-to-B P_{app} > 3.0, Efflux > 10: **Low**
A-to-B P_{app} > 3.0, 3 < Efflux < 10: **Moderate**
A-to-B P_{app} > 3.0, Efflux < 3: **High**

REVIEWER ASSESSMENT: TP-434 showed an efflux ratio of 3.6 through MDR1-MDCK monolayers and is classified as having a low brain penetration potential.

Study No.: Tetraphase-02-12Jun2013

In vitro interaction studies of eravacycline (TP-434) and TP-6208 with the human MDR1, BCRP and BSEP efflux (ABC) transporters, and with the human OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 and MATE2-K uptake transporters

Date(s): January 2016 to May 2016
Sponsor: TetraPhase Pharmaceuticals, Inc. Watertown, MA
Testing Facility: (b) (4)

METHODS
Eravacycline and its metabolite TP-6208 were evaluated as a substrate or inhibitor of the adenosine triphosphate-binding cassette (ABC) transporter MDR1 (ABCB1/phosphoglycoprotein [P-gp]), bile salt export pump (BSEP), breast cancer resistant protein (BCRP), and the human uptake transporters, multidrug and toxin extrusion protein (MATE1 and MATE2-K), organic anion transporter peptide (OATP1B1, OATP1B3, OAT1, and OAT3) and organic cation transporters (OCT1 and OCT2) using well-characterized intact cells (Chinese hamster ovary [CHO] and MDCKII) overexpressing the appropriate human transporters and membrane vesicles containing the respective human transporter of interest were used for uptake and inhibition experiments. Positive controls were used for both uptake and inhibition. Parental CHO cells (for OATP1B1, OATP1B3, OAT1, OCT1 and OCT2), parental MDCKII cells (for OAT3), and CAT-transfected MDCKII cells (for MATE1 and MATE2-K) were used as negative controls.

Reference ID: 4312284

For the vesicular transport inhibition assay, eravacycline (5 and 20 µg/mL) was incubated with membrane vesicle preparations and a radiolabelled probe substrate in the presence of 4 mM adenosine triphosphate (ATP) or adenosine monophosphate (AMP) for the negative control, and the amount of substrate inside the filtered vesicles was determined by LSC. For the substrate assays, inside-out membrane vesicles prepared from cells overexpressing human ABC transporters were incubated with 2 concentrations of eravacycline (1 and 5 µg/mL) for 2 and 20 minutes, and the amount accumulated inside the vesicles was determined by HPLC/MS-MS. Compounds were considered a substrate of a particular transporter if the fold accumulation value was >2.

RESULTS

Results from the vesicular transport inhibition assays and transport substrate experiments for eravacycline and TP-6208 are outlined in Table 1 and Table 2 below. The inhibition potential calculations of eravacycline with ABC (efflux) and SCL (uptake) transporters are listed in Table 3.

Table 1. Summary of eravacycline inhibition of transporters

Transporter	Buffer ID*	IC_{50}	Maximum inhibition (%) 36 µM (20 µg/mL)	89 µM (50 µg/mL)	179 µM (100 µg/mL)	537 µM (300 µg/mL)
MDR1	A	>20 µg/mL	29.3 26.1	NT	NT	NT
		72.3 µg/mL	13.6	NT	62.1	NT
MDR1	A[M-1]	>20 µg/mL	NT	NT	20.9 28.8 33.5	54.0 (INS) 60.7 (INS) 46.6 (INS)
BCRP	A	>20 µg/mL	NIO	NT	NT	NT
BCRP	A[M-1]	>100 µg/mL	NT	NT	NIO	32.0 (INS)
BSEP	B	>20 µg/mL	18.6	NT	NT	NT
OATP1B1	C	>20 µg/mL	NIO	NT	NT	NT
OATP1B3	C	>20 µg/mL	35.7	NT	NT	NT
OATP1B3	E[M-2]	>50 µg/mL	NT	41.7	NT	NT
OAT1	C	>20 µg/mL	12.2	NT	NT	NT
OAT3	C	>20 µg/mL	53.4	NT	NT	NT
OAT3	E[M-2]	22.9 µg/mL	NT	62.9	NT	NT
OCT1	C	>20 µg/mL	NIO	NT	NT	NT
OCT2	C	>20 µg/mL	NIO	NT	NT	NT
MATE1	D	>20 µg/mL	NIO	NT	NT	NT
MATE2-K	D	>20 µg/mL	NIO	NT	NT	NT

INS = compound was insoluble; NIO = no inhibition observed; NT = not tested

Reviewer Comment: Reviewer Comment: The applicant notes that potential inhibition of MDR1 and BCRP by eravacycline was evaluated at concentrations higher than 20 µg/mL to mimic intestinal exposure of these efflux transporters to eravacycline after an oral dose.

Inhibition of the MDR1-mediated transport by eravacycline at 20 µg/mL was 29.3% and 26.1% (performed on two separate dates). These results were generated with buffer A, the buffering capacity of which was reduced in the presence of 100 and 300 µg/mL eravacycline. In order to correct for pH changes, Buffer A[M-1] was made from buffer A, and was modified to kept the pH of the buffer constant. Using buffer A[M-1], three separate IC50 experiments were performed on

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separate days. At 100 µg/mL, eravacycline inhibited MDR1 by 20.9 %, 28.8%, and 33.5 % on each respective day.

Table 2. TP-6208: Summary of the accumulation by and inhibition of major human transporters

Transporter	Buffer ID*	**IC_{50} (µg/mL)**	**maximum inhibition (% of control)**	**Substrate**
MDR1	A	>10 µg/mL	no inhibition up to 10 µg/mL	No
BCRP	A	>10 µg/mL	no inhibition up to 10 µg/mL	No
BSEP	B	>10 µg/mL	no inhibition up to 10 µg/mL	No
OATP1B1	C	>10 µg/mL	no inhibition up to 10 µg/mL	No
OATP1B3	C	>10 µg/mL	no inhibition up to 10 µg/mL	No
OAT1	C	>10 µg/mL	no inhibition up to 10 µg/mL	No
OAT3	C	>10 µg/mL	no inhibition up to 10 µg/mL	No
OCT1	C	>10 µg/mL	no inhibition up to 10 µg/mL	No
OCT2	C	>10 µg/mL	no inhibition up to 10 µg/mL	No
MATE1	NT	>10 µg/mL	no inhibition up to 10 µg/mL	Not tested
MATE2-K	NT	>10 µg/mL	no inhibition up to 10 µg/mL	Not tested

NT = not tested

Table 3. Inhibition potential of eravacycline with ABC (efflux) and SCL (uptake) transporters

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Transporter	CC (µg/mL)	Buffer ID	MI (%)	IC50 (µg/mL) Exp.	IC50 (µg/mL) Est.	Ki Est.	Eravacycline Clinical Dose PO (200 mg) FDA: Hepatic Trps [I1]/IC50	Renal Trps [I]/IC50	EMA: Hep Uptake [Y]/IC50	Hep Efflux + Renal Trps [Z]/IC50	Eravacycline Clinical Dose IV (1mg/kg) FDA: Hepatic Trps [I1]/IC50	Renal Trps [I]/IC50	EMA: Hep Uptake [W]/IC50	Hep Efflux + Renal Trps [Z]/IC50	Hep Efflux + Renal Trps [Z]/Ki
SLC (uptake) transporters							> 0.1 = risk	>0.1 = risk	> 1 = risk	> 1 = risk	> 0.1 = risk	> 0.1 = risk	> 1 = risk	> 1 = risk	
OATP1B1	20	C	1.0		1980.0		0.00	NR	0.00	NR	0.00	NR	0.00	NR	ND
OATP1B3	20	C	35.7		36.0		0.01	NR	0.03	NR	0.04	NR	0.13	NR	ND
	50	E[M-2]	41.7		69.9		0.00	NR	0.02	NR	0.02	NR	0.07	NR	ND
OAT1	20	C	12.2		143.9		NR	0.00	NR	0.02	NR	0.00	NR	0.06	ND
OAT3	20	C	53.4		17.5	16.2	NR	0.00	NR	0.12	NR	0.01	NR	0.48	0.52
	50	E[M-2]	62.9	22.9	29.5	21.2	NR	0.00	NR	0.09	NR	0.01	NR	0.37	0.39
OCT1	20	C	1.0		1980.0		0.00	NR	0.00	NR	0.00	NR	0.00	NR	ND
OCT2	20	C	1.0		1980.0		NR	0.00	NR	0.00	NR	0.00	NR	0.00	ND
MATE1	20	D	1.0		1980.0		NR	0.00	NR	0.00	NR	0.00	NR	0.00	ND
MATE2-K	20	D	1.0		1980.0		NR	0.00	NR	0.00	NR	0.00	NR	0.00	ND

Transporter (date of experiment)	CC (µg/mL)	Buffer ID	MI (%)	IC50 (µg/mL) Exp.	IC50 (µg/mL) Est.	Eravacycline Clinical Dose PO (200 mg) FDA: Intestinal [I2]/IC50	Hepatic Trps [I1]/IC50	Renal Trps [I]/IC50	EMA: Intestinal [X]/IC50	Hep Efflux + Renal Trps [Z]/IC50	Eravacycline Clinical Dose IV (1 mg/kg q12h) FDA: Hepatic Trps [I1]/IC50	Renal Trps [I]/IC50	EMA: Hep Efflux + Renal Trps [Z]/IC50
ABC transporters						> 10 = risk	> 0.1 = risk	>0.1 = risk	> 1 = risk	> 1 = risk	> 0.1 = risk	> 0.1 = risk	> 1 = risk
MDR1 (P-gp) (19 Sep 2013)	20	A	29.3		48.3	16.6	0.00	0.00	1.66	0.04	0.03	0.00	0.17
MDR1 (P-gp) (28 April 2014)	20	A	26.1		56.6	14.1	0.00	0.00	1.41	0.04	0.02	0.00	0.15
MDR1 (P-gp)	100	A	62.1	72.3	61.0	11.1	0.00	0.00	1.11	0.03	0.02	0.00	0.12
MDR1 (P-gp) (18 April 2014)	100	A[M-1]	20.9		378.5	2.1	0.00	0.00	0.21	0.01	0.00	0.00	0.02
MDR1 (P-gp) (24 April 2014)	100	A[M-1]	28.8		247.2	3.2	0.00	0.00	0.32	0.01	0.01	0.00	0.03
MDR1 (P-gp) (07 May 2014)	100	A[M-1]	33.5		198.5	4.0	0.00	0.00	0.40	0.01	0.01	0.00	0.04
BCRP	20	A	1.0		1980.0	0.4	0.00	0.00	0.04	0.00	0.00	0.00	0.00
	100	A[M-1]	4.7		2027.7	0.4	0.00	0.00	0.04	0.00	0.00	0.00	0.00
BSEP	20	B	18.6		87.5	NR	0.00	NR	NR	0.02	0.01	NR	0.10

CC= concentration of eravacycline; Buffer ID as per Table 3; MI= maximal inhibition at the given highest concentration tested; Exp.=experimentally determined IC_{50} through fitting a curve on multiple concentration inhibition points; Est.= estimated IC_{50} determined per Equation 1; NR= not relevant as the transporter is not considered important in the given barrier.

Reviewer Comment: For oral eravacycline, the ratios for inhibition of intestinal, hepatic and renal MDR1, exceeded the FDA's cutoff value for inhibition of intestinal MDR1 but not hepatic or renal MDR1. However, the Sponsor is only seeking approval for the IV formulation, which did not exceed the cutoff for any of the transporters tested.

Reviewer Assessment: Eravacycline and its metabolite TP-6208 were not substrates for the major human uptake or efflux transporters *in vitro*. Clinically relevant drug interactions produced by the inhibition of these transporters by eravacycline or TP-6208 is unlikely after IV administration.

Study No.: Tetraphase-03-14Jul2014

Reference ID: 4312284

In vitro interaction studies of TP-498 with the human MDR1, BCRP and BSEP efflux (ABC) transporters, and with human OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 and MATE2-K uptake transporters

Date(s): January 2015
Sponsor: TetraPhase Pharmaceuticals, Inc. Watertown, MA
Testing Facility: (b) (4)

METHODS

The purpose of this study was to determine whether TP-498, the C-4 epimer of eravacycline, was a substrate or an inhibitor of the human ABC transporters MDR1 (ABCB1/P-gp), BCRP (ABCG2/MXR), BSEP (ABCB11/sP-gp) and the human uptake transporters OATP1B1 (OATP2, OATP-C), OATP1B3 (OATP8), OCT1, OCT2, OAT1, OAT3, MATE1 and MATE2-K. Well-characterized intact cells (HEK293, CHO and MDCKII) overexpressing the appropriate human transporters and membrane vesicles (prepared from Sf9 and proprietary human cells identified as K and M cells) containing the respective human transporter of interest were used for uptake and vesicular transport experiments, along with positive controls for both uptake and vesicular transport. the amount accumulated inside the vesicles was determined by HPLC/MS-MS.

RESULTS

Results from the vesicular transport inhibition assays and transport substrate experiments are outlined in Table 1 and Table 2 below

Table 1. TP-498: Summary of the accumulation by and inhibition of major human transporters

Transporter	Buffer ID*	IC_{50} (µg/mL)	Observed effect (% of control)	Substrate
MDR1	A	NA	no inhibition at 25 µg/mL	No
BCRP	A	NA	no inhibition at 25 µg/mL	No
BSEP	B	NA	no inhibition at 25 µg/mL	No
OATP1B1	C	NA	no inhibition at 25 µg/mL	No
OATP1B3	C	NA	24% inhibition at 25 µg/mL	No
OAT1	C	NA	no inhibition at 25 µg/mL	No
OAT3	C	NA	no inhibition at 25 µg/mL	No
OCT1	C	NA	no inhibition at 25 µg/mL	No
OCT2	C	NA	no inhibition at 25 µg/mL	No
MATE1	D	NA	no inhibition at 25 µg/mL	No
MATE2-K	D	NA	no inhibition at 25 µg/mL	No

Table 2. Fold accumulation values from vesicular transport substrate experiments with TP-498 (5 ug/mL and 1 ug/mL)

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		5 µg/mL	1 µg/mL
MDR1	2	0.71	0.90
	20	1.08	1.01
BCRP	2	1.23	1.39
	20	0.97	1.15
BSEP	2	0.93	BLOQ
	20	0.92	BLOQ
OATP1B1	2	0.77	0.36*
	20	1.26	1.02
OATP1B3	2	0.86	0.89
	20	0.53	0.75
OCT1	2	0.79	BLOQ
	20	0.78	1.03
OCT2	2	0.21**	BLOQ*
	20	0.21**	0.19*
OAT1	2	0.57	0.22*
	20	0.76	0.66
OAT3	2	0.59	0.25*
	20	0.67	0.71
MATE1	2	1.01	1.50
	20	0.78	0.84
MATE2-K	2	1.07	0.90
	20	0.79	0.86

BLOQ: Below the Limit of Quantitation

REVIEWER ASSESSMENT: TP-498 was not a substrate (defined as a fold accumulation >2) for any transporters in this study. The OATP1B3 mediated transport of CCK-8 was inhibited slightly with a maximum inhibition of 24% produced by 25 µg/mL of TP-498; however, no IC_{50} was determined in this study.

Study No. (b) (4) 58063

In Vitro Evaluation of TP-034 as an Inhibitor and a Substrate of Human P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1 and MATE2-K Transporters

Date(s): October 2015
Sponsor: TetraPhase Pharmaceuticals, Inc. Watertown, MA
Testing Facility: (b) (4)

METHODS
The ability of TP-034 (0.1, 0.3, 1, 3, 10 and 15 µM) to inhibit human ABC and SLC transporters was evaluated using the test systems and probe substrates outlined in Table 1. Experimental designs and test systems used to determine if TP-034 (1, 5 and 25 µM) is a substrate of human

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ABC and SLC transporters are outlined in Table 2. Samples were analyzed using a validated LC-MS/MS method. Known inhibitors were included as positive controls in all experiments.

Table 1. Evaluation of TP-034 as an inhibitor of human ABC and SLC transporters

Transporter	Test system	Probe substrate	Experimental design
P-gp	Caco-2	Digoxin	Bidirectional transport of the probe substrate across Caco-2 cells
BCRP	MDCKII-BCRP	Prazosin	Bidirectional transport of the probe substrate across MDCKII-BCRP and control MDCKII cells
BSEP	Vesicles from Sf9 cells	Taurocholic acid	Accumulation of the probe substrate into BSEP vesicles in the presence and absence of ATP
OATP1B1	HEK293	Estradiol-17β-glucuronide	Accumulation of the probe substrate into OATP1B1 and control cells
OATP1B3	HEK293	Estradiol-17β-glucuronide	Accumulation of the probe substrate into OATP1B3 and control cells
OAT1	HEK293	*p*-Aminohippurate	Accumulation of the probe substrate into OAT1 and control cells
OAT3	HEK293	Estrone-3-sulfate	Accumulation of the probe substrate into OAT3 and control cells
OCT1	HEK293	Tetraethylammonium bromide	Accumulation of the probe substrate into OCT1 and control cells
OCT2	HEK293	Metformin	Accumulation of the probe substrate into OCT2 and control cells
MATE1	HEK293	Metformin	Accumulation of the probe substrate into MATE1 and control cells
MATE2-K	HEK293	Metformin	Accumulation of the probe substrate into MATE2-K and control cells

Table 2. Evaluation of TP-034 as a substrate of human ABC and SLC transporters

Transporter	Test system	Experimental design
P-gp	MDCKII-MDR1	Bidirectional transport of the test article across MDCKII-MDR1 and control MDCKII cells
BCRP	MDCKII-BCRP	Bidirectional transport of the test article across MDCKII-BCRP and control MDCKII cells
BSEP	Vesicles from transfected Sf9 cells	Accumulation of test article in BSEP and control vesicles in the presence of ATP or AMP
OATP1B1	HEK293	Accumulation of the test article in OATP1B1 and control cells
OATP1B3	HEK293	Accumulation of the test article in OATP1B3 and control cells
OAT1	HEK293	Accumulation of the test article in OAT1 and control cells
OAT3	HEK293	Accumulation of the test article in OAT3 and control cells
OCT1	HEK293	Accumulation of the test article in OCT1 and control cells
OCT2	HEK293	Accumulation of the test article in OCT2 and control cells
MATE1	HEK293	Accumulation of the test article in MATE1 and control cells
MATE2-K	HEK293	Accumulation of the test article in MATE2-K and control cells

RESULTS

Inhibition data for TP-034 are summarized in Table 3 below.

Table 3. Inhibition studies with TP-034

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Transporter	Test system	Probe substrate	Inhibition at highest concentration of TP-034 tested (15 µM) [a]
P-gp	MDCKII	Digoxin (10 µM)	No inhibition
BCRP	MDCKII	Prazosin (1 µM)	20%
BSEP	Vesicles from Sf9 (insect) cells	[^{3}H]-Taurocholate (0.4 µM)	No inhibition
OATP1B1	HEK293	[^{3}H]-Estradiol-17β-glucuronide (50 nM)	20%
OATP1B3	HEK293	[^{3}H]-Estradiol-17β-glucuronide (50 nM)	23%
OAT1	HEK293	[^{3}H]-*p*-Aminohippurate (1 µM)	No inhibition
OAT3	HEK293	[^{3}H]-Estrone-3-sulfate (50 nM)	No inhibition
OCT1	HEK293	[^{14}C]-Tetraethylammonium bromide (5 µM)	No inhibition
OCT2	HEK293	[^{14}C]-Metformin (10 µM)	10%
MATE1	HEK293	[^{14}C]-Metformin (10 µM)	2%
MATE2-K	HEK293	[^{14}C]-Metformin (10 µM)	27%

Reviewer Comment: TP-034 caused less than 50% inhibition of all transporters examined at the highest concentration tested (TP-034 15 µM, or > 50-fold above the plasma C_{max} at steady state [$C_{max, ss}$]); hence, IC50 values could not be determined experimentally. Values of IC50 were estimated from the degree of inhibition observed and were used to calculate the Ratio value according to the basic model as outlined in the FDA's 2012 Guidance for Industry. In all cases, the values of Ratio fell below the FDA's cutoff value of ≥0.1.

Table 4. Estimation of IC50 for transporter inhibition and calculation of Ratio Values

Transporter type	Transporter	Inhibition at 15 µM (%)	Estimated IC_{50} (µM) [a]	FDA's *Ratio* value	FDA's *Ratio* equation and cutoff [b]
Hepatic efflux	P-gp	None	135	0.0019	Total $C_{max,ss}/IC_{50}$ Ratio ≥ 0.1
	BCRP	19.9	60.4	0.0041	
	BSEP	None	135	0.0019	
	MATE1	1.7	135	0.0019	
Hepatic uptake	OATP1B1	19.9	60.4	0.0041	
	OATP1B3	22.8	50.8	0.0049	
	OCT1	None	135	0.0019	
Renal uptake	OAT1	None	135	0.0019	Unbound $C_{max,ss}/IC_{50}$ *Ratio* ≥ 0.1
	OAT3	None	135	0.0019	
	OCT2	10.1	134	0.0019	
Renal efflux	P-gp	None	135	0.0019	
	BCRP	19.9	60.4	0.0041	
	MATE1	1.7	135	0.0019	
	MATE2-K	27.0	40.6	0.0062	

a IC_{50} values were estimated from the following equation:

$$IC_{50}\ (estimated) = \left(\frac{Maximum\ inhibition\ (\%) * [I]}{Actual\ inhibition\ (\%)}\right) - [I]$$

where the 'maximum inhibition' is assumed to be 100% and 'actual inhibition' is the degree of inhibition observed at [I], the highest concentration of TP-034 (i.e., 15 µM). When more than 90% of transporter activity remained in the presence of 15 µM TP-034, the degree of inhibition was assumed to be 10% in order to estimate a default value of IC_{50}. The highest concentration of TP-034 tested (i.e., 15 µM) is > 90× greater than the plasma $C_{max,ss}$ of TP-034.

b The equation for calculating *Ratio* value are based on the basic model described in the FDA's *Guidance for Industry* on drug interactions (FDA 2012). Following intravenous BID dosing to steady state with 1 mg/kg eravacycline (parent drug), the total (bound + unbound) plasma $C_{max,ss}$ of TP-034 is estimated to be 0.25 µM. Binding of TP-034 to human plasma proteins was assumed to be zero (fu_P = 1.0); hence, unbound plasma $C_{max,ss}$ of TP-034 is also 0.25 µM (conservative estimate).

TP-034 was demonstrated not to be a substrate of OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1 and MATE2-K transporters as evidenced by an uptake ratio of less than 2 with negligible changes in the presence of known inhibitors.

The accumulation of TP-034 into BSEP vesicles was concentration and time dependent. In the presence of the positive control inhibitor, cyclosporine, the accumulation of TP-034 into BSEP vesicles was not reduced. A follow-up experiment was carried out in control vesicles. TP-034 accumulated in BSEP vesicles to a much greater extent that in control vesicles suggesting TP-034 is a substrate for BSEP.

TP-034 was also identified as a potential substrate for the efflux transporters P-gp, BCRP (Table 5).

Table 5. Efflux ratios of MDCKII-MDR1 and MDCKII-BCRP with corresponding positive controls

Transporter	TP-034 Concentration	Efflux Ratio of TP-034	Efflux Ratio of Positive Control
MDCKII-MDR1	1 µM	2.56	42.6 Digoxin (10 µM)
	5 µM	3.11	
	25 µM	2.64	
MDCKII-BCRP	1 µM	3.49	6.46 Prazosin (1 µM)
	5 µM	2.87	
	25 µM	0.976	

Reviewer Comment: The applicant notes that when the efflux ratio of the positive control digoxin was reduced to 1.05 (indicating complete inhibition of P-gp), valspodar (an inhibitor) partially decreased the efflux ratio of TP-034 in MDR1-transfected cells (from 14.2% at 5 µM up to 46.7% at 25 µM TP-034). The low efflux ratio of TP-034 (2.56 to 3.11) compared with digoxin (42.6) and the relatively weak (14 to 47%) inhibition of TP-034 permeation by valspodar (compared with complete inhibition of digoxin efflux) suggest that TP-034 could be low-capacity substrate for P-gp.

Similarly, when the efflux ratio of the positive control prazosin was reduced to 0.938 (indicating complete inhibition of BCRP), the inhibitor Ko143 only partially decreased the efflux ratio of TP-034 in BCRP-transfected cells (approximately 50% at 1 and 5 µM TP-034 with no inhibition at 25 µM TP-034). The low and variable efflux ratio of TP-034 (0.9 to 3.49), and the relatively weak (zero to 55%) inhibition of TP-034 permeation by Ko143 (compared with complete inhibition of prazosin efflux) suggest that TP-034 could be a low-capacity substrate for BCRP.
The results suggesting that TP-034 is a substrate of BSEP are should be interpreted with caution. The uptake of TP-034 by BSEP vesicles was not appreciably inhibited by cyclosporine whereas

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the uptake of the positive control substrate taurocholate was strongly inhibited (> 90%) by cyclosporine.

REVIEWER ASSESSMENT: In this experiment, TP-034 was shown to cause no clinically relevant inhibition of any of the 11 transporters examined. However, it may act as a potential low-capacity substrate for the efflux transporters P-gp, BCRP and BSEP.

Study No.: AD09-06

The *in vitro* Protein Binding of TP-434 (eravacycline) in Mouse, Rat, Beagle Dog, Cynomolgus Monkey, and Human Plasma and the Blood:Plasma Distribution of TP-434 in Human Blood

Date(s): May 18, 2009 to June 1, 2009
Sponsor: TetraPhase Pharmaceuticals, Inc. Watertown, MA
Testing Facility: TetraPhase Pharmaceuticals, Inc. Watertown, MA

METHODS
Protein binding was determined by adding TP-434 to 1.0 mL of plasma from mice, rats, beagle dogs, cynomolgus monkeys and humans, and incubated for 10 minutes at 37ºC. Following centrifugation, filtrate aliquots and plasma were analyzed by HPLC-MS/MS and the peak area ratios of TP-434 were used to calculate the percent unbound for each sample.

The blood:plasma distribution ratio (B:P) of 0.5, 1, and 10 µM TP-434 in pooled (n=3) human blood in the presence of EDTA, heparin, and sodium citrate was also determined. Pooled whole blood collected with EDTA, heparin, or sodium citrate was incubated for 30 minutes at 37ºC. After centrifugation, TP-434 concentrations were measured by HPLC-MS/MS using appropriate standard curves and the B:P ratio calculated as the ratio of the concentration in both matrices.

RESULTS
Plasma binding was modest to low, and species-dependent (Table 1). The B:P distribution ratio of TP-434 was similar at concentrations ranging from 0.5 to 10 µM, but differed according to the anticoagulant used (Table 2).

Table 1. Protein Binding (% free) of 1 µM TP-434 in Plasma (EDTA)

Replicate	Mouse	Rat	Dog	Monkey	Human
1	57.1	11.0	56.6	19.4	11.5
2	60.8	10.5	54.0	18.7	11.9
3	60.2	11.0	52.8	17.4	11.2
mean ± SD	59.3 ± 2.0	10.8 ± 0.3	54.5 ± 2.0	18.5 ± 1.0	11.5 ± 0.4

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Table 2. Blood:Plasma Distribution Ratio for TP-434 in Human Blood in the Presence of Different Anticoagulants

B:P Distribution Ratio			
TP-434 Concentration	Anticoagulant		
µM	EDTA	heparin	Na Citrate
0.5	NS	1.3 ± 0.1	1.9 ± 0.2
1	2.6 ± 0.0	1.1 ± 0.2	2.0 ± 0.1
10	2.9 ± 0.1	0.9 ± 0.1	2.8 ± 0.1

NS; no samples

Reviewer Comment: The applicant notes that the influence of EDTA (vs. heparin) may reflect competition between the drug and anticoagulant for metal chelation, which is not an uncommon phenomenon for tetracyclines. Measuring serum concentrations of TP-434 may avoid potentially confounding effects of anticoagulants that work via metal chelation.

REVIEWER ASSESSMENT: Data from this experiment suggests that eravacycline is not preferentially taken up by or bound to blood cells. The B:P ratio was increased with increasing concentrations of TP-434 in this study only when EDTA or sodium citrate was present in the test system, which may reflect competition for metal ion chelation.

Study No.: TET-R4384

In Vitro Protein Binding of Eravacycline (TP-434) in Human Plasma, Serum Albumin and α1-Acid Glycoprotein

Date(s): June 2015 to July 2015
Sponsor: TetraPhase Pharmaceuticals, Inc. Watertown, MA
Testing Facility: (b) (4)

METHODS
The *in vitro* protein binding of 0.1, 0.5, 1.0, 5.0 and 10 µg/mL eravacycline was determined in pooled, mixed-gender human plasma and in solutions of human serum albumin (HSA) and human α1-acid glycoprotein (AGP) after dialysis for 4 h at 37°C under 5% CO2 with protection from light. Concentrations of eravacycline were determined by LC/MS/MS. Propranolol and warfarin were used as positive controls for the protein binding study.

RESULTS
The protein binding of eravacycline in human plasma was concentration-dependent with binding increasing with increasing drug concentration (Table 1). Protein binding of eravacycline to human AGP was also concentration-dependent; however, in AGP solution, drug binding

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decreased with increasing eravacycline concentration (Table 2). In HSA solution, the protein binding of eravacycline was consistent over the concentration range examined (Table 3).

For the positive control propranolol (1.0 µg/mL), the mean free fractions were 29.2, 57.2 and 8.3% in plasma, HSA solution and AGP solution, respectively. Warfarin (1.0 µg/mL) was highly bound in all matrices with mean free fractions of 1.0% in plasma, 0.6% in HSA solution and 2.7% in AGP solution.

Table 1. *In Vitro* Protein Binding of Eravacycline in Pooled, Mixed-Gender Human Plasma

Nominal Concentrations of Eravacycline	Eravacycline Concentrations		%Unbound (Free)	Mean %Unbound ± SD	%Bound	Mean %Bound ± SD
	PBS (ng/mL)	Plasma (ng/mL)				
0.1 µg/mL	19.9	60.0	33.2	31.6 ± 1.4	66.8	68.4 ± 1.4
	20.9	67.5	31.0		69.0	
	20.1	65.8	30.5		69.5	
0.5 µg/mL	80.1	291	27.5	26.7 ± 3.1	72.5	73.3 ± 3.1
	91.0	309	29.4		70.6	
	77.0	331	23.3		76.7	
1.0 µg/mL	168	654	25.7	24.6 ± 1.0	74.3	75.4 ± 1.0
	160	667	24.0		76.0	
	169	702	24.1		75.9	
5.0 µg/mL	700	3050	23.0	23.0 ± 1.0	77.0	77.0 ± 1.0
	632	2860	22.1		77.9	
	654	2730	24.0		76.0	
10 µg/mL	769	4060	18.9	13.1 ± 6.4	81.1	86.9 ± 6.4
	875	6100	14.3		85.7	
	323	5250	6.2		93.8	

PBS: 50 mM phosphate-buffered saline, pH 7.4
Plasma: Pooled, mixed-gender human plasma
SD: Standard deviation

Table 2. *In Vitro* Protein Binding of Eravacycline in Human α1-Acid Glycoprotein Solution

Nominal Concentrations of Eravacycline	Eravacycline Concentrations		%Unbound (Free)	Mean %Unbound ± SD	%Bound	Mean %Bound ± SD
	PBS (ng/mL)	AGP (ng/mL)				
0.1 µg/mL	3.45	8.56	40.3	40.4 ± 2.1	59.7	59.6 ± 2.1
	9.06	23.6	38.4		61.6	
	3.00	7.04	42.6		57.4	
0.5 µg/mL	46.2	129	35.8	34.6 (n=2)	64.2	65.4 (n=2)
	30.5	91.7	33.3		66.7	
	11.8	2.22	531.5*		ND	
1.0 µg/mL	4.17	199	2.1*	42.3 (n=2)	ND	57.7 (n=2)
	40.5	113	35.8		64.2	
	62.0	127	48.8		51.2	
5.0 µg/mL	529	1090	48.5	50.4 ± 2.2	51.5	49.6 ± 2.2
	620	1240	50.0		50.0	
	755	1430	52.8		47.2	
10 µg/mL	1650	2830	58.3	58.6 ± 1.8	41.7	41.4 ± 1.8
	1640	2880	56.9		43.1	
	1780	2940	60.5		39.5	

AGP: α_1-Acid glycoprotein from human plasma (1.8 mg/mL in PBS)
*Value was an outlier and was excluded from the calculation of the mean.
ND: Not determined

Table 3. *In Vitro* Protein Binding of Eravacycline in Human Serum Albumin

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Nominal Concentrations of Eravacycline	Eravacycline Concentrations		%Unbound (Free)	Mean %Unbound ± SD	%Bound	Mean %Bound ± SD
	PBS (ng/mL)	HSA (ng/mL)				
0.1 µg/mL	25.8	69.1	37.3	39.1 ± 1.7	62.7	60.9 ± 1.7
	28.9	73.7	39.2		60.8	
	26.8	65.8	40.7		59.3	
0.5 µg/mL	140	393	35.6	36.9 ± 2.3	64.4	63.1 ± 2.3
	140	393	35.6		64.4	
	134	339	39.5		60.5	
1.0 µg/mL	237	639	37.1	30.9 ± 5.5	62.9	69.1 ± 5.5
	187	647	28.9		71.1	
	175	659	26.6		73.4	
5.0 µg/mL	977	2910	33.6	35.6 ± 4.6	66.4	64.4 ± 4.6
	903	2800	32.3		67.8	
	1160	2840	40.8		59.2	
10 µg/mL	1750	5330	32.8	36.1 ± 2.9	67.2	63.9 ± 2.9
	1900	5120	37.1		62.9	
	1770	4610	38.4		61.6	

PBS: 50 mM phosphate-buffered saline, pH 7.4
HSA: Human serum albumin (41.8 mg/mL in PBS)
SD: Standard deviation

Reviewer Comment: At the highest concentration of eravacycline tested (10 µg/mL) the unbound fraction of drug decreased in human plasma (fu=13.1%), increased in AGP solution (fu=58.6%) and remained relatively unchanged in HSA solution (fu=36.1%). The Sponsor does not include a rationale for this phenomenon; however, its relevance is uncertain given that concentrations in vivo are significantly lower than 10 µg/mL.

REVIEWER ASSESSMENT: The protein binding of eravacycline in human plasma was concentration-dependent with binding increasing with increasing drug concentration. The mean free fractions of eravacycline in human plasma were 31.6 ± 1.4, 26.7 ± 3.1, 24.6 ± 1.0, 23.0 ± 1.0 and 13.1 ± 6.4% at 0.1, 0.5, 1.0, 5.0 and 10 µg/mL eravacycline, respectively.

Study No.: (b) (4)-001

The protein binding of eravacycline (TP-434) in plasma from rabbit, mouse, rat, human, cynomolgus monkey and African green monkey determined by in vitro microdialysis

Date(s): May 2016
Sponsor: TetraPhase Pharmaceuticals, Inc. Watertown, MA
Testing Facility: (b) (4)

METHODS
Plasma protein binding was studied in pooled (minimum of six animals) plasma from different species (rabbit, mouse, rat, human, cynomolgus monkey, and African green monkey) at four concentrations of eravacycline (0.1, 1, 10 and 100 µg/mL) in the absence and presence of the metabolite TP- 6208 using *in vitro* microdialysis. A sensitive HPLC-MS/MS method was used to quantify eravacycline concentrations in saline and plasma. The percent free fraction was calculated using Equation 1, where $C_{Dialysate}$ (T1, T2) is the dialysate collected between time interval T1 and T2, CPRT (T1) and CPRT (T2) are the concentrations of eravacycline in plasma at

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time T1 and T2, respectively. The calculated percent free fractions were averaged to calculate final percent free fraction.

Equation 1.

$$\%\ Free\ Fraction = \frac{C_{Dialysate}\ (T1,T2)}{CP_{RT}(T1)+CP_{RT}(T2)} \times \frac{100}{\%\ Probe\ Recovery} \times 100$$

RESULTS

Eravacycline showed concentration-dependent plasma protein binding in all species over the range of 0.1-100 ug/mL. The effect of a lower concentration of TP-6208 (0.1 µg/mL) on the plasma protein binding of eravacycline was investigated because 1 µg/mL TP-6208 significantly altered the free fraction of eravacycline in human plasma. In contrast to the results obtained with 1 µg/mL, TP-6208 (0.1 µg/mL) did not consistently decrease the plasma binding of eravacycline at concentrations between 0.1 and 3 µg/mL in human plasma (Table 1).

Table 1. Plasma protein binding of eravacycline (mean ± SD) in pooled plasma in the presence and absence of TP-6208 (1ug/mL) determined by microdialysis: Repeat experiment

	Mean (±SD) % Free eravacycline in human plasma (N=3)	
Total Concentration of Eravacycline	Eravacycline + TP-6208 (0.1 µg/mL)	Eravacycline only
0.1	13.2±2.3	12.8±3.3
0.3	6.3±0.4	4.2±0.6
1.0	3.1±1.4	5.2±0.6
3.0	1.5±1.3	1.0±0.2

Reviewer Comment: The steady state total C_{max} of eravacycline is 1.825 ug/mL as determined in previous studies. Data from this study projects the percent free drug in plasma at these concentrations to be approximately 1-5%. The percent free fraction of eravacycline observed between different lots of pooled human plasma was associated with significant variability in this study. The applicant notes that the reasons for such variability are unknown. There is also notable inter-study variability (up to 5-fold), which may be due to low affinity binding at lower concentrations, variability in pooled plasma sources or inter-laboratory variability in the methods used (equilibrium dialysis, MD, ultrafiltration).

REVIEWER ASSESSMENT: The percentage of free eravacycline in human plasma decreased with increasing concentrations, and was highly variable between experiments.

Reference ID: 4312284

Study No. (b) (4) 085084

In Vitro Evaluation of TP-434 as an Inhibitor of Human Cytochrome P450 Enzymes
Date(s): December 1, 2008 to January 15, 2009
Sponsor: TetraPhase Pharmaceuticals, Inc. Watertown, MA
Testing Facility: (b) (4)

METHODS

To evaluate TP-434 (eravacycline) as a direct inhibitor of CYP activity, pooled human liver microsomes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5) from 16 individuals were incubated with marker substrates, at concentrations approximately equal to their apparent *K*m, in the presence or absence of TP-434. Known direct and metabolism-dependent inhibitors of CYP enzymes were included as positive controls. Full incubation conditions are listed in **Table 1**.

Table 1: Summary of experimental conditions for enzyme assays

Enzyme	CYP Reaction	Substrate concentration (µM)	Incubation volume (µL)	Protein [a] (µg/mL)	Incubation time (min)	Preincubation time (min)	TP-434 Target concentrations (µM) [b]
CYP1A2	Phenacetin *O*-dealkylation	40	200	100	5	30	0, 0.0856, 0.257, 0.856, 2.57, 8.56, 25.7 and 85.6
CYP2B6	Efavirenz 8-hydroxylation	3	200	100	5	30	0, 0.0856, 0.257, 0.856, 2.57, 8.56, 25.7 and 85.6
CYP2C8	Amodiaquine *N*-dealkylation	1.5	200	12.5	5	30	0, 0.0856, 0.257, 0.856, 2.57, 8.56, 25.7 and 85.6
CYP2C9	Diclofenac 4´-hydroxylation	6	200	100	5	30	0, 0.0856, 0.257, 0.856, 2.57, 8.56, 25.7 and 85.6
CYP2C19	S-Mephenytoin 4´-hydroxylation	40	200	100	5	30	0, 0.0856, 0.257, 0.856, 2.57, 8.56, 25.7 and 85.6
CYP2D6	Dextromethorphan *O*-demethylation	7.5	200	100	5	30	0, 0.0856, 0.257, 0.856, 2.57, 8.56, 25.7 and 85.6
CYP3A4/5	Testosterone 6β-hydroxylation	100	200	100	5	30	0, 0.0856, 0.257, 0.856, 2.57, 8.56, 25.7 and 85.6
CYP3A4/5	Midazolam 1´-hydroxylation	4	200	50	5	30	0, 0.0856, 0.257, 0.856, 2.57, 8.56, 25.7 and 85.6

a The human liver microsomal sample used for these experiments was a pool of sixteen individuals (samples 286, 290, 312, 313, 315, 333, 334, 335, 336, 339, 348, 359, 364, 383, 389 and 390).
b High purity water was the vehicle used to dissolve the test article.

RESULTS

For the direct inhibition assays, positive control inhibited the enzyme activity in all cases. For time-dependent assays, positive control inhibited the enzyme activity in a metabolism-dependent manner for all additional zero-minute and 30 minute preincubations. Test article interference and test article suppression check samples performed as expected indicating that the addition of TP-434 had little or no impact on the validated analytical methods used in this study. Additionally, metabolite formation was directly proportional to protein concentration and incubation time in all cases. Results of the evaluation of TP-434 as a direct and time-dependent inhibitor of human CYP enzymes are summarized in **Table 2**.

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Table 2. Summary of results: *In vitro* evaluation of TP-434 as an inhibitor of human CYP enzymes

		Direct inhibition		Time-dependent inhibition		
		Zero-minute preincubation		30-minute preincubation		
Enzyme	CYP reaction	IC_{50} (μM) [a]	Maximum inhibition at 85.6 μM (%) [b]	IC_{50} (μM) [a]	Maximum inhibition at 85.6 μM (%) [b]	Potential for time-dependent inhibition [c]
CYP1A2	Phenacetin *O*-dealkylation	> 85.6	7.1	> 85.6	0.0	Little or no
CYP2B6	Efavirenz 8-hydroxylation	> 85.6	18	> 85.6	13	Little or no
CYP2C8	Amodiaquine *N*-dealkylation	> 85.6	45	> 85.6	46	Little or no
CYP2C9	Diclofenac 4´-hydroxylation	> 85.6	NA	> 85.6	1.6	Little or no
CYP2C19	*S*-Mephenytoin 4´-hydroxylation	> 85.6	5.3	> 85.6	11	Little or no
CYP2D6	Dextromethorphan *O*-demethylation	> 85.6	4.7	> 85.6	13	Little or no
CYP3A4/5	Testosterone 6β-hydroxylation	> 85.6	5.3	> 85.6	8.6	Little or no
CYP3A4/5	Midazolam 1´-hydroxylation	> 85.6	16	> 85.6	26	Little or no

a Average data (i.e., percent of control activity) obtained from duplicate samples for each test article concentration were used to calculate IC_{50} values. IC_{50} values were calculated with XLFit.

b Maximum inhibition (%) is calculated with the following formula and data for the highest concentration of test article evaluated (results are rounded to two significant figures): Maximum inhibition (%) = 100% − Percent solvent control.

c Time-dependent inhibition was determined by comparison of IC_{50} values with and without preincubation, by comparison of the maximum inhibition (%) with and without preincubation and by visual inspection of the IC_{50} plot.

NA Not applicable. No value was obtained as the rates at the highest concentration of TP-434 evaluated (85.6 μM) were higher than the control rates.

REVIEWER ASSESSMENT: In this study, there was little or no evidence that TP-434 caused direct inhibition of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 and the IC50 values for these enzymes were reported to be greater than the highest concentration of TP-434 evaluated (i.e., 85.6 μM). There was little or no evidence of time-dependent inhibition of any of the CYP enzymes evaluated by TP-434 as no distinct increase in inhibition was observed upon pre-incubation.

Despite evidence of direct inhibition of CYP2C8 by TP-434 (~45% enzyme inhibition at the highest concentration of TP-434 of 85.6 μM) *in vitro*, is unlikely to be clinically relevant at steady-state Cmax concentrations of TP-434 produced by a 1.0 mg/kg i.v. dose given every 12 h (1.8 μM)..
Study No. (b) (4)145065

In Vitro Evaluation of TP-498 as an Inhibitor of Human Cytochrome P450 Enzymes in Human Liver Microsomes
Date(s): August 26, 2014 to September 18, 2014
Sponsor: TetraPhase Pharmaceuticals, Inc. Watertown, MA
Testing Facility: (b) (4)

METHODS
To evaluate TP-498 as a direct, time-dependent and metabolism-dependent inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5, human liver microsomes from a pool of 200 individuals were incubated with CYP-selective substrates in the presence or

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absence of TP-498. Known direct and metabolism-dependent inhibitors of CYP enzymes were included as positive controls. Full incubation conditions are listed in **Table 1**.

Table 1: Summary of assay conditions to measure microsomal CYP enzyme activity

Enzyme	Enzyme reaction	Substrate concentration (μM)	Incubation volume (μL)	Protein [a] (μg/mL)	Incubation time (min)	Pre-incubation time (min)	TP-498	
							Target concentrations (μM)	Solvent volume [b] (μL)
CYP1A2	Phenacetin *O*-dealkylation	90	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30 and 100	2
CYP2B6	Efavirenz 8-hydroxylation	5	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30 and 100	2
CYP2C8	Amodiaquine *N*-dealkylation	2	200	12.5	5	30	0, 0.1, 0.3, 1, 3, 10, 30 and 100	2
CYP2C9	Diclofenac 4′-hydroxylation	12	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30 and 100	2
CYP2C19	*S*-Mephenytoin 4′-hydroxylation	60	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30 and 100	2
CYP2D6	Dextromethorphan *O*-demethylation	10	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30 and 100	2
CYP3A4/5	Testosterone 6β-hydroxylation	60	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30 and 100	2
CYP3A4/5	Midazolam 1′-hydroxylation	3	200	50	5	30	0, 0.1, 0.3, 1, 3, 10, 30 and 100	2

a The human liver microsomal sample used for these experiments was a pool of 200 individuals.
b Water was the vehicle used to dissolve the test article.

Results: The positive control inhibitors for direct inhibition and metabolism dependent inhibition for IC50 determinations inhibited enzyme activity as expected. Test article interference and test article suppression check samples performed as expected indicating that the addition of TP-498 had little or no impact on the validated analytical methods used in this study (data not reported). Additionally, metabolite formation was directly proportional to protein concentration and incubation time in all cases. The effects of TP-498 as a direct, time-dependent and metabolism-dependent inhibitor of human CYP enzymes are summarized in **Table 2**.

Table 2. Summary of results: *In vitro* evaluation of TP-498 as an inhibitor of human CYP enzymes

Enzyme	Substrate	Direct inhibition		Time-dependent inhibition		Metabolism-dependent inhibition		
		Zero-minute preincubation		30-minute preincubation without NADPH		30-minute preincubation with NADPH		Potential for metabolism-dependent inhibition [c]
		IC_{50} (μM) [a]	Inhibition observed at 100 μM (%) [b]	IC_{50} (μM) [a]	Inhibition observed at 100 μM (%) [b]	IC_{50} (μM) [a]	Inhibition observed at 100 μM (%) [b]	
CYP1A2	Phenacetin	> 100	NA	> 100	NA	> 100	NA	No
CYP2B6	Efavirenz	> 100	5.0	> 100	3.1	> 100	12	No
CYP2C8	Amodiaquine	> 100	30	> 100	35	> 100	27	No
CYP2C9	Diclofenac	> 100	3.8	> 100	4.1	> 100	7.8	No
CYP2C19	*S*-Mephenytoin	> 100	9.4	> 100	8.4	> 100	11	No
CYP2D6	Dextromethorphan	> 100	NA	> 100	5.9	> 100	NA	No
CYP3A4/5	Testosterone	> 100	7.2	> 100	5.1	> 100	29	24% [d]
CYP3A4/5	Midazolam	> 100	38	> 100	30	> 100	38	No

a Average data (i.e., percent of control activity) obtained from duplicate samples for each test article concentration were used to calculate IC_{50} values.
b Inhibition observed (%) is calculated with the following formula (results are rounded to two significant figures):
Inhibition observed (%) = 100% − Percent solvent control.
c Metabolism-dependent inhibition was determined by comparison of IC_{50} values both with and without preincubation and with and without NADPH-generating system present in the preincubation, by comparison of the observed inhibition (%) for all preincubation conditions and by visual inspection of the IC_{50} plots.
d This number represents the difference in percent inhibition observed after preincubation of 100 μM TP-498 with NADPH-fortified human liver microsomes for 30 minutes
NA Not applicable. No value was obtained as the rates at the highest concentration of TP-498 evaluated (100 μM) were higher than the control rates.

REVIEWER ASSESSMENT: Despite notable inhibition with CYP2C8 and CYP3A4/5, IC50 values for all enzymes in this experiment were above the assay's upper limit of 100 uM and DDI potentials are unlikely.

Reference ID: 4312284

Study No. (b) (4) 55034

In Vitro Evaluation of TP-034 as an Inhibitor of Human Cytochrome P450 Enzymes in Human Liver Microsomes

Date(s): July 30, 2015 to August 18, 2015

Sponsor: TetraPhase Pharmaceuticals, Inc. Watertown, MA

Testing Facility: (b) (4)

METHODS

The inhibitory potency of TP-034 was determined *in vitro* by measuring the activity of each CYP enzyme (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5) in pooled human liver microsomes in the presence and absence of TP-034. Incubation conditions are noted in Tables 1 and 2.

Table 1. Summary of assay conditions to measure microsomal CYP enzyme activity

Enzyme	Substrate	Substrate concentration (µM)	Incubation volume (µL)	Microsomal protein (µg/mL) [a]	Substrate incubation time (min)	Test article preincubation time (min)	TP-034	
							Target concentrations (µM)	Solvent volume (µL) [b]
CYP1A2	Phenacetin	90	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30, 100	20
CYP2B6	Efavirenz	5	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30, 100	20
CYP2C8	Amodiaquine	2	200	12.5	5	30	0, 0.1, 0.3, 1, 3, 10, 30, 100	20
CYP2C9	Diclofenac	12	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30, 100	20
CYP2C19	*S*-Mephenytoin	60	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30, 100	20
CYP2D6	Dextromethorphan	10	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30, 100	20
CYP3A4/5	Testosterone	60	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30, 100	20
CYP3A4/5	Midazolam	3	200	50	5	30	0, 0.1, 0.3, 1, 3, 10, 30, 100	20

a The human liver microsomal sample used for these experiments was a pool of 200 individuals (lot number 1210347).

b High purity sterile water was the solvent used to dissolve the test article.

Table 2. Summary of assay conditions to measure microsomal CYP enzyme activity (Metabolism-dependent inhibition of CYP2C8 by TP-034)

Enzyme	Substrate	Substrate concentration (µM)	Incubation volume (µL)	Microsomal protein (µg/mL) [a]	Substrate incubation time (min)	Test article preincubation times (min)	TP-034	
							Target concentrations (µM)	Solvent volume (µL) [b]
CYP2C8	Amodiaquine	2	200	12.5	5	0, 15, 30, 60, 90	0, 0.1, 0.3, 1, 3, 10, 30, 100	20

a The human liver microsomal sample used for this experiment was a pool of 200 individuals (lot number 1210347).

b High purity sterile water was the solvent used to dissolve the test article.

Results:

The positive control inhibitors for direct inhibition and metabolism dependent inhibition for IC50 determinations inhibited enzyme activity as expected. Test article interference and test article suppression check samples performed as expected indicating that the addition of TP-034 had little or no impact on the validated analytical methods used in this study. The effects of TP-034 as a direct, time-dependent and metabolism-dependent inhibitor of human CYP enzymes are summarized in **Table 3**.

Reference ID: 4312284

Table 3. Summary of results: *In vitro* evaluation of TP-034 as an inhibitor of human CYP enzymes

Enzyme	Substrate	Direct inhibition		Time-dependent inhibition		Metabolism-dependent inhibition		
		Zero-min preincubation		30-min preincubation without NADPH		30-min preincubation with NADPH		Potential for time-dependent inhibition and/or metabolism-dependent inhibition [c]
		IC_{50} (μM) [a]	Inhibition observed at 100 μM (%) [b]	IC_{50} (μM) [a]	Inhibition observed at 100 μM (%) [b]	IC_{50} (μM) [a]	Inhibition observed at 100 μM (%) [b]	
CYP1A2	Phenacetin	> 100	2.3	> 100	2.3	> 100	NA	Little or no
CYP2B6	Efavirenz	> 100	3.0	> 100	10.4	> 100	11.9	Little or no
CYP2C8	Amodiaquine	> 100	15.1	> 100	18.0	> 100	36.2	Yes [d]
CYP2C9	Diclofenac	> 100	NA	> 100	NA	> 100	7.1	Little or no
CYP2C19	*S*-Mephenytoin	> 100	NA	> 100	NA	> 100	11.4	Little or no
CYP2D6	Dextromethorphan	> 100	7.2	> 100	11.5	> 100	NA	Little or no
CYP3A4/5	Testosterone	> 100	5.0	> 100	NA	> 100	3.8	Little or no
CYP3A4/5	Midazolam	> 100	0.4	> 100	NA	> 100	9.9	Little or no

Table 4. Evaluation of TP-034 as a direct and metabolism-dependent inhibitor of CYP enzymes in human liver microsomes with estimates of the FDA's *R1* and *R2* values based on oral dosing to steady state with eravacycline

Enzyme	Substrate	IC_{50} (μM) [b]	Inhibition at 100 μM (%) [b]	Estimated IC_{50} (μM) [c]	Estimated K_i (μM) [d]	Estimated K_i,u (μM) [e]	FDA R_1 values		FDA R_2 values	
							Estimated Hepatic R_1 [f]	Estimated Intestinal R_1 [g]	Estimated Hepatic R_2 [h]	Estimated Intestinal R_2 [g]
CYP1A2	Phenacetin	> 100	2.3	4248	2124	2124	1.00008	NA	ND	NA
CYP2B6	Efavirenz	> 100	3.0	3233	1616.5	1616.5	1.0001	NA	ND	NA
CYP2C8	Amodiaquine	> 100	15.1	562	281	281	1.00057	NA	1.044269	NA
CYP2C9	Diclofenac	> 100	0 [i]	None	None	None	1.00000	NA	ND	NA
CYP2C19	*S*-Mephenytoin	> 100	0 [i]	None	None	None	1.00000	NA	ND	NA
CYP2D6	Dextromethorphan	> 100	7.2	1289	644.5	644.5	1.00025	NA	ND	NA
CYP3A4/5	Testosterone	> 100	5.0	1900	950	950	1.00017	NA	ND	NA
CYP3A4/5	Midazolam	> 100	0.4	24900	12450	12450	1.00001	NA	ND	NA

NA Not applicable ND Not determined

Reviewer Comment: There was no evidence of time- or metabolism-dependent inhibition of any CYP enzymes with the exception of CYP2C8. High concentrations of TP-034 caused metabolism-dependent inhibition of CYP2C8; however, based on estimates of R1 for reversible inhibition and R2 for metabolism-dependent inhibition, TP-034 is not likely to cause clinically relevant reversible or irreversible inhibition of either hepatic or intestinal CYP enzymes.

Reviewer Assessment: TP-034 is not likely to cause clinically relevant reversible or irreversible inhibition of CYP enzymes.

Study No. (b) (4) 135050

In Vitro Evaluation of TP-6208 as an Inhibitor of Human Cytochrome P450 Enzymes in Human Liver Microsomes
Date(s): June 19, 2013 to June 30 2013
Sponsor: TetraPhase Pharmaceuticals, Inc. Watertown, MA
Testing Facility: (b) (4)

METHODS
To evaluate TP-6208 as a direct, time-dependent and metabolism-dependent inhibitor of CYP activity (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5), human liver

Reference ID: 4312284

microsomes from a pool of sixteen individuals were incubated with marker substrates in the presence or absence of TP-6208. Known direct and metabolism-dependent inhibitors of CYP enzymes were included as positive controls. Full incubation conditions are indicated in Table 1.

Table 1: IC50 determinations: Summary of assay conditions to measure microsomal CYP enzyme activity – Direct, time-dependent and metabolism-dependent inhibition of enzymes by TP-6208

Enzyme	Enzyme reaction	Substrate concentration (µM)	Incubation volume (µL)	Protein [a] (µg/mL)	Incubation time (min)	Pre-incubation time (min)	TP-6208	
							Target concentrations (µM)	Solvent volume [b] (µL)
CYP1A2	Phenacetin *O*-dealkylation	40	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30, 100	20
CYP2B6	Efavirenz 8-hydroxylation	3	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30, 100	20
CYP2C8	Amodiaquine *N*-dealkylation	1.5	200	12.5	5	30	0, 0.1, 0.3, 1, 3, 10, 30, 100	20
CYP2C9	Diclofenac 4′-hydroxylation	6	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30, 100	20
CYP2C19	*S*-Mephenytoin 4′-hydroxylation	40	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30, 100	20
CYP2D6	Dextromethorphan *O*-demethylation	7.5	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30, 100	20
CYP3A4/5	Testosterone 6β-hydroxylation	70	200	100	5	30	0, 0.1, 0.3, 1, 3, 10, 30, 100	20
CYP3A4/5	Midazolam 1′-hydroxylation	4	200	50	5	30	0, 0.1, 0.3, 1, 3, 10, 30, 100	20

a The human liver microsomal sample used for these experiments was a pool of sixteen individuals (samples 286, 290, 312, 313, 315, 333, 334, 335, 336, 339, 348, 359, 364, 383, 389 and 390).

b High Purity water was the vehicle used to dissolve the test article.

Results:

The positive control inhibitors for direct inhibition and metabolism-dependent inhibition inhibited enzyme activity as expected. Test article interference and test article suppression check samples performed as expected indicating that the addition of TP-6208 had little or no impact on the validated analytical methods used in this study (data not reported). Results of the evaluation of TP-6208 as a direct, metabolism-dependent and time-dependent inhibitor of human CYP enzymes is summarized in Table 2.

Table 2. Summary of results: *In vitro* evaluation of TP-6208 as an inhibitor of human CYP enzymes

Enzyme	Enzyme reaction	Direct inhibition		Time-dependent inhibition		Metabolism-dependent inhibition		
		Zero-minute preincubation		30-minute preincubation without NADPH		30-minute preincubation with NADPH		Potential for metabolism-dependent inhibition [c]
		IC_{50} (µM) [a]	Inhibition observed at 100 µM (%) [b]	IC_{50} (µM) [a]	Inhibition observed at 100 µM (%) [b]	IC_{50} (µM) [a]	Inhibition observed at 100 µM (%) [b]	
CYP1A2	Phenacetin *O*-dealkylation	>100	4.1	>100	6.8	>100	11	Little or no
CYP2B6	Efavirenz 8-hydroxylation	>100	13	>100	0.9	>100	8.2	Little or no
CYP2C8	Amodiaquine *N*-dealkylation	>100	6.2	>100	4.2	>100	11	Little or no
CYP2C9	Diclofenac 4′-hydroxylation	>100	6.0	>100	7.6	>100	6.2	Little or no
CYP2C19	*S*-Mephenytoin 4′-hydroxylation	>100	3.3	>100	NA	>100	NA	Little or no
CYP2D6	Dextromethorphan *O*-demethylation	>100	NA	>100	0.8	>100	4.1	Little or no
CYP3A4/5	Testosterone 6β-hydroxylation	>100	4.7	>100	6.4	>100	3.4	Little or no
CYP3A4/5	Midazolam 1′-hydroxylation	>100	NA	>100	NA	>100	5.9	Little or no

REVIEWER ASSESSMENT: There is negligible direct, time- or metabolism-dependent inhibition of any of the CYP enzymes by TP-6208.

Study No.: 10TETPP2

Reference ID: 4312284

Induction of CYP1A2, 2B6, and 3A4 Enzyme Activities in Fresh Human Hepatocytes

Date(s): January 11, 2011
Sponsor: TetraPhase Pharmaceuticals, Inc. Watertown, MA
Testing Facility: (b) (4)

METHODS

The *in vitro* induction effects of TP-434-046 (eravacycline; 0.1, 1, and 10 µM) on CYP1A2, 2B6, and 3A4 enzyme activities were evaluated using fresh human hepatocytes from three donors. Positive controls were treated in parallel with the induction media spiked with β-naphthoflavone at 10 µM for CYP1A2, phenobarbital at 1000 µM for CYP2B6, or rifampicin at 50 µM for CYP3A4.Vehicle controls were treated in parallel with the induction media containing 0.1% DMSO.

Results:

The induction effects of TP-434-046 and the positive chemical inducers on CYP enzyme activities in fresh human hepatocytes are shown in Table 1. Cell viabilities are shown in Table 2.

Table 1. Induction of Enzyme Activity in Human Hepatocytes
a) Induction of CYP1A2

Donor	Compound	Treatment	Resorufin Formation (pmol/well/min)[a]	Fold-Induction[b]	% of BNF-Treated Cells[c]
1	Control	Solvent	0.187 ± 0.16	1.0	0
		10 µM BNF	1.13 ± 0.07***	6.1	100
	TP-434-046	0.1 µM	0.078 ± 0.04	0.42	-12
		1 µM	0.074 ± 0.05	0.40	-12
		10 µM	0.054 ± 0.00	0.29	-14
2	Control	Solvent	0.094 ± 0.04	1.0	0
		10 µM BNF	4.62 ± 0.19***	49	100
	TP-434-046	0.1 µM	0.075 ± 0.02	0.80	-0.43
		1 µM	0.056 ± 0.01	0.60	-0.84
		10 µM	0.068 ± 0.02	0.72	-0.59
3	Control	Solvent	0.035 ± 0.01	1.0	0
		10 µM BNF	0.663 ± 0.05***	19	100
	TP-434-046	0.1 µM	0.018 ± 0.00	0.51	-2.7
		1 µM	0.025 ± 0.00	0.70	-1.7
		10 µM	0.019 ± 0.00	0.54	-2.5

b) Induction of CYP2B6

Reference ID: 4312284

Donor	Compound	Treatment	OH Bupropion Formation (pmol/well/min)[a]	Fold-Induction[b]	% of PB-Treated Cells[c]
1	Control	Solvent	0.387 ± 0.08	1.0	0
		1000 µM PB	9.97 ± 2.41***	26	100
	TP-434-046	0.1 µM	0.295 ± 0.02	0.76	-0.96
		1 µM	0.315 ± 0.03	0.81	-0.75
		10 µM	0.224 ± 0.02	0.58	-1.7
2	Control	Solvent	0.815 ± 0.15	1.0	0
		1000 µM PB	6.05 ± 0.59***	7.4	100
	TP-434-046	0.1 µM	0.551 ± 0.09	0.68	-5.0
		1 µM	0.583 ± 0.08	0.72	-4.4
		10 µM	0.264 ± 0.04	0.32	-11
3	Control	Solvent	0.335 ± 0.11	1.0	0
		1000 µM PB	5.89 ± 0.84***	18	100
	TP-434-046	0.1 µM	0.246 ± 0.06	0.73	-1.6
		1 µM	0.291 ± 0.12	0.87	-0.80
		10 µM	0.180 ± 0.06	0.54	-2.8

c) Induction of CYP3A4

Donor	Compound	Treatment	6β-OH Testosterone Formation (pmol/well/min)[a]	Fold-Induction[b]	% of RIF-Treated Cells[c]
1	Control	Solvent	61.4 ± 7.64	1.0	0
		50 µM RIF	348 ± 30.0***	5.7	100
	TP-434-046	0.1 µM	61.4 ± 12.8	1.0	0
		1 µM	55.9 ± 15.2	0.91	-1.9
		10 µM	16.7 ± 3.38*	0.27	-16
2	Control	Solvent	52.2 ± 3.60	1.0	0
		50 µM RIF	446 ± 117***	8.6	100
	TP-434-046	0.1 µM	55.6 ± 20.6	1.1	0.88
		1 µM	47.0 ± 5.58	0.90	-1.3
		10 µM	15.4 ± 4.56	0.29	-9.3
3	Control	Solvent	5.32 ± 1.24	1.0	0
		50 µM RIF	130 ± 4.64***	24	100
	TP-434-046	0.1 µM	5.54 ± 0.19	1.0	0.18
		1 µM	4.51 ± 0.05	0.85	-0.66
		10 µM	2.56 ± 0.13	0.48	-2.2

a: Data were expressed as the mean ± SD of three individual measurements (***p<0.001, compared with the vehicle-treated group).
b: Fold-induction was calculated based on the enzyme activity (formation rate of the probe substrate metabolite) of the test compound or the positive inducer to that of the vehicle-treated cells (solvent control).
c: Percentage of enzyme activity relative to the positive inducer-treated cells (USA FDA Draft Guidance: Drug Interaction Studies, September 2006; Hewitt NJ, et al., Chem Biol Interact, 2007, 168:51-56).

When the three donor hepatocytes were exposed to TP-434-046, the cell viability relative to the solvent controls (0.1% DMSO) ranged from 88-115% at 0.1 µM, 97-100% at 1 µM, and 81-95% at 10 µM, suggesting that TP-434-046 has little impact on cell viability.
Reviewer Assessment: TP-434-046 did not show any inductive effects on CYP1A2, 2B6, or 3A4 on the three hepatocytes evaluated. TP-434-046 also had little impact on cell viability.

Reference ID: 4312284

Study No. (b) (4) 53026

***In Vitro* Evaluation of TP-034 as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes**

Date(s): July 30, 2015 to September 15, 2015
Sponsor: TetraPhase Pharmaceuticals, Inc. Watertown, MA
Testing Facility: (b) (4)

METHODS

Three preparations of cryopreserved human hepatocytes from three separate donors were treated once daily for three consecutive days with dimethyl sulfoxide (DMSO, 0.1% v/v, vehicle control), flumazenil (25 µM, negative control), one of eight concentrations of TP-034 (eravacycline; 0.01, 0.1, 0.3, 1, 3, 7.5, 10 or 30 µM) or one of three known human CYP inducers [omeprazole (50 µM), phenobarbital (750 µM) and rifampin (20 µM)]. The highest concentration of TP-034 tested was 120× plasma $C_{max,ss}$ of TP-034 (0.25 µM) following intravenous dosing to steady state with the highest clinical doses of eravacycline. After treatment, the cells were incubated with the appropriate marker substrates for the analysis of phenacetin *O*-dealkylation (marker for CYP1A2), bupropion hydroxylation (marker for CYP2B6) and midazolam 1'-hydroxylation (marker for CYP3A4/5) by LC/MS/MS.

RESULTS

At the time of isolation the viability of each hepatocyte preparation was between 81.7 and 91%. Treatment of hepatocytes with TP-034 caused little or no LDH release (≤ 4.5%), relative to the positive control.

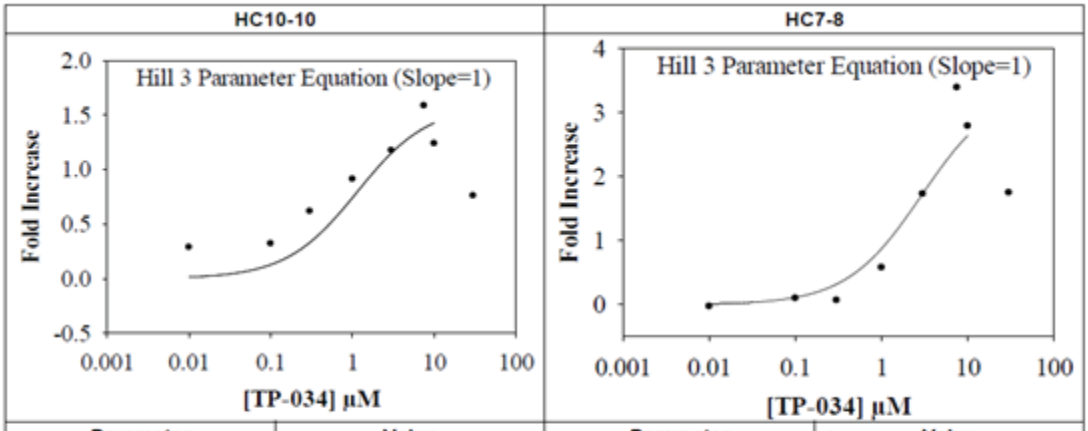
The enzyme induction studies with TP-034 at concentration ≥ 120 plasma $C_{max,ss}$ suggest that TP-034 has no potential to cause clinically relevant induction of CYP1A2. However, based on estimates of *E*max and EC50 for induction of CYP2B6 and CYP3A4 mRNA levels by TP-034, the value of *R*3 fell below 0.9 in two and three cultures of human hepatocytes, respectively (Figures 1 and 2). These results suggest TP-034 may have the potential to cause clinically relevant induction of CYP2B6 and CYP3A4.

Reviewer Comment: The potential for clinically relevant induction based on the value of R3 was calculated according to the following equation, where d is a scaling factor set to 1 for the basic model and [I] is total (bound+unbound) plasma concentration at steady state, which is 0.15 uM for TP-034. Values of R3 less than 0.9 were considered potentially clinically relevant induction based on the FDA 2012 Guidance on Drug-drug Interactions.

Reference ID: 4312284

$$R_3 = \frac{1}{1 + d\ (\frac{E_{max} \cdot [I]}{EC_{50} + [I]})} < 0.9$$

Figure 1. Estimates of *E*max, EC50 and *R*3 for induction of CYP2B6 mRNA in cultured human hepatocytes treated with TP-034



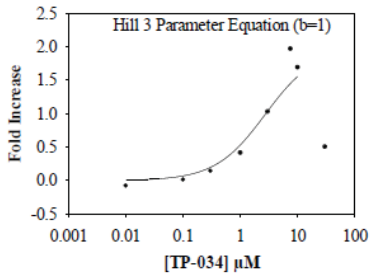
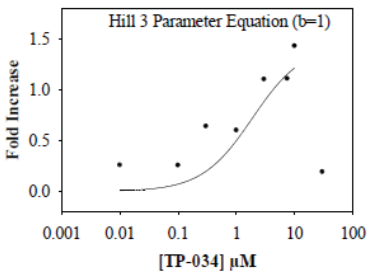
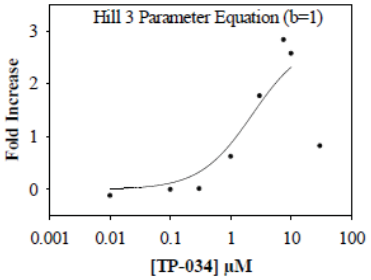
Parameter	Value	Parameter	Value
E_{max} (fold)	1.59 ± 0.27	E_{max} (fold)	3.41 ± 0.94
EC_{50} (µM)	1.14 ± 0.75	EC_{50} (µM)	2.90 ± 2.28
Slope	1.00	Slope	1.00
R^2	0.790	R^2	0.912
Equation	Sigmoidal Hill [a]	Equation	Sigmoidal Hill [a]
R_3 [§]	0.836	R_3 [§]	0.849
R_3 [†]	0.778	R_3 [†]	0.787

a The slope was manually set to 1
§ Calculations are based on a plasma *C*max,ss of 0.16 µM (for oral dosing)
† Calculations are based on a plasma *C*max,ss of 0.25 µM (for intravenous dosing)

Reviewer Comment: TP-034 increased CYP2B6 mRNA levels more than 20% of positive control in HC7-8 (63.6%) and less than 20% in HC10-10 (8.02%). In both cultures of human hepatocytes the values of R_3 were slightly below the FDA cutoff of 0.9. While these results may suggest TP-034 to cause induction of CYP2B6, it is not likely to be clinically significant

Figure 2. Estimates of *E*max, EC50 and *R*3 for induction of CYP3A4 mRNA in cultured human hepatocytes treated with TP-034

Reference ID: 4312284

HC10-10		HC10-8		HC7-8	
					
Parameter	**Value**	**Parameter**	**Value**	**Parameter**	**Value**
E_{max} (fold)	1.98 ± 0.48	E_{max} (fold)	1.44 ± 0.42	E_{max} (fold)	2.84 ± 0.63
EC_{50} (µM)	2.70 ± 1.93	EC_{50} (µM)	1.89 ± 1.81	EC_{50} (µM)	2.27 ± 1.57
Slope	1.00	Slope	1.00	Slope	1.00
R^2	0.925	R^2	0.673	R^2	0.927
Equation	Sigmoidal Hill [a]	Equation	Sigmoidal Hill [a]	Equation	Sigmoidal Hill [a]
R_3 §	0.900	R_3 §	0.899	R_3 §	0.842
R_3 †	0.856	R_3 †	0.856	R_3 †	0.780

a The slope was manually set to 1
§ Calculations are based on a plasma Cmax,ss of 0.16 µM (for oral dosing)
† Calculations are based on a plasma Cmax,ss of 0.25 µM (for intravenous dosing)

Reviewer Comment: TP-034 caused > 2-fold change in CYP3A4 mRNA levels in all three cultures of human hepatocytes but in all cases, the increases were less than 20% of positive controls (see table below).

CYP3A4/5 and CYP3A4												
Treatment group	Activity						mRNA					
	HC10-10		HC10-8		HC7-8		HC10-10		HC10-8		HC7-8	
	Fold change	% Positive control	Fold change	% Positive control	Fold change	% Positive control	Fold change	% Positive control	Fold change	% Positive control	Fold change	% Positive control
0.1% DMSO	1.00	0	1.00	0	1.00	0	1.00	0	1.00	0	1.00	0
0.01 µM TP-034	0.955	−0.514	1.44	2.45	0.965	−0.194	0.921	−0.782	1.26	2.45	0.880	−0.442
0.1 µM TP-034	1.03	0.293	1.38	2.12	0.982	−0.0971	1.01	0.119	1.26	2.43	0.994	−0.0221
0.3 µM TP-034	1.08	0.942	1.75	4.22	1.08	0.427	1.14	1.42	1.64	6.05	1.01	0.0442
1 µM TP-034	1.33	3.78	1.82	4.58	1.50	2.77	1.41	4.10	1.60	5.67	1.62	2.28
3 µM TP-034	1.72	8.22	2.27	7.11	2.02	5.62	2.03	10.2	2.11	10.4	2.77	6.51
7.5 µM TP-034	1.85	9.79	2.43	8.03	2.66	9.14	2.97	19.5	2.11	10.5	3.83	10.4
10 µM TP-034	1.84	9.60	2.42	8.01	2.21	6.64	2.69	16.8	2.43	13.5	3.57	9.47
30 µM TP-034	0.669	−3.79	0.894	−0.594	1.13	0.692	1.50	4.98	1.19	1.82	1.82	3.02
25 µM Flumazenil	1.19	2.16	1.27	1.52	0.991	−0.0478	1.17	1.70	1.26	2.41	1.14	0.526
20 µM Rifampin	9.73	100	18.8	100	19.1	100	11.1	100	11.6	100	28.2	100

CYP2B6												
Treatment group	Activity						mRNA					
	HC10-10		HC10-8		HC7-8		HC10-10		HC10-8		HC7-8	
	Fold change	% Positive control	Fold change	% Positive control	Fold change	% Positive control	Fold change	% Positive control	Fold change	% Positive control	Fold change	% Positive control
0.1% DMSO	1.00	0	1.00	0	1.00	0	1.00	0	1.00	0	1.00	0
0.01 µM TP-034	1.19	1.48	1.31	2.60	1.05	1.69	1.29	1.46	1.41	3.89	0.975	−0.468
0.1 µM TP-034	1.18	1.41	1.27	2.27	1.00	0.0680	1.32	1.63	1.07	0.682	1.10	1.89
0.3 µM TP-034	1.29	2.20	1.56	4.70	1.03	1.03	1.62	3.13	1.46	4.31	1.07	1.29
1 µM TP-034	1.51	3.90	1.57	4.81	1.60	19.0	1.91	4.62	1.41	3.88	1.58	10.9
3 µM TP-034	1.87	6.68	1.83	6.95	2.45	46.0	2.18	5.95	1.76	7.23	2.73	32.5
7.5 µM TP-034	1.84	6.45	1.77	6.49	4.13	99.4	2.59	8.02	1.81	7.71	4.40	63.6
10 µM TP-034	1.74	5.69	1.93	7.77	3.22	70.6	2.24	6.27	1.93	8.77	3.80	52.4
30 µM TP-034	0.656	−2.65	1.05	0.408	2.14	36.3	1.76	3.85	1.59	5.54	2.75	32.8
25 µM Flumazenil	1.23	1.77	1.20	1.66	1.02	0.752	1.14	0.708	1.37	3.53	1.08	1.48
750 µM Phenobarbital	14.0	100	12.9	100	4.14	100	20.8	100	11.6	100	6.34	100

Table continued on next page.

Reviewer Assessment: The *R*3 values for CYP 3A4 and CYP2B6 fell slightly below the FDA's cutoff of 0.9 in two and three cultures of human hepatocytes, respectively, using the total concentration of TP-034. These results may suggest TP-034 has the potential to cause clinically relevant induction of CYP2B6 and CYP3A4; however, the results particularly associate with CYP3A4 should be interpreted with caution given that mRNA increases in the control arm were outside the prespecified acceptance window.

Study No. (b) (4) 133065

***In Vitro* Evaluation of TP-6208 as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes**

Date(s): June 18, 2013 to July 30, 2013
Sponsor: TetraPhase Pharmaceuticals, Inc. Watertown, MA
Testing Facility: (b) (4)

METHODS

Three preparations of cryopreserved human hepatocytes from three separate donors were treated once daily for three consecutive days with dimethyl sulfoxide (DMSO, 0.1% v/v, vehicle control), flumazenil (25 µM, negative control), one of six concentrations of TP-6208 (0.01, 0.1, 1, 3, 10 or 30 µM) or one of three known human CYP inducers [omeprazole (50 µM), phenobarbital (750 µM) and rifampin (20 µM)]. After treatment, the cells were incubated with the appropriate marker substrates for the analysis of phenacetin *O*-dealkylation (marker for CYP1A2), bupropion hydroxylation (marker for CYP2B6) and midazolam 1'-hydroxylation (marker for CYP3A4/5) by LC/MS/MS.

RESULTS

At the time of isolation the viability of each hepatocyte preparation was between 77 and 85%. Treatment of cultured human hepatocytes with up to 30 µM TP-6208 resulted in little or no

LDH release (<20% of the positive LDH control) at 24, 48 or 72-hour time points. Positive controls caused anticipated and appropriate increases in CYP enzyme expression.

Overall, treatment of cultured human hepatocytes with up to 30 µM TP-6208 had little or no effect on CYP1A2 activity (range of 0.690- to 1.07-fold), on CYP2B6 activity (range of 0.775- to 1.85-fold) or on CYP3A4/5 activity (range of 0.816- to 1.49-fold).

Similar to the negligible effect on activity, treatment of cultured human hepatocytes with up to 30 µM TP-6208 produced little or no increase of CYP1A2 mRNA (range of 0.865- to 1.70-fold), CYP2B6 mRNA (range of 0.908- to 1.57-fold) or CYP3A4 mRNA levels (range 0.760- to 1.51-fold).

REVIEWER ASSESSMENT: Treatment of hepatocytes with up to 30 µM TP-6208 produced little or no increase (< 2-fold) in CYP1A2, CYP2B6, or CYP3A4 mRNA and enzyme activity levels.

Study No (b) (4) 143046

***In Vitro* Evaluation of Eravacycline and TP-498 as Inducers of Cytochrome P450 Expression in Cultured Human Hepatocytes**

Date(s): August 27, 2014 to October 6, 2014
Sponsor: TetraPhase Pharmaceuticals, Inc. Watertown, MA
Testing Facility: (b) (4)

METHODS
Three cryopreserved preparations of cultured human hepatocytes from three separate livers were treated once daily for three consecutive days with dimethyl sulfoxide flumazenil (negative control), one of eight concentrations of TP-498 (0.04, 0.2, 2, 4, 10, 20, 60 or 100 µM), one of thirteen concentrations of eravacycline (0.06, 0.1, 0.3, 0.6, 1, 2, 3, 6, 10, 30, 60, 100 or 200 µM) or one of three known human CYP inducers [omeprazole (50 µM), phenobarbital (750 µM) and rifampin (20 µM) as positive controls]. After treatment, the cells were incubated with the appropriate marker substrates for the analysis of phenacetin *O*-dealkylation (marker for CYP1A2), bupropion hydroxylation (marker for CYP2B6) and midazolam 1′-hydroxylation (marker for CYP3A4/5) by LC-MS/MS.

RESULTS
Cultured human hepatocytes treated with TP-498 at concentrations of 20 µM or above exhibited mild cytotoxicity. Treatment of cultured human hepatocytes with up to 3 µM eravacycline did not cause any detectable cytotoxicity, while those treated with eravacycline at concentrations of 6 µM exhibited mild cytotoxicity and those treated with concentrations of 100 µM or above exhibited severe cytotoxicity.

Treatment of cultured human hepatocytes with TP-498 at concentrations of up to 4 to 10 µM or with eravacycline at concentrations of up to 3 µM (concentrations that did not alter culture morphology and were not associated with cytotoxicity) did not induce CYP activity or mRNA

Reference ID: 4312284

levels (≤ 2.0-fold change or ≤ 10% of positive control response) for CYP1A2, CYP2B6 and CYP3A4.

REVIEWER ASSESSMENT: CYP1A2, CYP2B6 and CYP3A4 were not induced with TP-498 at concentrations of up to 4 to 10 µM or with eravacycline at concentrations of up to 3 µM. The reason for the marked decreases in CYP activity and mRNA levels after incubation with high concentrations of TP-498 or eravacycline was not investigated. The Sponsor suggests that these changes in CYP activity and mRNA levels may be secondary to sublethal cytotoxicity observed at these concentrations.

STUDY NO.: TP-434-016

A Phase 1, Open-Label Clinical Study to Assess the Impact of Itraconazole on Eravacycline Pharmacokinetics in Healthy Subjects

Date(s): May 26, 2015 to October 13 2015
Sponsor: Tetraphase Pharmaceuticals, Inc. Watertown, MA
Clinical Site: Medpace CPU, Cincinnati, Ohio
Analytical Site: (b) (4)

METHODS

This was a Phase 1, prospective, single-center, open-label clinical study to assess the PK interactions of itraconazole with eravacycline in healthy subjects. In Part A, subjects received a single 1.0 mg/kg dose of IV eravacycline on Day 1 as a 60-minute infusion, after breakfast and again on Day 10. Subjects received itraconazole 200 mg po every 12 hours on Day 8 and then every 24 hours from Day 9 to Day 10. Intravenous eravacycline was stopped after the second dosing on the morning of Day 10. Itraconazole was stopped after dosing on the morning of Day 10.

PK Sample Collection: Blood samples for PK analysis of eravacycline and metabolites were collected on Day 1 and Day 10 pre-dose and up to 48 hours after the start of the IV infusion.

Drug Products: Eravacycline for IV administration was supplied as a sterile injectable lyophilized powder in a 10 mL vial. Eravacycline drug product contains (b) (4) mg (TP-434 free base equivalents) of lyophilized powder and mannitol as an inactive (b) (4) Itraconazole was supplied as a 10mg/ml oral solution (Lot # EKB3D00).

Analytical Methods: Concentrations of eravacycline and metabolites, TP-498, TP-6208, and TP-034 in human plasma samples were measured by LC-MS/MS. The performance of the bioanalytical assays is acceptable.

RESULTS

The results of PK parameters of eravacycline and its metabolites (TP-498, TP-6208, and TP-034) on Day 1 and Day 10 are summarized in Tables 1 and 2.

Table 1. Eravacycline PK Parameters Following 1.0 mg/kg Intravenous Infusion of Eravacycline on Day 1 and Day 10

Reference ID: 4312284

	Eravacycline					
	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (h*ng/mL)	$t_{1/2}$ (h)	CL (mL/min/kg)	V_{ss} (L/kg)
Day 1						
N	10	10	10	10	10	10
Mean	1100	nr	4320	14	3.79	3.42
SD	475	nr	1250	2.4	1.03	0.730
Min	767	1.0	2880	11	2.01	2.12
Median	939	1.0	4250	15	3.52	3.41
Max	2310	1.1	7330	19	5.55	4.59
Geometric mean	1030	nr	4180	14	3.65	3.34
CV% geometric mean	36.1	nr	27.0	17	29.4	22.8
Day 10						
N	10	10	10	10	10	10
Mean	1160	nr	5700	19	2.57	3.37
SD	420	nr	1090	3.6	0.500	0.562
Min	741	1.0	4360	15	1.45	2.76
Median	1070	1.0	5410	19	2.70	3.17
Max	2260	1.1	8200	28	3.22	4.52
Geometric mean	1110	nr	5610	19	2.51	3.33
CV% geometric mean	30.7	nr	18.0	17	22.9	16.1

Table 2. PK Parameters of Metabolites Following 1.0 mg/kg Intravenous Infusion of Eravacycline on Day 1 and Day 10

a) Day 1

	TP-498				TP-6208				TP-034			
	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (h*ng/mL)	$t_{1/2}$ (h)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (h*ng/mL)	$t_{1/2}$ (h)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (h*ng/mL)	$t_{1/2}$ (h)
Day 1												
N	10	10	10	0	10	10	10	5	10	10	10	4
Mean	84.1	nr	700	nd	63.3	nr	1730	13	33.5	nr	1050	16
SD	34.0	nr	172	nd	21.3	nr	434	2.3	9.05	nr	242	1.6
Min	54.7	1.0	409	nd	37.4	6.0	1220	11	19.6	6.0	770	14
Median	71.3	1.0	687	nd	59.0	8.1	1770	12	32.3	12	1030	16
Max	166	1.1	1040	nd	100	12	2380	17	47.1	24	1460	18
Geometric mean	79.3	nr	680	nd	60.2	nr	1680	13	32.3	nr	1030	16
CV% geometric mean	35.7	nr	25.8	nd	34.3	nr	25.6	16	28.8	nr	22.8	10

b) Day 10

	TP-498				TP-6208				TP-034			
	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (h*ng/mL)	$t_{1/2}$ (h)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (h*ng/mL)	$t_{1/2}$ (h)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (h*ng/mL)	$t_{1/2}$ (h)
Day 10												
N	10	10	10	0	10	10	10	0	10	10	10	0
Mean	87.5	nr	970	nd	19.0	nr	626	nd	9.91	nr	342	nd
SD	30.3	nr	136	nd	7.20	nr	235	nd	2.23	nr	117	nd
Min	57.8	1.0	810	nd	11.0	8.0	372	nd	6.69	8.0	130	nd
Median	78.1	1.0	921	nd	16.7	12	508	nd	10.2	12	355	nd
Max	153	1.1	1210	nd	31.3	12	1020	nd	14.0	36	515	nd
Geometric mean	83.5	nr	962	nd	17.8	nr	591	nd	9.68	nr	320	nd
CV% geometric mean	32.3	nr	13.8	nd	37.6	nr	36.4	nd	23.1	nr	42.9	nd

Table 3. Analysis of Pharmacokinetic Parameters on Day 10 vs. Day 1

Molecule	PK Parameter (Unit)	n	Ratio of Geom. Mean (%)	90% CI for Ratio (%)	P-value
Eravacycline	C_{max} (ng/mL)	10	107.88	97.83, 118.96	0.1889
	AUC_{0-t} (h*ng/mL)	10	134.28	124.13, 145.26	<0.0001
TP-498	C_{max} (ng/mL)	10	105.31	94.91, 116.86	0.3856
	AUC_{0-t} (h*ng/mL)	10	141.34	128.46, 155.52	<0.0001
TP-6208	C_{max} (ng/mL)	10	29.66	26.44, 33.26	<0.0001
	AUC_{0-t} (h*ng/mL)	10	35.24	31.80, 39.05	<0.0001
TP-034	C_{max} (ng/mL)	10	29.96	26.63, 33.71	<0.0001
	AUC_{0-t} (h*ng/mL)	10	31.10	26.08, 37.09	<0.0001

REVIEWER ASSESSMENT: Following administration with itraconazole on Day 10, mean eravacycline AUC0-t increased approximately 32%. Similarly, there was a reduction in mean eravacycline clearance of approximately 32% and in mean AUC of its metabolites, TP-6208 and TP-034, of approximately 65%.

STUDY NO.: TP-434-020

A Phase 1, Open-Label Clinical Study to Assess the Impact of Rifampin on Eravacycline Pharmacokinetics in Healthy Subjects

Date(s): August 3, 2015 to October 21, 2015
Sponsor: Tetraphase Pharmaceuticals, Inc. Watertown, MA
Clinical Site: Medpace CPU, Cincinnati, Ohio
Analytical Site: (b) (4)

METHODS

This was a Phase 1, prospective, single-center, open-label clinical study to assess the PK interactions of oral rifampin with eravacycline in healthy subjects.

Reference ID: 4312284

The treatment period consisted of 19 days, including a washout period. Subjects received single 1.0 mg/kg dose of IV eravacycline on Day 1 as a 60-minute infusion and again on Day 17. Subjects received rifampin 600 mg po every 24 hours from Day 8 to Day 17. Study drugs were administered under fasting conditions.

PK Sample Collection: Blood samples for PK analysis of eravacycline and metabolites were collected on Day 1 and Day 17 pre-dose and up to 48 hours after the start of the IV infusion.

Drug Products: Eravacycline for IV administration was supplied as a sterile injectable lyophilized powder in a 10 mL vial. Eravacycline drug product contains (b) (4) mg (TP-434 free base equivalents) of lyophilized powder and mannitol as an inactive (b) (4) Rifampin was supplied as a 600 mg capsule (Lot # ME130564).

Analytical Methods: Concentrations of eravacycline and metabolites, TP-498, TP-6208, and TP-034 in human plasma samples were measured by LC-MS/MS. The performance of the bioanalytical assays is acceptable.

RESULTS

Following coadministration with rifampin, the mean C_{max} of eravacycline was unchanged, while the mean AUC0-24h was decreased approximately 25%, mean CL increased approximately 54%, and the apparent half-life for eravacycline decreased approximately 27%. The results of PK parameters of eravacycline and its metabolites (TP-498, TP-6208, and TP-034) on Day 1 and Day 17 are summarized in Tables 1 and 2.

Table 1. Eravacycline PK Parameters Following 1.0 mg/kg Intravenous Infusion of Eravacycline on Day 1 and Day 17

Reference ID: 4312284

	Eravacycline						
	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-inf} (h*ng/mL)	AUC_{0-24h} (h*ng/mL)	$t_{1/2}$ (h)	CL_S (mL/min/kg)	V_{ss} (L/kg)
Day 1							
N	12	12	12	12	12	12	12
Mean	1170	nr	5380	4100	15	3.20	2.85
SD	186	nr	962	589	2.0	0.595	0.290
Min	845	0.98	3790	3210	11	2.35	2.41
Median	1160	1.0	5380	4090	15	3.10	2.85
Max	1580	1.1	7110	5150	18	4.39	3.26
Geometric mean	1160	nr	5300	4060	15	3.15	2.84
CV% geometric mean	16.0	nr	18.4	14.5	14	18.4	10.3
Day 17							
N	12	12	12	12	12	12	12
Mean	1260	nr	3520	3090	11	4.94	2.49
SD	281	nr	726	568	2.3	1.08	0.513
Min	903	1.0	2380	2280	6.2	3.53	1.69
Median	1160	1.0	3600	3120	11	4.63	2.53
Max	1800	1.1	4720	3880	15	7.00	3.19
Geometric mean	1230	nr	3450	3040	11	4.83	2.44
CV% geometric mean	21.6	nr	21.6	19.0	23	21.6	22.1

Table 2. PK Parameters of Metabolites Following 1.0 mg/kg Intravenous Infusion of Eravacycline on Day 1 and Day 17

	TP-498				TP-6208				TP-034			
	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (h*ng/mL)	$t_{1/2}$ (h)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (h*ng/mL)	$t_{1/2}$ (h)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (h*ng/mL)	$t_{1/2}$ (h)
Day 1												
N	12	12	12	0	12	12	12	6	12	12	12	0
Mean	30.9	nr	286	nd	63.2	nr	1110	15	36.9	nr	734	nd
SD	5.42	nr	54.0	nd	14.2	nr	230	2.5	7.92	nr	153	nd
Min	24.5	0.98	224	nd	46.6	8.0	835	11	27.7	6.0	562	nd
Median	28.0	1.0	270	nd	60.3	12	1090	15	36.5	12	731	nd
Max	38.4	1.1	390	nd	95.2	12	1540	19	53.6	24	1070	nd
Geometric mean	30.5	nr	281	nd	61.9	nr	1090	15	36.2	nr	721	nd
CV% geometric mean	17.4	nr	17.7	nd	21.4	nr	20.7	17	20.9	nr	20.4	nd
Day 17												
N	12	12	7	0	12	12	12	12	12	12	12	12
Mean	37.0	nr	228	nd	139	nr	2080	9.6	73.6	nr	1270	14
SD	6.89	nr	35.0	nd	21.5	nr	250	1.3	13.6	nr	218	3.2
	TP-498				TP-6208				TP-034			
	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (h*ng/mL)	$t_{1/2}$ (h)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (h*ng/mL)	$t_{1/2}$ (h)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (h*ng/mL)	$t_{1/2}$ (h)
Min	28.3	1.0	196	nd	110	4.0	1640	7.5	60.2	2.0	984	9.2
Median	35.1	1.0	213	nd	134	6.0	2070	10	69.5	4.0	1250	14
Max	52.5	1.1	278	nd	197	8.0	2710	11	111	6.0	1790	22
Geometric mean	36.4	nr	226	nd	138	nr	2070	9.5	72.6	nr	1260	14
CV% geometric mean	17.6	nr	14.9	nd	14.3	nr	11.7	14	16.5	nr	16.3	22

Reviewer Comment: Rifampin altered the PK of eravacycline by increasing the conversion of eravacycline to the metabolites TP-6208 and TP-034. These metabolites are thought to be inactive.

Table 3. Analysis of Pharmacokinetic Parameters

Molecule	PK Parameter (Unit)	n	Ratio of Geom. Mean (%)	90% CI for Ratio (%)	P-value
Eravacycline	C_{max} (ng/mL)	12	106.47	97.97, 115.70	0.2030
	AUC_{0-t} (h*ng/mL)	12	67.92	63.49, 72.67	<0.0001
TP-498	C_{max} (ng/mL)	12	119.57	110.97, 128.82	0.0012
	AUC_{0-t} (h*ng/mL)	12	35.15	30.82, 40.09	<0.0001
TP-6208	C_{max} (ng/mL)	12	222.32	203.70, 242.65	<0.0001
	AUC_{0-t} (h*ng/mL)	12	147.04	134.85, 160.34	<0.0001
TP-034	C_{max} (ng/mL)	12	200.76	184.64, 218.28	<0.0001
	AUC_{0-t} (h*ng/mL)	12	138.27	127.54, 149.92	<0.0001

REVIEWER ASSESSMENT: Concomitant administration of eravacycline and rifampin to healthy subjects resulted in a decrease in AUC0-inf by 35%, an increase in CL 54% and a decrease in half-life of 27%, with negligible effects on Vss (13% decrease) and C_{max} (8% increase).

TP-434-P1-SAD-1: Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Pharmacokinetics of Single Ascending Doses of TP-434

Date(s): 10/4/2009 – 11/27/2009
Sponsor: Tetraphase Pharmaceuticals, Inc., Watertown, MA
Clinical Site: Cetero Research, Fargo, ND

METHODS

Study Design: Study TP-434-P1-SAD-1 was a single-center, double-blind, placebo-controlled, randomized, single-ascending-dose study to assess the safety, tolerability, and PK of IV TP-434 (eravacycline, ERV) in 56 healthy male and female subjects. Subjects were randomized to receive 0.10 mg/kg, 0.25 mg/kg, 0.50 mg/kg, 1.00 mg/kg, 1.50 mg/kg, 2.00 mg/kg, or 3.00 mg/kg IV ERV or placebo over 30 minutes on Day 1 (active:placebo = 3:1). Safety was monitored over 9 days. 16 plasma and 6 urine samples were collected over 5 days.

ERV was the drug product and was supplied as lyophilized powder for reconstitution with sterile water prior to IV administration.

Analytical Methods: Bioanalytical assays TSLS09-137 and TSLS09-136 were used to measured ERV concentrations in plasma and urine, respectively. The performance was satisfactory.

Reference ID: 4312284

RESULTS

Pharmacokinetics:
The PK parameters identified in this study are displayed in Table 159.

Plasma
Table 159 and Table 160 report the plasma PK Parameters identified for ERV and TP-498, respectively.

Table 159. PK Parameters of ERV after a Single Dose of ERV.

PK Parameters	Dose Group 1: 0.10 mg/kg TP-434	Dose Group 2: 0.25 mg/kg TP-434	Dose Group 3: 0.50 mg/kg TP-434	Dose Group 4: 1.00 mg/kg TP-434	Dose Group 5: 1.50 mg/kg TP-434	Dose Group 6: 2.00 mg/kg TP-434	Dose Group 7: 3.00 mg/kg TP-434
N	6	6	6	6	6	6	6
AUC_{0-24} (ng•h/mL)	436.76 (17.76)	968.70 (12.86)	1946.77 (18.74)	4072.37 (18.60)	6329.83 (15.00)	9172.84 (13.27)	18148.33 (22.06)
AUC_{0-t} (ng•h/mL)	428.00 (21.22)	1153.89 (16.54)	2502.89 (25.91)	5297.91 (22.15)	8495.57 (17.28)	11972.12 (14.25)	22443.50 (20.71)
$AUC_{0-\infty}$ (ng•h/mL)	554.18 (23.21)	1309.11 (16.16)	2678.65 (25.55)	5511.06 (21.28)	8856.79 (18.26)	12347.54 (15.35)	23145.23 (20.71)
C_{max} (ng/mL)	227.0 (24.45)	466.5 (22.70)	993.5 (17.50)	1888 (27.84)	3233 (22.60)	4917 (16.99)	9730 (16.94)
T_{max}[a] (h)	0.50 (0.47 - 0.55)	0.50 (0.25 - 0.63)	0.50 (0.50 - 0.55)	0.53 (0.52 - 0.67)	0.52 (0.50 - 0.53)	0.50 (0.50 - 0.50)	0.50 (0.48 - 0.58)
$t_{1/2}$ (h)	12.66 (23.92)	16.45 (13.30)	19.63 (28.03)	20.24 (28.02)	22.66 (17.99)	22.25 (12.41)	25.62 (9.70)
CL (L/h)	13.85 (18.99)	16.50 (17.47)	15.80 (14.98)	14.65 (12.11)	13.35 (14.43)	13.24 (9.81)	11.06 (25.37)
V_{ss} (L)	186.26 (27.69)	280.23 (10.98)	294.42 (18.67)	268.39 (24.18)	270.56 (15.07)	250.36 (11.87)	184.75 (23.43)
V_z (L)	251.70 (29.47)	385.32 (10.29)	436.51 (21.36)	427.82 (31.11)	428.30 (10.54)	425.38 (14.98)	405.62 (23.82)
CL/Weight (L/h/kg)	0.19 (21.29)	0.20 (17.11)	0.20 (24.56)	0.19 (19.83)	0.17 (19.05)	0.17 (14.92)	0.14 (24.52)
V_{ss}/Weight (L/kg)	2.46 (14.76)	3.33 (11.59)	3.57 (13.50)	3.37 (20.36)	3.51 (15.42)	3.10 (9.44)	2.28 (26.40)
V_z/Weight (L/kg)	3.31 (15.49)	4.58 (12.28)	5.28 (14.51)	5.34 (26.16)	5.55 (8.61)	5.24 (9.61)	4.93 (17.98)

Source: Adapted from Table 6 in the PK Report.

Table 160. PK Parameters of TP-498 after a Single Dose of ERV.

PK Parameters	Dose Group 1: 0.10 mg/kg TP-434	Dose Group 2: 0.25 mg/kg TP-434	Dose Group 3: 0.50 mg/kg TP-434	Dose Group 4: 1.00 mg/kg TP-434	Dose Group 5: 1.50 mg/kg TP-434	Dose Group 6: 2.00 mg/kg TP-434	Dose Group 7: 3.00 mg/kg TP-434
N	6	6	6	6	6	6	6
AUC_{0-24} (ng•h/mL)	2.22 (27.94)	71.08 (48.43)	204.72 (14.11)	395.51 (12.93)	593.90 (12.76)	773.37 (11.31)	1344.76 (14.87)
AUC_{0-t} (ng•h/mL)	1.87 (30.89)	60.23 (64.51)	362.92 (31.53)	962.11 (27.34)	1502.03 (20.50)	1979.49 (14.35)	3193.94 (16.45)
$AUC_{0-\infty}$ (ng•h/mL)	NC (NC)	NC (NC)	607.37 (26.56)[b]	1222.21 (24.19)	1755.54 (17.31)	2251.56 (15.59)	3569.97 (16.40)
C_{max} (ng/mL)	6.713 (22.19)	11.78 (25.18)	28.87 (13.57)	52.13 (18.18)	83.83 (23.96)	156.5 (12.08)	345.9 (24.91)
T_{max}[a] (h)	0.48 (0.25 - 0.55)	0.50 (0.25 - 0.58)	0.50 (0.50 - 0.58)	0.53 (0.52 - 0.67)	0.52 (0.25 - 0.53)	0.50 (0.50 - 0.50)	0.50 (0.48 - 0.58)
$t_{1/2}$ (h)	NC (NC)	NC (NC)	33.21 (2.21)[b]	31.21 (13.59)	29.16 (5.89)	29.38 (8.71)	27.38 (8.97)

Tmax reported as median (min=max), b: n=3, NC = Not Calculated
Source: Adapted from Table 8 in the PK Report.

Reference ID: 4312284

Reviewer Comment: The mean extrapolation ratio (AUCinf/AUC0-t) for ERV AUCinf exceeds 1.2 in subjects in the 0.10 mg/kg cohort. The mean extrapolation ratio for TP-498 AUCinf exceeds 1.2 in subjects in the 0.5 and 1.0 mg/kg cohorts. Therefore, the PK profiles in the respective dose cohorts were not adequately characterized. However, the PK profile for 1 mg/kg ERV, the proposed dose, was appropriately captured.

Urine

Table 161 and Table 162 report urine PK parameters of ERV and TP-498, respectively.

Table 161. Mean (CV%) Urine PK Parameters of ERV after a Single Dose.

PK Parameters	Dose Group 1: 0.10 mg/kg TP-434	Dose Group 2: 0.25 mg/kg TP-434	Dose Group 3: 0.50 mg/kg TP-434	Dose Group 4: 1.00 mg/kg TP-434	Dose Group 5: 1.50 mg/kg TP-434	Dose Group 6: 2.00 mg/kg TP-434	Dose Group 7: 3.00 mg/kg TP-434
N	6	6	6	6	6	6	6
Ae (mg)	1.44 (34.0)	3.53 (16.6)	6.30 (30.0)	13.51 (26.9)	19.26 (16.2)	24.52 (24.2)	32.68 (11.3)
Fe (%)	18.75 (18.3)	16.67 (11.9)	15.07 (18.1)	16.80 (12.8)	16.55 (10.0)	14.91 (11.6)	13.43 (16.5)
CLr (L/h)	2.59 (25.1)	2.71 (10.9)	2.39 (27.2)	2.45 (13.1)	2.20 (15.6)	1.97 (13.3)	1.46 (19.2)

Source: Adapted from Table 9 in the PK Report.

Table 162. Mean (CV%) Urine PK Parameters of TP-498 after a Single Dose.

PK Parameters	Dose Group 1: 0.10 mg/kg TP-434	Dose Group 2: 0.25 mg/kg TP-434	Dose Group 3: 0.50 mg/kg TP-434	Dose Group 4: 1.00 mg/kg TP-434	Dose Group 5: 1.50 mg/kg TP-434	Dose Group 6: 2.00 mg/kg TP-434	Dose Group 7: 3.00 mg/kg TP-434
N	6	6	6	6	6	6	6
Ae (mg)	0.34 (34.1)	0.94 (14.9)	1.65 (30.5)	3.72 (28.0)	4.54 (20.2)	7.08 (24.0)	9.56 (15.4)
Fe (%)	4.50 (17.2)	4.43 (8.1)	3.96 (19.8)	4.63 (18.8)	3.89 (14.0)	4.32 (13.6)	3.91 (16.0)
CLr (L/h)	NC (NC)	NC (NC)	2.75 (34.6)[a]	3.06 (16.7)	2.61 (18.1)	3.15 (16.9)	2.71 (14.7)

Source: Adapted from Table 10 in the PK Report.

Dose Proportionality

As shown in Table 159 and Table 163, ERV AUC increased proportionally with increasing doses over the dose range of 0.25 to 3 mg/kg. C_{max} increased in a slightly greater than dose proportional fashion over the dose range of 0.25 to 3 mg/kg.

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Table 163. Dose Proportionality Assessment of ERV in Plasma.

PK Parameters	Dose Range	Linear Power Models	Value	Standard Error	95% CI
AUC_{0-24}	0.5 to 3.00 mg/kg	Intercept	3.10	0.22	2.65 – 3.54
		Ln(Dose)	1.20	0.05	1.10 – 1.29
AUC_{0-t}	0.25 to 3.00 mg/kg	Intercept	3.43	0.14	3.14 – 3.72
		Ln(Dose)	1.18	0.03	1.12 – 1.24
C_{max}	1.00 to 3.00 mg/kg	Intercept	1.42	0.39	0.61 – 2.23
		Ln(Dose)	1.40	0.08	1.23 – 1.56

Source: Adapted from Table 7 of the PK Report.

Safety:
The most common adverse events were nausea and vomiting, which had a higher incidence in higher dose cohorts (2 and 3 mg/kg). Nausea was reported in 3 (50%) subjects administered 2 mg/kg ERV and in 5 (83.3%) subjects administered 3 mg/kg ERV. Vomiting was reported in 3 (50%) subjects administered 3 mg/kg ERV. Neither nausea nor vomiting was reported in any subject taking ERV doses less than 2 mg/kg.

Reviewer Comment: Nausea and vomiting appear to be dose-related.

REVIEWER ASSESSMENT: ERV was well-tolerated at IV doses up to 1.5 mg/kg. ERV AUC increased proportionally, and C_{max} increased slightly greater than dose proportionally with increasing doses over the dose range of 0.25 to 3 mg/kg. Based on the low fraction (<20%) of administered dose excreted in urine, it appears that ERV is primarily nonrenally eliminated. Nausea and vomiting appear to be dose-limiting toxicities associated with IV doses greater than 1.5 mg/kg.

TP-434-P1-MAD-1: Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Pharmacokinetics of Multiple Ascending Dose Regimens of TP-434

Date(s): 11/8/2009 – 2/12/2010
Sponsor: Tetraphase Pharmaceuticals, Inc., Watertown, MA
Clinical Site: Cetero Research, Fargo, ND

METHODS
Study Design: Study TP-434-P1-MAD-1 was a single-center, double-blind, placebo-controlled, randomized, multiple-ascending-dose study to assess the safety, tolerability, and PK of IV TP-434 (eravacycline, ERV) in healthy subjects. Subjects were randomized to receive 0.50 mg/kg infused over 30 minutes QD, 1.50 mg/kg infused over 30 minutes QD, 1.50 mg/kg infused over 60 minutes QD, or 1.00 mg/kg infused over 60 minutes BID ERV or placebo for 10 days

Reference ID: 4312284

(active:placebo = 6:2). Safety was monitored over 24 days. 36 or 37 plasma samples (one additional sample in the 1.00 mg BID cohort) and 12 urine samples were collected over 14 days.

ERV was the drug product and was supplied as lyophilized powder for reconstitution with sterile water prior to IV administration.

Analytical Methods: Bioanalytical assays (b) (4) 09-137 and (b) (4) 09-136 were used to measured ERV concentrations in plasma and urine, respectively. The performance was satisfactory.

RESULTS

Pharmacokinetics:

Plasma

Table 164 and Table 165 report the plasma PK Parameters identified for ERV on Day 1 and Day 10, respectively.

Reference ID: 4312284

Table 164. PK Parameters of Single Dose Eravacycline Infusion in Healthy Subjects.

PK Parameters	TP-434 Infusion Duration of 30 min		TP-434 Infusion Duration of 60 min	
	Dose Group 1: 0.50 mg/kg, q24h	Dose Group 2: 1.50 mg/kg, q24h	Dose Group 3: 1.50 mg/kg, q24h	Dose Group 4: 1.00 mg/kg, q12h
N	6	6	6	6
AUC_{0-12} (ng•h/mL)	1644.78 (17.88)	4894.40 (8.93)	5926.42 (15.71)	4304.88 (13.79)
AUC_{0-24} (ng•h/mL)	2096.27 (20.89)	6002.73 (8.77)	7171.11 (15.33)	5106.52 (14.39)
AUC_{0-t} (ng•h/mL)	2089.37 (20.83)	5986.97 (8.76)	7153.26 (15.33	4296.16 (13.79)
$AUC_{0-\infty}$ (ng•h/mL)	2639.23 (28.45)	7014.95 (10.68)	8384.94 (15.88)	5630.03 (16.06)
C_{max} (ng/mL)	1078 (17.95)	3447 (7.08)	2785 (22.02)	2125 (15.25)
T_{max}[a] (h)	0.50 (0.50 - 0.50)	0.50 (0.48 - 0.50)	1.00 (1.00 - 1.02)	1.00 (1.00 - 1.02)
$t_{1/2}$ (h)	12.67 (22.59)	11.04 (11.91)	11.35 (23.37)	8.64 (20.51)
CL (L/h)	13.85 (27.26)	18.30 (10.45)	14.32 (18.86)	13.97 (15.27)
V_{ss} (L)	171.19 (16.48)	187.94 (6.58)	149.56 (42.64)	105.32 (18.67)
V_z (L)	243.22 (15.02)	288.81 (5.11)	238.59 (35.93)	170.68 (14.88)
CL/Weight (L/h/kg)	0.20 (31.29)	0.22 (10.59)	0.18 (18.95)	0.18 (14.69)
V_{ss}/Weight (L/kg)	2.49 (11.63)	2.22 (11.14)	1.83 (27.95)	1.37 (21.12)
V_z/Weight (L/kg)	3.54 (13.43)	3.42 (10.24)	2.95 (21.99)	2.22 (18.03)

[a] Median (Min - Max)

Source: Adapted from Table 7 in the PK Report, Mean (CV%).

Reviewer Comment: Because Dose Group 4 (1 mg/kg BID) was given 2 doses on Day 1, the 24-hr single-dose concentration was extrapolated based on the concentration-time profile from one dose, i.e., 0hr to 12hr. The extrapolated 24-hr concentration was used to estimate the AUC0-24. For the purpose of this review, this use of extrapolation introduces too much error to be valid.

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Table 165. PK Parameters of ERV after a Multiple Daily or Twice Doses of ERV on Day 10.

PK Parameters	TP-434 Infusion Duration of 30 min		TP-434 Infusion Duration of 60 min	
	Dose Group 1: 0.50 mg/kg, q24h	Dose Group 2: 1.50 mg/kg, q24h	Dose Group 3: 1.50 mg/kg, q24h	Dose Group 4: 1.00 mg/kg, q12h
N	6	3[b]	6	4[c]
AUC_{0-12} (ng•h/mL)	2065.14 (28.28)	6003.59 (16.58)	5611.35 (10.18)	6308.79 (14.95)
AUC_{0-24} (ng•h/mL)	2901.52 (30.44)	8051.05 (19.06)	7591.81 (11.76)	9006.82 (15.40)
AUC_{0-t} (ng•h/mL)	4799.67 (36.13)	12121.13 (23.34)	11845.84 (17.01)	14967.40 (17.99)
C_{max} (ng/mL)	931.3 (16.58)	3403 (9.34)	1892 (10.25)	1825 (15.53)
T_{max}[a] (h)	0.50 (0.50 - 0.50)	0.50 (0.50 - 0.50)	1.00 (0.50 - 1.02)	1.00 (1.00 - 1.00)
$t_{1/2}$ (h)	35.83 (48.46)	29.09 (14.01)	30.16 (16.98)	38.73 (32.36)
CL_{ss} (L/h)	12.71 (28.73)	15.91 (13.70)	15.80 (21.69)	12.61 (15.92)
V_{ss} (L)	346.53 (22.99)	337.66 (14.21)	378.17 (29.97)	312.10 (16.88)
CL_{ss}/Weight (L/h/kg)	0.19 (31.58)	0.19 (18.23)	0.20 (12.84)	0.16 (17.03)
V_{ss}/Weight (L/kg)	5.03 (20.21)	4.04 (18.06)	4.67 (7.71)	4.00 (15.04)
R(AUC)	1.37 (14.5)	1.32 (9.1)	1.07 (7.3)	1.39 (17.3)
R(C_{max})	0.881 (21.3)	0.947 (3.2)	0.704 (20.3)	0.828 (23.4)

[a] Median (Min - Max)
[b] Subjects 10, 14, and 15 were excluded from the summary statistics due to early discontinued dosing.
[c] Subjects 25 and 30 were excluded from the summary statistics due to early discontinued dosing.

Source: Adapted from Table 8 in the PK Report, Mean (CV%).

Reviewer Comment: The t1/2 for the 1.00 m/kg Q12 group is based on the AUC_{0-t} instead of the AUCinf. In addition, only 4 subjects were included in the calculation for the 1 mg/kg Q12 cohort, of which one subject had a high outlying value for AUC. For these reasons, the value of t/12 is unreliable. The accumulation ratio for AUC, R(AUC), appears to consistently show accumulation of around 35% regardless of dose.

As shown in Table 165, eravacycline AUC0-24 and C_{max} are roughly dose proportional between 0.5 mg/kg QD and 1.5 mg/kg QD.

Urine

Table 166 and Table 167 report urine PK parameters of ERV on Day 1 and Day 10, respectively.

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Table 166. Urine PK Parameters of ERV after a Single Dose of ERV, Mean (CV%).

PK Parameters	TP-434 Infusion Duration of 30 min		TP-434 Infusion Duration of 60 min	
	Dose Group 1: 0.50 mg/kg, q24h	Dose Group 2: 1.50 mg/kg, q24h	Dose Group 3: 1.50 mg/kg, q24h	Dose Group 4: 1.00 mg/kg, q12h
N	6	6	6	6
Ae_{0-24} (mg)	4.27 (18.9)	11.37 (28.5)	11.99 (33.5)	16.68 (15.0)
Fe_{0-24} (%)	12.38 (12.0)	9.05 (30.7)	9.88 (18.4)	10.78 (11.5)
CLr (L/h)	2.10 (25.4)	1.90 (27.5)	1.69 (35.4)	3.27 (7.6)

Source: Adapted from Table 11 in the PK Report

Table 167. Urine PK Parameters of ERV after Multiple Doses of ERV on Day 10, Mean (CV%).

PK Parameters	TP-434 Infusion Duration of 30 min		TP-434 Infusion Duration of 60 min	
	Dose Group 1: 0.50 mg/kg, q24h	Dose Group 2: 1.50 mg/kg, q24h	Dose Group 3: 1.50 mg/kg, q24h	Dose Group 4: 1.00 mg/kg, q12h
N	6	3	6	4
Ae_{0-96} (mg)	9.02 (29.4)	29.75 (19.3)	24.71 (29.8)	31.48 (19.7)
Fe_{0-96} (%)	26.02 (22.8)	23.55 (15.4)	20.53 (17.2)	40.26 (17.2)
CLr (L/h)	3.16 (18.2)	3.70 (6.6)	3.25 (28.4)	5.07 (22.5)

Source: Adapted from Table 12 in the PK Report.

Reviewer Comment: It appears that the urine excretion of ERV increases over time. However, the urine collection interval on Day 1 may have been too short to capture all ERV excreted in the urine. Similarly, the ERV collected in the urine on Day 10 may have been from doses before Day 10 although the calculation of Fe(0-96) assumes that all of the excreted drug came from one dose.

Safety:
The most common adverse events were related to infusion site conditions and nausea. Nausea appeared to show a relationship with dose. Nausea was reported once in the placebo cohort, 0 times in the 0.5 mg/kg cohort, 3 times in 2(33%) subjects in the 1.5 mg/kg over 30 minutes cohort, 9 times in 5 (83%) subjects in the 1.5 mg/kg over 60 minutes cohort, and 7 times in 4(67%) subjects in the 1.00 mg/kg BID cohort. Vomiting was only reported in one subject each in the 1.50 mg/kg over 30 minutes cohort and the 1.00 mg/kg cohort.

REVIEWER ASSESSMENT: The PK profile was not adequately assessed on Day 1 in the 1.00 mg/kg BID cohort. It appears that ERV has a long distribution phase. This may explain why the V increased from Day 1 to Day 10. This disagrees with the finding in the SAD study. However, the result in this study is more reflective of steady-state dosing.

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Nausea appears to be the most common side effect of ERV based on the results from this study and the SAD study.

TP-434-013: A Phase 1, Open-Label Study to Assess the Single-Dose Pharmacokinetics of Eravacycline in Subjects with Impaired Hepatic Function and Healthy Subjects

Date(s): 10/2/2013 – 2/21/2014
Sponsor: Tetraphase Pharmaceuticals, Inc., Watertown, MA
Clinical Site: 3 sites in the US

METHODS

Study Design: Study TP-434-013 was a multicenter, open-label study to assess the safety, tolerability, and PK of a single dose of 1.5 mg/kg IV TP-434 (eravacycline, ERV) in healthy subjects and subjects with mild, moderate, and severe hepatic impairment per the Child-Pugh scale. 11 blood samples for PK analysis each of ERV, TP-498, and TP-6208 were collected.

Analytical Methods: Bioanalytical assay (b) (4) 12262 was used to measured ERV, TP-6208, and TP-498 concentrations in plasma. The performance was generally satisfactory with a few concerns. The calibration curve range was 5-500 ng/mL. However, the C_{max} and other points in the concentration-time profile were above 500 ng/mL. Dilution quality control samples were assayed at 2500 ng/mL (above all measured concentrations), but only 2 times (2/24/14 and 2/26/14) out of 8 analytical runs from 12/11/13 to 3/13/14.

In addition, the validation reported listed a long-term stability of 54 days at -20C to -70C, but the study started on 10/2/13, and the first batch of samples was not assayed until 12/13/13, approximately 72 days later. Some of these samples were reanalyzed on 2/24/14, over 120 days from the study start date. However, other validation methods for ERV list long-term stability up to 3 months at -70C and 12 months at -80C.

RESULTS

Table 168 reports the plasma PK Parameters identified for ERV, TP-498, and TP-6208.

Table 168. PK Parameters of ERV, TP-498, and TP-6208 after a Single Dose of ERV in Healthy Subjects and Subjects with Mild, Moderate and Severe Hepatic Impairment Mean(CV%).

	Healthy Subjects	Mild Hepatic Impairment	Moderate Hepatic Impairment	Severe Hepatic Impairment

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Analyte	PK Parameter	Mean (CV%)	n	Mean (CV%)	n	Ratio to Healthy Subjects	Mean (CV%)	n	Ratio to Healthy Subjects	Mean (CV%)	n	Ratio to Healthy Subjects
ERV	AUC_{0-97} (ng*hr/mL)	3740 (14.5%)	5	4580 (19.5%)	4	122%	5330 (42.5%)	6	143%	7910 (32%)	6	212%
	AUC_{INF} (ng*hr/mL)	3810 (15.3%)	5	4730 (21.5%)	4	124%	5680 (50.1%)	5	149%	8330 (32.2%)	6	219%
	C_{max} (ng/mL)	1160 (28.1%)	6	1330 (26.9%)	6	115%	1340 (23.2%)	6	116%	1360 (17.5%)	6	118%
	$T_{1/2}$ (hr^{-1})	16.3 (38%)	5	21.4 (46.7%)	4	131%	21.6 (36.8%)	5	132%	25.6 (16.9%)	6	157%
TP-498	AUC_{0-97} (ng*hr/mL)	999 (9.72%)	5	1400 (29.4%)	5	140%	1420 (35.6%)	5	142%	2250 (18.4%)	6	225%
	AUC_{INF} (ng*hr/mL)	1080 (10.8%)	5	1580 (29.3%)	5	146%	1720 (42.2%)	5	160%	2760 (24%)	6	255%
	C_{max} (ng/mL)	127 (31.3%)	6	163 (71.5%)	6	128%	126 (73.9%)	6	99.50%	156 (71.1%)	6	123%
	$T_{1/2}$ (hr^{-1})	27 (4.31%)	5	30.8 (17.4%)	5	114%	37.6 (20.1%)	5	139%	39.6 (14.4%)	6	147%
TP-6208	AUC_{0-97} (ng*hr/mL)	2940 (19.8%)	6	3080 (39.7%)	4	105%	2690 (20.8%)	4	91.70%	2860 (46.9%)	3	97.50%
	AUC_{INF} (ng*hr/mL)	3030 (20.1%)	6	3220 (38.6%)	4	106%	2920 (21.7%)	4	96.50%	3110 (42.3%)	3	103%
	C_{max} (ng/mL)	82.3 (12.6%)	6	72.4 (43.6%)	6	87.90%	56 (54.2%)	6	68.10%	40.3 (84.4%)	6	49%
	$T_{1/2}$ (hr^{-1})	18 (14.8%)	6	19.8 (26.9%)	4	110%	21.8 (52.2%)	4	121%	24.7 (24.9%)	3	137%

Source: Reviewer's Table

REVIEWER ASSESSMENT: Results of this study show that eravacycline AUC increased with the severity of hepatic function, with 2-fold higher AUC in patients with severe hepatic impairment relative to healthy volunteers. However, the plasma exposure of eravacycline in the healthy volunteer cohort is significantly lower than seen in other Phase 1 trials.

TP-434-014: A Phase 1, Open-Label Study to Assess the Single-Dose Pharmacokinetics of Eravacycline in Subjects with End Stage Renal Disease and Healthy Subjects

Date(s): 1/8/2014 – 3/3/2014
Sponsor: Tetraphase Pharmaceuticals, Inc., Watertown, MA
Clinical Site: 2 sites in the US

METHODS

Study Design: Study TP-434-014 was a multicenter, open-label study to assess the safety, tolerability, and PK of a single dose of 1.5 mg/kg IV TP-434 (eravacycline, ERV) in healthy and subjects and subjects with end stage renal disease (ESRD). 11 blood samples for PK analysis each of ERV, TP-498, and TP-6208 were collected. For subjects receiving dialysis, ERV was

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administered on a day when dialysis was not administered, and at least 8 samples of each analyte were collected within 24 hours of dosing.

ERV was the drug product. It was supplied as lyophilized powder for reconstitution with sterile water prior to IV administration.

Analytical Methods: Bioanalytical assay (b) (4)-12262 was used to measured ERV, TP-6208, and TP-498 concentrations in plasma. The performance was satisfactory.

RESULTS

Pharmacokinetics:

Table 169 reports the plasma PK Parameters for ERV, TP-498, and TP-6208.

Table 169. PK Parameters of ERV, TP-498, and TP-6208 after a Single Dose of ERV in Healthy Subjects and ESRD Patients, Mean(CV%).

	Healthy Subjects			End-Stage Renal Disease Patients		
Analyte	PK Parameter	Mean (CV%)	n	Mean (CV%)	n	Ratio to Healthy Volunteers
ERV	AUC_{0-97} (ng*hr/mL)	4810 (13.1%)	6	4610 (19.5%)	6	95.90%
	AUC_{INF} (ng*hr/mL)	4920 (13%)	6	4750 (17.5%)	6	96.50%
	C_{max} (ng/mL)	1350 (16.4%)	6	1540 (42.9%)	6	114%
	$T_{1/2}$ (hr^{-1})	20.5 (34.8%)	6	22.2 (40.2%)	6	109%
TP-498	AUC_{0-97} (ng*hr/mL)	1090 (20.9%)	5	1500 (13.9%)	5	138%
	AUC_{INF} (ng*hr/mL)	1540 (18.3%)	5	1810 (18.1%)	5	118%
	C_{max} (ng/mL)	78.3 (11.3%)	6	160 (27.4%)	6	204%
	$T_{1/2}$ (hr^{-1})	58.2 (32.9%)	5	37.5 (18%)	5	64.40%
TP-6208	AUC_{0-97} (ng*hr/mL)	3980 (39.8%)	5	4050 (38%)	6	102%
	AUC_{INF} (ng*hr/mL)	4100 (39.7%)	5	4430 (36.8%)	6	108%
	C_{max} (ng/mL)	91 (43.6%)	6	85.6 (37.6%)	6	94.10%
	$T_{1/2}$ (hr^{-1})	17.5 (7.99%)	5	24.6 (35.9%)	6	141%

Source: Reviewer's Table

Protein Binding: In Study (b) (4)-006, the protein binding in samples from subjects in the present study, TP-434-014, was analyzed. However, out of 72 samples, 65 samples had free concentrations of ERV that were below the limit of quantification, 10 ng/mL. The frequency of BLQ samples did not appear to correlate with the concentration in plasma.

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REVIEWER ASSESSMENT: Results of this study showed no change in ERV AUC, C_{max}, or T1/2 between healthy subjects and subjects with ESRD. This agrees with the fact that ERV appears to be primarily metabolized. However, the plasma PK in the healthy volunteer cohort is significantly lower than seen in other Phase 1 trials. In addition, the protein binding substudy is inconclusive because most of the samples were below the limit of quantification.

TP-434-012: An Open-Label, Single Dose Study Designed to Assess the Mass Balance Recovery and Metabolite Substudy (TET-P2989), Metabolite Profile and Identification of Metabolite Structure for [14C]-Eravacycline in Healthy Male Subjects after Oral and Intravenous Dosing

Date(s): 7/9/2014 – 8/4/2014
Sponsor: Tetraphase Pharmaceuticals, Inc., Watertown, MA
Clinical site: Quotient Clinical, Nottingham NG11 6JS, UK

METHODS

Study Design: Study TP-434-012 was a single center, open-label study to assess the mass balance recovery of a single dose of 100 mg oral TP-434 (eravacycline, ERV) and 60 mg IV ERV in healthy male subjects. 26 plasma samples for analysis of total radioactivity (TR), ERV, TP-498, and TP-6208 were collected. 26 whole blood samples for analysis of TR were collected. 9 plasma samples for metabolite identification were collected. 14 urine samples were collected for analysis of TR, ERV, TP-498, TP-6208, and metabolite identification. 12 samples of feces were collected for analysis of TR and metabolite identification.

Reviewer Comment: Only the mass balance for IV ERV was reviewed because this NDA only covers IV ERV.

Drug Product and Dose: 60 mg [14C]-eravacycline was administered as a single IV dose by a 60-minute infusion containing NMT 3.8 MBq (105 µCi) 14C.

Analytical Methods: An LC-MS/MS assay (b) (4) 266344QB03) was used to measure ERV, TP-6208, and TP-498 concentrations in plasma. A separate HPLC-MS/MS bioanalytical assay was developed for the metabolite substudy (TET-P2989). However, the assay for TET-P2989 was not able to discriminate between TP-498 and TP-6208. Radioactivity was determined using a liquid scintillation counter. Overall, the performance of each bioanalytical assay was acceptable.

RESULTS

Study Population: In total, 5 subjects enrolled and completed the IV ERV arm of the study. There were no major clinical pharmacology-related protocol violations.

Reference ID: 4312284

Pharmacokinetics:

Table 170 shows the mean mass balance recovery over the course of the study.

Table 170. Mean Mass Balance Recovery of Total Radioactivity Following a Single Dose of [14C]-ERV.

Collection Time (h)	Mean Cumulative Ae (ng equiv)		Mean Cumulative %Ae (%)	
	Urine (N = 4)	Feces (N = 4)	Urine (N = 4)	Feces (N = 4)
Pre-dose	NC	NC	NC	NC
0 – 6	4337921.300	NC	7.488	NC
0 – 12	7386432.700	NC	12.730	NC
0 – 24	11028798.350	92597.815	18.998	0.023
0 – 48	15595818.975	959450.020	27.125	0.335
0 – 72	17464071.375	24543381.230	30.350	16.023
0 – 96	18449756.425	48430086.178	32.048	27.465
0-120	19145282.000	66193504.650	33.248	35.038
0-144	19565632.275	80624037.003	33.973	40.968
0-168	19808548.375	84414227.508	34.390	42.543
0-192	19955354.000	89609491.143	34.640	45.135
0-216	20059173.425	90246672.220	34.820	45.383
0-240	20140135.225	94028542.365	34.960	47.013
0-264	NC	94327228.928	NC	47.065
0-288	NC	95542812.088	NC	47.695
Total	**115883568.170**		**82.753**	

NC: not calculated

Source: Adapted from Table 11.4.2 of the CSR.

Reviewer Comment: Of the total radioactivity recovered, 42.3% was collected in the urine, and 57.6% was collected in the feces.

Table 171 reports the plasma PK Parameters identified for ERV, TP-498, and TP-6208.

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Table 171. PK of ERV, TP-498, and TP-6208 After a Single Dose of 60 mg [14C]-ERV.

Parameter	ERV	TP-498	TP-6208
Tmax (hr)	1.000 (0.55-1.00)	1.00 (0.55-1.00)	13.000 (9.03-13.03)
C_{max} (ng/mL)	1100 (13.5)	20.4 (18.9)	42.8 (28.9)
$AUC_{0\text{-}last}$ (ng.h/mL)	4360 (9.8)	323 (27.9)	1480 (28.3)
$AUC_{0\text{-}24}$ (ng.h/mL)	3330 (10.0)	181 (15.6)	784 (29.0)
$AUC_{0\text{-}inf}$ (ng.h/mL)	4380 (11.4) [n=2]	NC	1780 (26.9) [n=2]
$AUC_{\%extrap}$ (%)	4.04 (34.2) [n=2]	NC	8.46 (47.6) [n=2]
$T_{1/2}$ (hr)	18.23 (5.0) [n=2]	NC	18.77 (17.8) [n=2]
$MRT_{0\text{-}nf}$ (hr)	15.86 (8.9) [n=2]	NC	NC
$MRT_{0\text{-}last}$ (hr)	14.08 (16.3)	NC	NC
CL (mL/min)	228 (13.8) [n=2]	NC	NC
CL_R (mL/min)	41.9 (16.6)	85.7 (35.5)	7.56 (12.2)
V_{ss} (L)	217 (4.9) [n=2]	NC	NC

NC: Not calculated

Source: Adapted from Tables 11.4.3, 11.4.4, and 11.4.5 in the CSR.

Metabolite Identification: Samples collected in the ADME study were used to identify the metabolites of ERV in plasma, urine, and feces as shown in Table 172,
Source: Adapted from Table 10 of the Metabolite Substudy CSR.
Table 173, and Table 174, respectively.

Table 172. Distribution of Total Radioactivity in Pooled Plasma from 0-24 Hours After a Single IV Dose of 60mg [14C]-ERV.

			Mean ± SD Percent of Radioactivity in Plasma Extract		
Dose Route	**Subject #**	**Total Radioactivity (dpm/mL)**	**TP-498/TP-6208**	**Eravacycline**	**TP-034**
IV	6	520	25.5	60.9	7.9
	7	510	29.2	43.8	0.0
	8	590	35.2	59.8	1.2
	9	430	28.3	68.7	0.0
	10	580	30.3	63.1	3.0
		526 ± 64.3	**29.7 ± 3.6**	**59.3 ± 9.3**	**2.4 ± 3.3**

Source: Adapted from Table 10 of the Metabolite Substudy CSR.

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Table 173. Distribution of Total Radioactivity in Urine After a Single IV Dose of 60mg [14C]-ERV.

Dose Route	Subject	Total DPM/mL	Percent of Total Radioactivity (Mean ± SD)					
			Unknown* Rt ~5 min	TP-498/TP-6208	M734b	Eravacycline	TP-034	M572b
IV	6	2942	7.24	17.7	4.68	59.37	4.52	2.18
	7	415	12.8	14.4	4.4	62.00	6.40	ND
	8	312	6.43	13.57	ND	72.86	3.57	ND
	9	1079	3.68	15.94	1.77	64.71	4.36	2.18
	10	382	5.75	14.38	2.56	56.87	9.90	2.56
		1026 ± 1115	7.18 ± 3.41	15.20 ± 1.64	3.35 ± 1.41	63.16 ± 6.16	5.75 ± 2.54	2.31 ± 0.22

ND: not detected, and it was included in the calculations of the mean and SD as 0.0 value.
* Unknown: identity of this polar metabolite (retention time of approximately 5 min) could not be established by mass spectrometry or other techniques TP-498 co-eluted with TP-6208 and M590b.

Source: Adapted from Table 13 of the Metabolite Substudy CSR

Table 174. Distribution of Total Radioactivity in Feces After a Single IV Dose of 60mg [14C]-ERV.

Metabolite	Retention Time	Percent (%) of Radioactivity Injected onto Column					
		Sub 6	Sub 7	Sub 8	Sub 9	Sub 10	Mean± SD
Unknown*	5.0	1.12	1.23	0.92	1.94	1.64	1.37 ± 0.41
M590a	21.4	2.99	3.71	2.62	2.88	5.93	3.63 ± 1.35
M734a	22.2	2.37	2.97	1.44	1.84	3.45	2.41 ± 0.82
TP-498/TP-6208	25.8	17.69	18.91	14.62	16.93	17.6	17.15 ± 1.59
M590b	26.4	8.9	10.88	10.68	10.43	10.66	10.31 ± 0.8
M734b	28.0	7.16	6.59	4.6	5.26	6.72	6.07 ± 1.09
Eravacycline	31.0	42.23	41.21	41.26	40.31	29.54	38.91 ± 5.28
TP-034	33.8	1.91	1.72	3.16	2.5	2.63	2.38 ± 0.58
Unknown	36.4	1.48	1.01	1.87	1.91	2.41	1.74 ± 0.52
M572a	41.2	3.02	2.33	3.71	3.52	5.56	3.63 ± 1.2
M572b	47.0	6.1	5.73	11.55	8.54	8.26	8.04 ± 2.33

Source: Adapted from Table 18 of the Metabolite Substudy CSR.

Based on the mass spectra and fragmentation patterns of the samples collected, the Applicant proposed the metabolic structures and metabolic pathways shown in **Figure 14**.

Figure 14. Proposed Metabolic Pathways of [14C]-ERV and Metabolic Structures.

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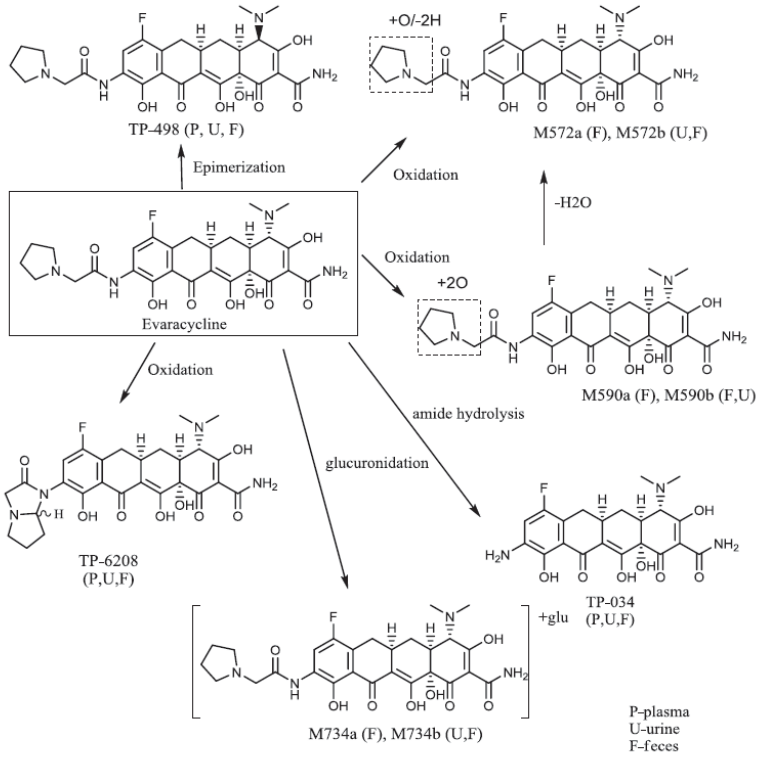

SOURCE: Adapted from Figure 14 of the Metabolite Substudy CSR.

REVIEWER ASSESSMENT: The results of this ADME study suggest that ERV is eliminated by metabolism, biliary excretion, and renal excretion. ERV was the predominant species in plasma, urine, and feces. TP-498, TP-034, and TP-6208 appeared to be the major metabolites.

16 Division Director (Clinical)

Concur with review.

17 Office Director (OAP)

Concur with review.

Reference ID: 4312284

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GREGORY F DIBERNARDO
08/27/2018

EDWARD M COX
08/27/2018