26 July 2018
EMA/540193/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xerava

International non-proprietary name: eravacycline

Procedure No. EMEA/H/C/004237/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

%CV	coefficient of variation (expressed as a percentage)
ABC	ATP-binding cassette superfamily of transport proteins
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AM	alveolar macrophage
APACHE II	Acute Physiology and Chronic Health Evaluation II
aPTT	activated partial prothrombin time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the plasma concentration-time curve
BAL	broncho-alveolar lavage
BCS	Biopharmaceutics Classification System (for drug molecules)
CA	community-acquired
CE	clinically evaluable (population)
CE-EOT	clinically evaluable End-of-Treatment (analysis population)
CE-TOC	clinically evaluable Test-of-Cure (analysis population)
CFU	Colony forming unit
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
cIAI	complicated intra-abdominal infection
CL	apparent total body (systemic) clearance of drug (also Cl)
CLSI	Clinical & Laboratory Standards Institute
Cmax	maximum observed plasma concentration
c-MITT	clinically modified Intent-to-Treat (analysis population)
CMQ	Company-defined Medical Queries
CQA	Critical quality attribute
CPP	Critical process parameter
CRAB	carbapenem-resistant Acinetobacter baumannii
CRE	carbapenem-resistant Enterobacteriaceae
CRO	contract research organisation
CSR	Clinical Study Report
cUTI	complicated urinary tract infection
CYP	cytochrome P450 isoenzymes
DBP	diastolic blood pressure
EC	European Commission
ECG	electrocardiogram
EDTA	ethylene diamine tetrasodium dehydrate (also ethylenediamine tetraacetate)
EMA	European Medicines Agency
EOT	end of treatment
ERC	Evaluability Review Committee
ESBL	extended spectrum beta-lactamase
ESRD	end-stage renal disease
EU	European Union
FDA	United States Food and Drug Administration

FMO	flavin monooxygenases
FU	follow-up
fu	the free (unbound) fraction of a protein in solution
g	gram(s)
GC	Gas chromatography
GC-HS	Headspace gas chromatography
GC-MS	Gas chromatography – mass spectrometry
GLP	Good Laboratory Practices
HDPE	High density polyethylene
HED	human equivalent dose
HPLC	High-performance liquid chromatography
HR	heart rate
HSA	human serum albumin
IC50	concentration required to inhibit a reaction, enzyme, or cell growth by 50%
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
ICU	intensive care unit
INR	International Normalised Ratio
IR	Infrared
ITT	Intent-to-Treat (analysis population)
i.v.	intravenous(ly)
JP	Japanese Pharmacopoeia
KF	Karl Fischer titration
kg	kilogram(s)
LDPE	Low density polyethylene
LFT	liver function test
MAD	multiple ascending dose (study design)
MBC	minimum bactericidal concentration
MDCK	Madin-Darby canine kidney
MDR	multidrug resistance
ME	microbiologically evaluable (population)
mg	milligram(s)
MIC	minimum inhibitory concentration
MIC50	MIC of at least 50% of clinical isolates tested
MIC90	MIC of at least 90% of clinical isolates tested
Micro-ITT	microbiologically evaluable intent-to-treat (population)
Micro-MITT	microbiologically-evaluable Modified Intent-to-Treat analysis population
min	minute(s)
MITT	modified Intent-to-Treat (analysis population)
mL	millilitre(s)
MRSA	methicillin-resistant Staphylococcus aureus
NI	non-inferiority
NMR	Nuclear magnetic resonance
NOAEL	no-observed adverse effect level
p.o.	oral(ly)
PAMPA	parallel artificial membrane permeability assay (system)
PD	pharmacodynamics

PDCO	Paediatric Committee
PDE	Permitted daily intake
Ph. Eur.	European pharmacopoeia
PIP	Paediatric Investigation Plan
PK	pharmacokinetics
PK/PD	pharmacokinetic/pharmacodynamic relationship
ppm	parts per million
q12h	every 12 hours
q24h	every 24 hours
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
QTcI	QT interval corrected for the individual subject
QTPP	Quality target product profile
RH	Relative humidity
RPP	ribosomal protection proteins
SAC	Surgical Adjudication Committee
SAD	single ascending dose (study design)
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA Query
TBil	total bilirubin
TEAE	treatment emergent adverse event
TOC	Test of cure
TP-034	metabolite of eravacycline
TP-434	eravacycline
TP-498	C-4 epimer (metabolite) of eravacycline
TP-6208	metabolite of eravacycline
UK	United Kingdom
ULN	upper limit of normal
USA	United States of America
USP	United States Pharmacopoeia
UV	Ultraviolet
Vd	volume of distribution
Vss	volume of distribution at steady state
WFI	Water for injections
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Tetraphase UK Limited submitted on 21 July 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Xyravio, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 June 2015.

The applicant applied for the following indication

"Xyravio is indicated for the treatment of complicated intra-abdominal infections (cIAI) in adults, see section 5.1.

Consideration should be given to official guidance on the appropriate use of antibacterial agents."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0336/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0336/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance eravacycline contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received Scientific advice from the CHMP:

Scientific advice	date	Area
EMA/CHMP/SAWP/551751/2013	19 September 2013	The Scientific advice pertained to clinical aspects of the dossier.
EMEA/H/SA/2579/3/2013/PED/SME/II	6 January 2014	The Scientific advice pertained to clinical aspects of the dossier.
EMEA/H/SA/2579/2/FU/1/2016/SME/II	13 October 2016	The Scientific advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Svein Rune Andersen

The application was received by the EMA on	21 July 2017
The procedure started on	17 August 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	6 November 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	3 November 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	13 November 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 December 2017
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product: -GCP inspection at two clinical investigator sites located in Latvia and Ukraine and the Sponsor Tetraphase Pharmaceuticals Inc in USA were conducted during December 2017-January 2019 in connection with the conduct of pivotal trial with protocol number TP-434-008. The outcome of the inspection carried out was issued on 12 March 2018	12 March 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	27 March 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	04 May 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 May 2018
The CHMP agreed on a list of outstanding issues to be sent to the	31 May 2018

applicant on	
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 June 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	11 July 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Xerava on	26 July 2018

The medicinal product name was changed from Xyravio to Xerava on 25 June 2018.

The Applicant for Xerava was changed to Tetraphase Pharmaceuticals Ireland Limited on 25 June 2018.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The indication applied for this medicinal product is *treatment of complicated intra-abdominal infection (cIAI) in adults.*

Intra-abdominal infections include a wide spectrum of pathological conditions, ranging from uncomplicated appendicitis to faecal peritonitis (Menichetti, 2009). In uncomplicated IAIs the infectious process only involves a single organ and does not proceed to peritoneum. Complicated intra-abdominal infection extends beyond the hollow viscus of origin into the peritoneal space and is associated with either abscess formation or peritonitis (Solomkin, 2010). The peritoneal contamination may result from spontaneous perforation (e.g. appendicitis, perforated ulcer or diverticulitis), surgical intervention, or trauma.

Intra-abdominal infections are also classified into community-acquired intra-abdominal infections (CA-IAIs) and healthcare-acquired intra-abdominal infections (HA-IAIs). CA-IAIs are acquired in the community; HA-IAIs develop in hospitalised patients or residents of long-term care facilities. They are characterised by an increased mortality because of both the underlying patient health status and the increased likelihood of infection caused by multi drugs resistant organisms (Pieracci, 2007).

2.1.2. Epidemiology

The most common types of complicated intra-abdominal infections include complicated appendicitis, cholecystitis and post-operative infection (Sartelli, 2014). Complicated intra-abdominal infections represent the second most common cause of morbidity and mortality after pneumonia in the intensive care unit (ICU) (Vincent, 2009), and remain responsible for 20% of the severe sepsis cases in the ICU (Herzog, 2010). Among patients who develop persistent or recurrent hospital-acquired cIAI following apparently successful surgical source control, mortality may exceed 50% (Herzog, 2010).

2.1.3. Aetiology and pathogenesis

Complicated intra-abdominal infections are usually polymicrobial in nature. Community-acquired cIAIs account for around 70% of cases (Eckmann, 2011), and the major pathogens involved are usual residents of the gastrointestinal tract, including Enterobacteriaceae, streptococci, and certain anaerobes (particularly *Bacteroides fragilis*). Healthcare-associated cIAIs arising post-operatively during hospitalisation, however, commonly involve more resistant flora, which may include extended spectrum β-lactamase (ESBL)-producing *Klebsiella pneumoniae* and *Escherichia coli*, carbapenemase-producing *K. pneumoniae*, enterococci, and non-bacterial organisms including *Candida* spp (Brook, 2000; Coates, 2005; Herzog, 2010; Sartelli, 2012; Eckmann, 2013; Gonzalez-Villoria, 2016).

2.1.4. Clinical presentation, diagnosis

The clinical presentation of complicated intra-abdominal infections is non-specific. Patients with cIAI may present with abdominal pain or flank pain accompanied by signs and symptoms of systemic illness such as fever, elevated blood cell count, increased heart rate and increased respiratory rate. The diagnosis is established during surgical procedures such as laparotomy, laparoscopy or percutaneous drainage or confirmed by a sonogram or radiographic imaging.

2.1.5. Management

The management of complicated intra-abdominal infections usually involves surgical and/or percutaneous drainage, removal of diseased tissue and adequate source control in conjunction with the use of broad-spectrum antibiotics or antibiotic combinations (Sartelli, 2010; Solomkin, 2010).

The emergence of antimicrobial resistance has created a growing unmet need for the development of new antibacterials, including for the treatment of cIAI, despite several antibacterial agents are already approved for this indication. The increasing rate of drug resistance means that currently available treatments are becoming insufficient and there is an urgent need for novel broad-spectrum antibiotics.

About the product

Eravacycline is a fluorocycline belonging to the tetracycline class of antibiotics.

Eravacycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit, thus preventing the incorporation of amino acid residues into elongating peptide chains.

The proposed indication is as follows:

Xerava is indicated for the treatment of complicated intra-abdominal infections (cIAI) in adults, (see section 5.1).

Considerations should be given to official guidance on the appropriate use of antibacterial agents.

The proposed posology is as follows:

Adults

The recommended dose regimen of Xerava is 1.0 mg/kg every 12 hours for 4 to 14 days.

The duration of therapy should be guided by the severity of infection and the patient's clinical response.

Renal impairment

No dose adjustment is necessary in patients with renal impairment.

Method of administration

Intravenous use.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a powder for concentrate for solution for infusion containing 50 mg eravacycline as active substance.

Other ingredients are: mannitol (E421), sodium hydroxide (for pH adjustment) and hydrochloric acid (for pH adjustment).

The product is available in type I glass vials with chlorobutyl rubber stoppers and aluminium caps as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of eravacycline dihydrochloride is [(4*S*,4a*S*,5a*R*,12a*S*)-4-(dimethylamino)-7-fluoro-3,10,12,12a-tetrahydroxy-1,11-dioxo-9-[2-(pyrrolidin-1-yl)acetamido]-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide] dihydrochloride corresponding to the molecular formula $C_{27}H_{31}FN_4O_8.2HCl$. It has a relative molecular mass of 631.48 g/mol and the following structure:

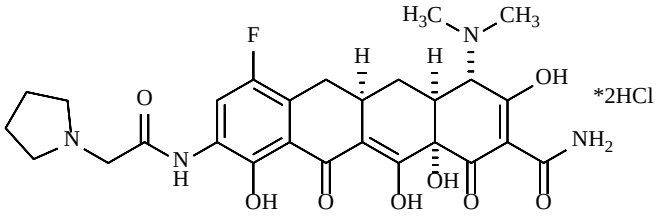


Figure 1: active substance structure

The chemical structure of eravacycline was elucidated by a combination of 1D and 2D ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, infrared spectroscopy, ultraviolet spectroscopy and single crystal x-ray crystallography.

Eravacycline dihydrochloride is a pale yellow to orange solid, somewhat hygroscopic, crystalline solid, freely soluble in water and polar organic solvents. A number of different polymorphic forms have been identified with variable levels of solvation depending on the recystallisation solvent. The solid state properties of the different active substance crystalline forms were measured by microscopy, x-ray powder diffraction (XRPD), dynamic vapour sorption and thermogravimetric analysis. Since the active substance is dissolved in aqueous solution as part of the finished product manufacturing process, then polymorphic form does not impact any of the critical quality attributes (CQAs) of the finished product. The polymorphic form is controlled by an XRPD test in the active substance specification.

Eravacycline contains 4 chiral centres. Enantiopurity is ensured via control of the starting materials, the manufacturing process and the active substance specification.

Manufacture, characterisation and process controls

Eravacycline is synthesized in 4 main steps using well-defined custom-synthesized starting materials. The synthetic process to each starting material was provided, including information on fate and purge of impurities which was used to justify the proposed specifications. The applicant's proposed starting materials were considered acceptable.

Adequate in-process controls are applied during the synthesis and are clearly listed for each individual step. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The final crystallization step ensures the correct solvates are routinely formed.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. All impurities specified in the active substance originate in the later steps of the synthetic process and are controlled to suitable levels. Limits for potential genotoxic impurities are included in the active substance specification. The limits are well below the acceptable intake based on ICH M7 and are considered acceptable.

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process. The order of bond formation has remained the same, with only changes in reagents, solvents, work-ups and crystallizations introduced to improve yields, active substance quality, and enable scale up.

The active substance is packaged in double LDPE bags, placed inside a heat-sealed aluminium bag with desiccant, all stored inside an HDPE drum. The primary packaging complies with the EC directive 2002/72/EC and EC 10/2011 as amended, and Ph. Eur. 3.1.4.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC), chloride content (ion chromatography), polymorphic form (XRPD), impurities (HPLC), assay (HPLC), residual solvents (GC), residue of benzene (GC-HS), 1-methyl-2-pyrrolidone (HPLC), methyl chloride content (GC-MS), ethyl chloride (GC-MS), moisture content (KF), residue on ignition (Ph. Eur.), specific optical rotation (Ph. Eur.), endotoxins (Ph. Eur.) and bioburden (Ph. Eur.). The active substance specifications are based on the active substance CQAs and include tests for each CQA.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. Limits for potentially genotoxic impurities are set in line with ICH M7. Limits for residual solvents have been set according to ICH Q3C. Palladium content is controlled in an intermediate so no test is required in the active substance specification.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 20 laboratory, pilot and production scale batches of the active substance were provided. The batches were manufactured by 4 different manufacturers, 3 of which were used during clinical trials. The fourth is the proposed commercial manufacturer. The results were within specification at the time of testing and consistent from batch to batch. Comparability between the batches used in pivotal clinical trials and those from the proposed commercial manufacturer has been demonstrated.

Stability

Stability data from 7 pilot to production scale batches of active substance from the 2 manufacturers using the same process, including 3 from the proposed commercial manufacturer stored in the intended commercial package for up to 30 months under long term conditions (5±3 ºC) and for up to 24 months under accelerated conditions (25 ºC / 60% RH) according to the ICH guidelines were provided. Additional studies were carried out at -20 ºC (up to 24 months) and at 40 ºC/75% RH (up to 3 months).

The parameters tested in the stability studies are appearance, polymorphic form, impurities, assay, residual ethanol, alkyl chloride content, water content, endotoxins, and bioburden. The analytical methods used were the same as for release. No trends were observed for any of the measured parameters under long term conditions, other than a decrease in assay in the first batch. However, the later batches show no sign of decreased assay. At higher temperature, impurities increased and the content of ethanol dropped as a result of evaporation.

Forced degradation studies were carried out under thermal (80 ºC), photolytic, hydrolytic (aqueous acid or base) and oxidative conditions. The active substance degrades under all stressed conditions, including light exposure. This study demonstrates that the analytical methods are stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 30 months at 5±3 ºC in the proposed container which provides sufficient protection from moisture, heat and light.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is a pale yellow lyophilised powder for concentrate for solution for infusion, presented in a type I glass vial with rubber stopper and aluminium seal. A 3 mg overfill of eravacycline is applied to allow the withdrawal of 50 mg eravacycline freebase. The lyophilised powder is reconstituted with a volume of 5 mL of sterile water for injections (WFI) resulting in a final volume of approximately 5.3 ml. The overfill is considered justified. The reconstitution volume corresponds to the approximate volume that is removed during lyophilisation and provides a concentration of reconstituted drug product of 10 mg/ml. The reconstituted solution is further diluted with 0.9% sodium chloride for injection and administered as an intravenous infusion. The target final solution concentration of eravacycline free-base in the infusion preparation is 0.3 mg/ml.

Eravacycline is hygroscopic, photosensitive, highly soluble in aqueous media but prone to epimerisation in solution. It was therefore decided to develop a lyophilised formulation of eravacycline for clinical development, thereby affording a product that would only be in solution for a limited time to allow for reconstitution and intravenous administration. As a dry lyophilised cake, eravacycline finished product was expected to have a longer shelf life than a solution formulation. Formulation development studies were conducted to provide a suitable and stable formulation that would satisfy the requirements of the quality target product profile (QTPP) summarised in Table 1.

Table 1: QTPP for Xerava finished product

QTPP Element	Target	Justification
Route of Administration	Intravenous infusion	To provide product efficacy
Dose	1.0 mg/kg (FB) every 12 hours	To provide product efficacy; dose

		defined in the clinical trials
Dosage Form	Lyophilised powder for reconstitution for infusion	To provide a suitable and stable formulation
Dosage Strength	Able to withdraw 50 mg (FB)/vial	Suitable for in the clinic use
Active Ingredient	Eravacycline	Safety and efficacy defined through the pre-clinical and clinical studies. Active substance quality controlled through in-process controls and specifications.
Excipients	Acceptable for intravenous administration	To ensure the product is safe for patient use
Compliance	Meets pharmacopoeial and regulatory requirements for parenteral products.	To ensure the product is safe for patient use
Container Closure System	Container closure that ensures sterility of the product, and enables reconstitution and removal of the labelled amount. Product to be provided in single dose vial.	To ensure the product is safe for patient use and to provide a suitable product for in clinic use
Shelf Life	At least 24 months at refrigerated storage conditions	To provide a commercially suitable finished product

The QTPP was defined to ensure that the product is suitable for use in clinical practice. Based on this, CQAs of the finished product were defined. A criticality assessment and the associated control elements including release tests, process parameters and in-process controls (IPCs) were adequately described.

Mannitol was selected as a bulking agent as it is known to allow efficient lyophilisation and helps generate a stable and uniform cake. The amount of mannitol was optimised for the lyophilisation process, to allow rapid reconstitution, and to afford an isotonic solution for infusion. The solubility and stability of eravacycline are pH and temperature dependent. Accordingly, the pH of the lyophilisation initial solution is adjusted with NaOH and potentially, HCl. WFI is used as the dissolution solvent to minimise bioburden and the active substance is added to a pre-cooled mannitol solution in WFI. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The lyophilisation cycle was developed, considering freezing temperature and time, temperature ramp rate, pressure and drying times and temperatures. The optimised conditions ensure a robust cycle, elegant cake, and fast reconstitution time. A robustness study was conducted, varying temperature and pressure around the defined set-points which demonstrated that a suitable cake is regularly produced.

Since eravacycline degrades at high temperature, and given that the finished product is a lyophilised cake, terminal heat sterilisation is not possible. Therefore, sterile filtration and aseptic processing was selected as the method of choice to afford a sterile product for intravenous infusion, in line with the decision trees in annex of the note for guidance on development pharmaceutics. The suitability of the chosen filter was confirmed following investigations on bacterial retention, bubble point, membrane compatibility and extractables.

Compatibility of intermediate solutions with other manufacturing equipment was also demonstrated. Hold times have been defined for different steps of the manufacturing process, and process parameters have been defined to minimise degradation. CPPs were defined for each step of the manufacturing process and are considered justified.

Early clinical trials were conducted with a slightly different formulation and manufacturing process, and using a different polymorph of active substance. However, given that the active substance is dissolved prior to lyophilisation and the lyophilisates are reconstituted before intravenous infusion, the different formulations are considered comparable. The proposed commercial process and formulation was used during phase III clinical trials.

Compatibility of the finished product with different reconstitution media was investigated. Minimal differences were observed between WFI, 0.9% saline solution and 5% dextrose solution, with all showing similar levels of degradation. Extractables and leachables studies were conducted with a variety of common infusion sets and bags. No extractables or leachables were identified which are known compounds of concern.

The primary packaging is a type I glass vial with a blowback feature with rubber stopper and aluminium seal. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. Prior to final closure, vials are filled with a nitrogen headspace using the blowback feature to minimise oxidative degradation on storage.

Manufacture of the product and process controls

The manufacturing process consists of 6 main steps: preparation of the bulk solution and adjustment of pH; bioburden-reducing filtration; sterile filtration; aseptic filling; lyophilisation; sealing. Bioburden is tested routinely prior to each filtration step. The process is considered to be a non-standard manufacturing process.

The manufacturing process has been validated on 3 consecutive production scale batches using the described process. The aseptic filling process was validated with 3 consecutive “worst case scenario” media fill runs. There were no contaminated units. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls, including pH and bioburden are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance of container, lyophilisate and reconstituted solution (visual and Ph. Eur.), visible particles (Ph. Eur.), identity (HPLC, UV), assay (HPLC), impurities (HPLC), content uniformity (Ph. Eur.), residual water (KF), pH of reconstituted solution (Ph. Eur.), particulate matter (Ph. Eur.), endotoxins (Ph. Eur.), sterility (Ph. Eur.), and reconstitution time.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented. A risk assessment in line with ICH Q3D was carried out by the applicant. All sources of potential elemental impurities were considered, including those introduced intentionally. The applicant provided batch analysis data, using ICP-MS, for all class 1, 2A and three class 3 metals (in line with ICH Q3D), demonstrating that levels are well below the PDE in each case. The limits for degradants are considered justified given the batch data and the levels qualified toxicologically.

Batch analysis results were provided for 26 batches manufactured on pilot to production scale and used throughout the clinical development program. Of these, 4 were manufactured on production scale at the commercial site, using active substance sourced from the proposed commercial source. Overall,

the data provided confirms the consistency of the manufacturing process and its ability to manufacture to the intended product specification. The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 primary stability batches of finished product from the proposed commercial manufacturer stored for up to 24 months under long term conditions (5±3 ºC) and for up to 6 months under accelerated conditions (25 ºC / 60% RH) according to the ICH guidelines were provided. The batches of finished product were made by previous manufacturer involved in clinical trials, but using the same process. Data from 5 additional supportive batches, stored for up to 12 months under long term and accelerated conditions were also provided. Apart from one supportive batch, the finished product batches were manufactured using a different source of active substance, though the manufacturing route was the same and the active substance is considered representative. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Additional data was generated on batches stored at -20 ^{o}C and at 40 ^{o}C / 75% RH.

Samples were tested for appearance of lyophilisate and reconstituted solution, assay, impurities, residual water, pH of reconstituted solution, particulate matter, endotoxins, sterility and reconstitution time. The analytical procedures used are stability indicating.

The only parameters showing any significant change are assay, impurities and water content. For assay, no trends were observed at -20, 5 or 25 ^{o}C with a decrease in assay observed only at 40 ^{o}C. Levels of impurities remained stable at -20 and 5 ^{o}C, though a slight upward trend was observed at 25 ^{o}C and a significant increase in impurities noted at 40 ^{o}C. Water remained constant at -20 and 5 ^{o}C. A slight, within specification, upward trend was observed at 25 ^{o}C and a larger increase in water content was observed at 40 ^{o}C. Therefore, the applicant proposed storage under refrigerated conditions.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. An increase in impurities was observed, indicating that the product should be stored inside the cardboard carton to prevent exposure to light.

In use stability studies were carried out on both the concentrated solution in WFI in vials, and the diluted 0.9% NaCl solution in infusion bags. It was demonstrated that the concentrate is stable for up to 1 hour at 25 ^{o}C once reconstituted in WFI in vials. The diluted 0.9% NaCl solution in infusion bags is stable for up to 12 hours at 25 ^{o}C and for up to 72 hours stored at 5±3 ^{o}C, i.e. under refrigerated conditions. However, from a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Based on available stability data, the proposed shelf-life of 24 months at 5±3 ^{o}C in a refrigerator as stated in the SmPC (section 6.3) is acceptable. The vials should be kept inside the cardboard carton to protect the finished product from exposure to light.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. Suitable information on storage, handling and reconstitution of the finished product have been provided and is included in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

As already mentioned, eravacycline is a fluorocycline and belongs to the tetracycline class of antibiotics. Eravacycline differs from other tetracyclines based on modifications at C-7 (fluorine atom) and C-9 (pyrrolidinoacetamido group) on the phenyl ring. These modifications confer increased activity and stability against tetracycline-specific efflux and resistance due to ribosomal protection proteins (RPP).

2.3.2. Pharmacology

Primary pharmacodynamic studies

The applicant of this marketing authorisation application has conducted several *in vitro* and *in vivo* studies to address the primary pharmacodynamics of eravacycline.

Eravacycline is primarily bacteriostatic and has a broad spectrum of *in vitro* activity against a variety of aerobic and anaerobic Gram-negative and Gram-positive bacteria, including important pathogens that cause intra-abdominal infections with MIC90 values ranging from lower values up to 1 to 4 mg/L. Also against *A. baumanii* the MIC90 values were ranging from 1 to 4 mg/L in different data sets. The poorer activity against *P. aeruginosa* with MIC90 values of 16 to 32 mg/L is similar to what has been seen with other agents of the tetracycline class.

Eravacycline was evaluated *in vivo* using several non-clinical efficacy models of serious hospital- and community-acquired infections produced by pathogens including *E. coli* (tetracycline-resistant and ESBL producing strains), *K. pneumoniae* (ESBL strains), *S. aureus* (methicillin- and tetracycline-resistant strains), *Streptococcus pyogenes*, *Streptococcus pneumoniae* (tetracycline-resistant strain), and *B. fragilis*. Overall, eravacycline was efficacious in most of the non-clinical models used.

The *in vitro* and *in vivo* primary pharmacodynamics studies are presented in more detail in the clinical section of this assessment report.

Secondary pharmacodynamic studies

During the assessment the applicant has submitted the final study report of a receptor binding study (off target screening). CHMP noted some deficiencies in the overall response. Despite the fact that a significant inhibition (62-74%) was observed for the human muscarinic M2 receptor, the LCK kinase and acetylcholinesterase enzyme, no follow-up studies were conducted in order to determine IC50 and Ki values. Moreover, the applicant did not discuss the potential biological consequences of binding to these three targets (M2, LCK, acetylcholinesterase) which would have been expected, given that the exposure margin was approximately 6-fold to the unbound clinical C_{max} of eravacycline. Nevertheless, CHMP noted that in the clinical trials there were no obvious side effects observed with regard to enhanced cholinergic transmission (e.g. hypotension, bradycardia, bronchoconstriction and hypersecretion) or any anti-cholinergic effects (e.g. dry mouth, tachycardia, urinary retention, blurred vision and hyperthermia). Thus, CHMP agreed that it appeared that eravacycline displays a low risk for off target effects at clinical relevant plasma concentration.

Safety pharmacology programme

The potential of eravacycline to alter cardiovascular, respiratory system and CNS was examined as part of the safety pharmacology dossier provided. Studies conducted consisted of *in vivo* intravenous studies on the central nervous system in rats, and the cardiovascular and respiratory system in dogs. Furthermore, an *in vitro* cardiovascular electrophysiology study was performed on cells expressing the hERG gene.

Cardiovascular

It was not possible to establish the *in vitro* hERG channel inhibition due to insolubility, and this was thus reported as >22.2 µM (14.0 µg/mL). At 22.2 µM the inhibition was only 8%. The hERG assay was conducted in the absence of proteins; eravacycline in humans is moderately protein bound in plasma (unbound fraction 15-20%). The most conservative estimate, with the highest C_{max} (5.5 µg/mL) and highest fraction unbound (20%), gave a 13 fold exposure margin (14 µg/mL/(0.2x5.5 µg/mL)) to the highest measured inhibitory concentration. The exposure margin to the IC_{50} could thus be set as >13-fold.

In vivo cardiac safety pharmacology (telemetry) studies in dogs did not show any signal for QT prolongation at the doses tested (5, 15, and 30 mg/kg). However, the administration of eravacycline doses of 15 and 30 mg/kg caused increase in heart rate and blood pressure associated with quantitative changes in ECG intervals, namely shortenings of the PR and QT intervals. The symptoms were suggested to be associated with acute histamine-release, which in turn has been suggested to be more pronounced in rats and dogs than in humans. Consequently, CHMP agreed that it was not possible to definitely conclude, based on this study, whether eravacycline produces QT prolongation. The thorough QT/QTc study in healthy subjects (TP-434-004) did not reveal any concerns for the cardiac safety profile for eravacycline (assessed in more detail in the clinical section). The NOAEL for hemodynamic parameters and ECG activity was set at 5 mg/kg with C_{max} of 5.45 µg/mL and an AUC_{last} of 15.5 µg·h/mL (~2x margin to clinical exposure).

Respiratory

The effect of eravacycline on the respiratory system was investigated in telemerized dogs in the same study in which the cardiovascular parameters were addressed (doses 5, 15, and 30 mg/kg). A dose-dependent increase in respiratory rate was observed during the dosing and 30-60 min after the infusion end (48-50% increase at maximum). Values returned to baseline within 4 hours after the

infusion start. The NOAEL for respiratory parameters in dogs was determined to be 5 mg/kg with C_{max} of 5.45 µg/mL and an AUC_{last} of 15.5 µg·h/mL (~2x margin to clinical exposure).

Central nervous system

The CNS effects were investigated by means of a functional observation battery in rats that were administered 0, 4, 30, and 60 mg/kg eravacycline. No clinical observations were noted after administration of 4 mg/kg. Administration of 30 and 60 mg/kg was associated with clinical observations of laboured breathing, swelling, and skin erythema, with changes in CNS activity and excitability (including reduction in rearing counts and activity/arousal and instances of muscle fasciculation) and with effects on the ANS, sensorimotor system, neuromuscular system (including ataxia and gait pattern abnormalities), as well as with decreased body temperature. Some of these changes were severe, but all were transient. The only time points investigated in the study were 5 min and 24 h after end of infusion. In the autoradiography studies (TTP-01) it was shown that the amount of eravacycline that distributes to the brain is low and that the limited distribution that do occur takes place immediately. CHMP agreed nevertheless that in the current setting it is not possible to evaluate the duration of the response or establish whether there was a delay in any reactions. Potential CNS effects based on clinical signs of toxicity were noted in the toxicity studies. Numerous clinical signs were observed in the rat and dog, whereas no CNS-related clinical signs were observed in the monkey. Of the noted clinical observations, some, but not all, can be attributed to an acute release of histamine.

It was observed that there were signs of changes in thermoregulation in both rat and dog in the safety pharmacology and toxicology studies. After a single dose, rats have shown reduced body temperature and dogs show increased body temperature. Following repeated doses, rats after 14d and 13w have shown wet furs and extra salivation at lower doses, and lower body temperature at higher doses, while dogs (14d) showed signs of reduced temperature.

No pharmacokinetic evaluation was performed in the rat CNS study. However, based on a separate PK study in rats, the NOAEL dose 4 mg/kg produced an eravacycline back-extrapolated maximum plasma concentration (Cp0) value of 11.4 and 11.0 µg/mL in male and female rats, respectively, and an area under the concentration versus time curve from time 0 to the last quantifiable time point ($AUC_{0\text{-}last}$) value of 8.85 and 9.79 µg x h/mL in males and females, respectively. This compares with the clinical median C_{max} of 1.1 µg/mL and AUC0-24 of 7.0 µg x h/mL (~1.3 x margin to clinical exposure).

Conclusion on safety pharmacology

The applicant has investigated the safety pharmacology of eravacycline in accordance with the current EU regulatory guidelines. The most important observed pharmacological effect of eravacycline was the ability to liberate histamine. CHMP agreed nevertheless that the clinical relevance of this in humans is limited.

Pharmacodynamic drug interactions

The applicant has conducted studies evaluating fractional inhibitory concentrations when eravacycline was combined with other agents. In general, the antimicrobial interaction of eravacycline with other antibacterial agents for aerobic Gram-positive and Gram-negative bacteria and for *B. fragilis* was found to be indifferent for nearly all antibiotic combinations and bacteria evaluated. Data generated from these studies are presented in the clinical section of this assessment report.

2.3.3. Pharmacokinetics

The combined Cmax values from the phase 2 and 3 studies in patients ranged from 0.2 to 5.5 µg/mL, with a median value of 1.1 µg/mL. The corresponding exposure expressed as AUC0-24 ranged from 1.4 to 21.2 µg x h/mL, with a median of 7.0 µg x h/mL. With the submission of the new Phase 3 study the pharmacokinetic parameters were updated. The applicant was asked to clarify how the clinical AUC used for the calculation of exposure margins was derived. The applicant responded that the nonclinical exposure margins were calculated using the AUC and Cmax values (i.e. calculated AUC_{0-24} = 13.5 µg*h/mL and Cmax= 1.53 µg/mL) derived from the population pharmacokinetics (popPK), using patient data from clinical phase III studies (TETR-CSC-106) analysis. The applicant has consequently updated the exposure margins, which have been reflected in section 5.3 of the Xerava SmPC.

Methods of analysis

Eravacyline and its metabolites TP498, TP-6208, and TP-034 were quantified by liquid chromatography tandem mass spectrometry (LC-MS/MS) in plasma samples of mouse, rat, rabbit, dog, monkey and human. Metabolite concentrations and patterns in plasma, urine, faeces, bile and homogenates of liver from rat, dog and human ADME studies were obtained by high performance liquid chromatography (HPLC). Metabolite structural elucidation was carried out using validated LC-MS/MS and HPLC MS/MS. The bioanalytical methods are, in general, considered adequate and performed in accordance with GLP compliance.

Absorption

The ability of eravacycline to cross cell membranes was assessed *in vitro* using MDCK cells, a common model for evaluating intestinal absorption and blood brain barrier penetration, and the PAMPA system was used to evaluate eravacycline's potential to cross an artificial membrane. Passive permeability was low in all *in vitro* assays tested, suggesting that eravacycline has a low potential to cross the blood-brain barrier and for passive transcellular absorption.

After a single intravenous dose, the T_{max} values ranged from 0.1 to 2 h in the plasma of mice, rats, rabbit dogs and monkeys, which is similar to T_{max} in humans (1 h).

Following intravenous injection, exposure (C_{max} and AUC) to eravacycline increased with increasing doses, but this increase was generally greater than proportional to the increase in dose, and systemic clearance and volume of distribution decreased with increasing doses in rats, dogs, and cynomolgus monkeys. Plasma clearance of eravacycline was dose-dependent and low in all species, ranging from 0.104 L/h/kg in rabbits to 0.487 L/h/kg in cynomolgus monkey. The decline in systemic plasma concentrations of eravacycline after i.v. doses was multiphasic, indicating distribution and elimination processes. The plasma systemic half-life was moderate ($T_{1/2}$ = 5.2 – 7.2 h) in rats and rabbits and 10 to 15 h in dogs and monkeys. The plasma half-life was variable in humans, ranging from 8.65 to 25.62 h in the SAD and MAD studies. The volume of distribution (Vd) was moderate and ranged from 0.7 to 4 L/kg across species.

There was little or no accumulation (<2-fold) of eravacycline after repeated intravenous dosing and there was no obvious gender difference in the pharmacokinetics parameters of eravacycline after single or multiple doses.

Absorption of eravacycline metabolites

The PK parameters of the eravacycline metabolites TP-498 and TP-6208 after a single i.v. dose of eravacycline were examined in various non-clinical species. In all species where measured, plasma concentrations of the major human eravacycline metabolites (TP-498 and TP-6208) increased with

dose, but were lower than those of eravacycline. TP-498 AUC represented between 9% and 25% of eravacycline AUC in monkey, dog and rabbit and 7% to 16% in human. The systemic exposure of TP-498 was not evaluated in the rat. The exposure (AUC) of TP-6208 was between 0.2% and 2.5% of the eravacycline exposure in rabbit and dog and 27 to 40% in human. There were no obvious sex differences in the PK parameters for TP-498 and TP 6208.

Distribution

Tissue distribution in pigmented rats was evaluated by quantitative whole body autoradiography (QWBA) after single intravenous dosing. The distribution of radiolabelled eravacycline was rapid, widespread and concentrated in the trachea, adrenal gland, liver, and aorta. Radioactivity was generally BLQ 21 days post-dose, with the exception of the uveal tract, bone (including teeth and tracheal hyaline cartilage), thyroid, aorta, bone marrow and pigmented fur. A concentration of radioactivity in the uveal tract and pigmented fur is consistent with the binding of eravacycline to melanin-containing structures, which has been observed with other tetracycline antibiotics. Given the lack of ocular adverse effects in the non-clinical studies (see also toxicology section) or in the clinic, CHMP agreed that the binding of eravacycline to melanin does not appear to be associated with any obvious risk for adverse ocular effects in patients.

Eravacycline passed the placental barrier in rats and rabbits (see also toxicology section). Foetal plasma concentrations were in the same range of maternal drug plasma concentrations.

Protein binding was species-dependent with highest binding in monkey (ranging from 94.7% to 99.6% at 0.1 to 100 µg/mL). Moreover, the protein binding *in vitro* was inversely related to the concentration, with the percent free fraction (fu) decreasing with increasing concentrations of eravacycline, which is a rather unusual profile. In all species, eravacycline showed concentration-dependent protein binding where the fraction unbound eravacycline decreased with an increase in the total concentration. A mechanistic reason for these differences has not been explored. Furthermore, the plasma protein binding of eravacycline was decreased in the presence of high (1 µg/mL) concentrations of the major human metabolite TP-6208, suggesting that these compounds compete for common binding sites. Regarding the other metabolites, the protein binding of eravacycline in the presence and absence of TP-498, the epimer of eravacycline, was not determined because of the uncontrolled interconversion of TP-498 and eravacycline. TP-034 is present in plasma at low levels (approximately 30-fold lower than TP-434) and was accordingly not included in the protein binding studies. This binding interaction (displacement) between eravacycline and its metabolite(s) is unlikely to be of clinical relevance since the protein binding in humans is moderate (<90% at concentrations exceeding the clinical therapeutic concentrations by 10-fold (i.e. at 10 µg/mL)).

The blood:plasma concentration ratios in samples with heparin were between 0.90 and 1.3 in humans, suggesting that eravacycline is not preferentially taken up by or bound to blood cells. The blood:plasma distribution ratio of eravacycline in animals was not reported by the applicant, but this was considered acceptable by CHMP.

Metabolism

Unchanged eravacycline is the major drug-related component in rat, dog and human plasma and urine after a single IV dose. Qualitatively similar metabolites are found in the plasma of humans, rats and dogs. The metabolic turnover of eravacycline is, however, very slow, with negligible loss (e.g., <15%) up to 4 h after incubation with concentrations of 1-100 µM in competent liver microsomes, intestinal microsomes, hepatocytes, or S9 fractions of rat, dog, monkey and human. *In vitro* studies examining the metabolic turnover of eravacycline by hepatocytes and subcellular fractions together with *in vivo* studies have shown that oxidative metabolism by oxidation of the pyrrolidine ring via CYP3A4 and FMO

enzymes to the cyclised metabolite TP-6208, chemical epimerisation at C-4 to TP-498 and hydrolysis of the amide side chain to TP-034 appeared to be the predominant metabolic pathways in animals and humans.

The metabolites of eravacycline formed *in vivo* were identified in plasma and excreta from rat, dog, cynomolgus monkey, and human following i.v. administration of eravacycline using LC/MS/MS methods. The exposure to metabolites (especially TP-6208 and TP-034) was low in animals compared to humans. In order to reach adequate plasma concentrations in the toxicology studies, the human metabolites TP-6208 and TP-034, were dosed to animals in some of the toxicology studies in order to qualify them adequately.

Following a single intravenous administration of eravacycline in the human mass balance study, most of the circulating radioactivity in the 0-24 hour (AUC_{0-24h}) pooled sample attributable to eravacycline (59.3 ± 9.3%, range 44-69%), TP-498/TP-6208 (29.7 ± 3.6%, range 26-35%) and TP-034 (2.4 ± 3.3%, range 0-8%).

The major human metabolites TP-6208/ TP-498 as well as the minor metabolite TP-034 are not considered to be reactive or pharmacologically active by CHMP.

Metabolites in milk

Metabolites in milk were assessed following a repeated intravenous dose of eravacycline (3, 5, 10 mg/kg/day) in the developmental and perinatal/postnatal reproduction studies in rats. The major component in milk and maternal plasma was eravacycline. In addition, the major human metabolites TP-498 and TP-6208 are found in rat milk after eravacycline dosing, and also in foetal rat plasma. Concentrations of TP-498 in rat milk were 14 to 19-fold lower than concentrations of eravacycline and TP-6208 concentrations were several 100-folds lower compared with eravacycline concentrations.

The wording proposed by the applicant with regard to breast-feeding in section 4.6 of the SmPC was considered appropriate by CHMP.

Excretion

Mass balance data was obtained from rats, dogs and humans. Overall, the results indicate that elimination pathways for eravacycline in rats and humans are similar; the majority of absorbed drug-related radioactivities indicate that faecal and/or biliary elimination (rat 66%, human 48%) is the major route of excretion for eravacycline and/or its metabolites, and a somewhat smaller fraction is eliminated into urine (rat 25%, human 35%). In humans, parent compound accounted for approximately 20% in each excreta.

In conclusion, the non-clinical pharmacokinetic profile of eravacycline is considered by CHMP to have been adequately characterized. Rats and monkey were chosen by the applicant as target species for the toxicology studies, since eravacycline dosing was not well tolerated in dogs due to a histamine-like response. As a result of quantitative differences in the metabolic profile in non-clinical species and humans, the animals received intravenous dosing of the major human metabolites in selected pivotal toxicity studies to allow for complete evaluation of the toxicity of eravacycline.

2.3.4. Toxicology

The nonclinical toxicological profile of eravacycline has been investigated in line with the principles and practices outlined in ICH and OECD. All pivotal studies followed GLP regulations. The rat was chosen as the rodent species and the monkey as the non-rodent species, as eravacycline metabolism is similar to humans with regards to formation of the TP-6208 metabolite. Dogs were also used for repeat-dose

toxicity studies and rabbits were used during reproductive toxicity studies. All pivotal studies used the intended IV route of administration.

Some PK studies were done in chimpanzees, but this species is not to be used for non-clinical testing.

Single dose toxicity

The applicant has not presented any pivotal GLP single dose toxicity studies, which was considered acceptable. The acute toxicity in relation to the intended clinical use data was not considered a concern by CHMP.

Repeat dose toxicity

Morbidity and mortality

Morbidity and mortality were observed in both in rats and dogs, but not in monkeys.

In the 14-day GLP study in rats, administration of 40 mg/kg/day resulted in morbidity in 3 animals on day 11 and 12. Also in the 13 weeks study three animals (one per dose group) were euthanized on days 29, 115 and 60. These animals displayed numerous clinical signs among the most pronounced was swelling of extremities, dry red material on several parts of the body, wet fur, skin erythema, salivation and laboured breathing. Treatment–related macroscopic findings included pale discoloration of the liver that correlated microscopically with hepatocyte cytoplasmic vacuolation in the liver and bilaterally enlarged forepaws and hind paws that correlated microscopically to oedema and necrosis of the skin/subcutis likely due to vasculopathy and moderate fibrosis.

In dogs, treatment-related mortality was observed at ≥12 mg/kg/day. In this group 4/10 animals were euthanized during dosing and the rest before end of recovery. Similarly, 6/10 animals in the high-dose group (20 mg/kg/day) were euthanized during dosing and the rest before the end of recovery. These deaths were due to severe loss of body weight (-22.3% to -29.0% from baseline), diminished appetite, numerous gastrointestinal clinical signs, and/or dehydration. In this study dosing was ended on Day 7 for all of the 20 mg/kg/day animals.

Clinical observations

In rats, treatment–related clinical signs were generally present in a dose-dependent manner and were more severe, observed more frequently, and took longer to resolve in the 40-mg/kg/day group. Observations at ≥4 mg/kg/day included skin erythema, chromodacryorrhea, stereotypic behaviour, wet fur, urine staining, and dry red material (nose, mouth, face, eyes, forepaws, forelimbs, abdomen, and/or tail). At higher doses (≥20 mg/kg/day) swelling, lacrimation, ataxia, salivation, and nasal and/or tail discharge was observed. In the 40-mg/kg/day group loss of body temperature, laboured breathing, vocalisation, facial oedema, apparent blood around the eyes (porphyrin staining), hunched posture, and rough hair coat were observed. The onset of skin erythema, swelling, chromodacryorrhea, lacrimation, ataxia, salivation, loss of body temperature, laboured breathing, stereotypic behaviour, nasal and/or tail discharge, vocalisation, and facial oedema generally began shortly after dosing, as early as 1 minute post dose, and lasted minutes to approximately 4 hours post-dose, with recovery by 4 hours.

In dogs, reversible acute skin reactions (hives, skin erythema, and swelling) were apparent in all of the animals administered ≥12 mg/kg/day for 14 days and were sometimes accompanied by scratching. Following administration of ≥12 mg/kg/day gastrointestinal clinical signs were severe and included emesis (sometimes more than once per day) and soft/mucoid faeces; these signs were often

accompanied by salivation and green/orange/black faeces. Some similar findings were also present in the 2 mg/kg/day group. In addition, observations of shivering and animals cold to touch were recorded (see also discussion on safety pharmacology).

In monkey, diarrhoea, watery diarrhoea, soft faeces, emesis (containing white, yellow, or red material), excessive salivation, thinness, dermal atonia, inappetence, and/or pale gums were found in the 18-mg/kg/day group (at >72 times the patient exposure) . With the exception of soft faeces, all clinical observations occurred intermittently and only during the second week of the dosing period. In the prolonged 13-week study there were no clinical observations.

Body weight and food consumption

In rats, dosing for 14 days was associated with statistically significant decreases in mean body weight in the 20- and 40-mg/kg/day males (-7.0% and -21.8%, respectively) on Day 14. During the recovery phase, the 40-mg/kg/day males exhibited a statistically significant decrease in mean body weight on Day 21 (-20.3%) and non-statistically significant decreases in mean body weight on Days 28 and 35, suggesting a trend toward recovery. In this group a statistically significant decreases (-20.8%) in mean food consumption was observed after 14 days. Mean food consumption was comparable to that of the control group during the 3-week recovery period, indicating a full recovery. Also in the 13 week study body weights and body weight gains over the entire dosing period were significantly reduced in the 16 mg/kg/day males (-12%). During the recovery period, mean body weights continued to be significantly reduced in these males. However, there was a rebound in weight gain for the overall recovery period and body weight gains were comparable among the 5 dose groups. There was no treatment-related effect on body weights, food consumption and body weight gains during the dosing period in the female rats.

Also in dogs, the data show a decrease in food consumption (up to -29%); however considering the overall mortality in this study the data are uncertain.

In monkeys, in the 14 day study, weight was lost in the high-dose group males (up to -16.6%) and females (up to -18%). After dosing, the data showed body weight gains in these animals (ranging from +11% to +16.9%). Also in the 90 days study in the male monkeys dosed ≥4 mg/kg/day, body weights were decreased up to 10.6%, which were resolved after recovery.

Haematology and coagulation

In rats, 14 days administration of ≥20 mg/kg/day was associated with statistically significant, dose-dependent decreases (up to -26%) in mean RBC, haemoglobin, and haematocrit. In addition, decreases in mean absolute reticulocyte count and mean corpuscular volume (up to -75%) were present in the 40-mg/kg/day males and decreases in mean absolute eosinophil count (up to -84%) in the 20-mg/kg/day females and 40-mg/kg/day males/females. All these effects were most likely a consequence of eravacycline-induced bone marrow hypoplasia. The decrease in mean absolute lymphocyte count (up to -39%) in the 40-mg/kg/day males may be correlated with the microscopic findings of lymphoid depletion. In the 13-week study erythrocytes, haemoglobin, and haematocrit were significantly decreased (up to -16.2%) and mean corpuscular haemoglobin and mean corpuscular volume were significantly increased (up to +6.3%) in the 16 mg/kg/day males at the end of the dosing period. Lymphocyte and basophil counts were significantly decreased (up to -54.7%) in ≥8 mg/kg/day males and eosinophils were significantly decreased (up to -59.9%) in the 16 kg/kg/day males. All treatment-related haematology parameters had reached levels comparable to control values at the end of recovery.

In dogs, several parameters were affected including decreases in mean absolute reticulocyte counts, platelet counts, absolute lymphocyte counts, absolute monocyte counts, absolute eosinophil counts, absolute basophil counts, and absolute large unstained cell counts on day 15 at 12 mg/kg/day. These changes correlated to the bone marrow atrophy and lymphoid atrophy in the thymus, spleen, and lymph nodes, which was also reflected by decreases in the absolute and relative mean spleen (up to -86.3%) and thymus (up to -77.0%) weights at ≥12 mg/kg/day. The recovery data was hampered by the mortality in this study.

In monkeys, changes in the 18-mg/kg/day males and females included alterations of lower RBC indices (RBC, haemoglobin, and haematocrit) in females and lower reticulocyte count and lower platelet count in males. Test article-related decreased anti-KLH immunoglobulin G (IgG) antibody levels were observed in the 8-mg/kg/day males and females on Days 41, 43, 47, 53, and 57, consistent with impairment of immune function.

In dogs, treatment-related changes included prolongation of mean PT (up to +25%) and APTT (up to +66%) at 12 mg/kg/day on Day 15 and prolongation of mean PT (up to +33%) and APTT (up to +42%) at 20 mg/kg/day on Day 8. Changes in electrolyte values such as slight decreases (up to -16% from control or baseline) in mean potassium, calcium, sodium, and chloride values were also observed in some of the animals at ≥12 mg/kg/day at the end of the dosing phase.

In monkeys, higher APTT, lower cholesterol, higher urea nitrogen, higher bilirubin, and lower urine pH in the 18-mg/kg/day group males and females. All of these findings were recoverable.

Clinical chemistry

In rats, statistically significant increases in mean fibrinogen values were observed in 40-mg/kg/day dosed males (+72%), as well as the 4-, 20-, and 40-mg/kg/day dosed females (up to +91%). The changes in fibrinogen correlated with mild to moderate fibrosis and minimal to marked chronic-active inflammation at the administration site of the 40-mg/kg/day dosed animals. Dose-dependent decreases in mean total protein values were noted on Day 15 for the 20- and 40-mg/kg/day males (up to -11%) and 40-mg/kg/day females (-9%). This decrease correlated with statistically significant decreases in albumin and albumin/globulin ratio levels. The changes were considered to be non-adverse at 40 mg/kg/day. By Day 36, all treatment-related serum chemistry parameters had reached levels comparable to control values, indicating full recovery.

Macro / Microscopic observations

Effects on lymphoid and bone marrow systems

At the day 15 necropsy in rat, treatment–related organ weight changes were present in the spleen and thymus of 40 mg/kg/day males and females. Microscopically findings of minimal to moderate bone marrow hypoplasia and minimal to moderate increase in haemosiderin pigmentation and minimal to mild macrophage hyperplasia in the spleen were observed. After recovery a moderate bone marrow hypoplasia was still observed. Also in the 13 week rat study at 8 mg/kg/day, a decreased thymus weight was recorded. In this study the incidence of microscopic findings and/or severity grade of mandibular, mesenteric lymph nodes and gut-associated lymphoid tissue were increased at ≥4 mg/kg/day. These findings were characterized by a decreased lymphoid cellularity resulting in a decrease in size and often density of lymphocytes and/or germinal centres. All changes were recoverable.

In dog dosed at ≥2 mg/kg/day, a decrease in splenic weights were recorded (up to -86.3%), correlated with lymphoid atrophy. In addition, there was haemorrhage in lymph nodes, bone marrow atrophy, and lymphoid atrophy in the thymus, and lymph nodes.

In monkey dosed at ≥2 mg/kg/day, lower spleen and thymus weights were recorded (up to -26.7% and -52.1% respectively); and histopathologic changes of bone marrow depletion, lymphoid depletion in the spleen, thymus, axillary lymph nodes, mandibular lymph nodes, mesenteric lymph nodes, and Peyer's patches was observed in the high-dose group (18 mg/kg/day). All but thymus changes were recoverable.

Effects on the male reproductive system

In rats, administration of eravacycline for 14 days caused reductions in the weight of the prostate, epididymis, testis and seminal vesicles at ≥8 mg/kg/day. The effect on the weight of the seminal vesicle correlated with microscopic findings of mild to moderate atrophy and decrease in secretions. After recovery, minimal to mild degeneration of the seminiferous tubules was observed, as well as minimal to mild oligospermia, and minimal to moderate cellular debris in the epididymides. Additional findings in the 13 week study included: decreased release of residual bodies, uptake of residual bodies by Sertoli cells, spermatid retention in the seminiferous tubules, increase of spermatid head retention in Sertoli cells, and vacuolation of Sertoli cells, decreased sperm, cribriform change and abnormal shaped sperm. The effect on the male reproductive organs and potential effect on fertility were specifically addressed in dedicated fertility studies (see reproductive toxicity section).

No effects on male reproductive organs were observed in monkey or dog.

Bone discoloration

In rat at the end of the 13 week dosing period, yellow discoloration of the calvaria and femurs was observed in 1/10 males at 8 mg/kg/day and in 7/9 males at 16 mg/kg/day; yellow discoloration of the calvarium was observed in 1/10 females at 16 mg/kg/day and yellow discoloration of the femur was observed in 1/10 and 4/10 females at 8 and 16 mg/kg/day, respectively. No microscopic correlate to the yellow discoloration was observed in the bone tissue of the calvaria or femurs, and these changes were considered non-adverse. Similarly, at the recovery necropsy, yellow discoloration of the femurs (3/5 males and females) and calvaria (2/5 females) was observed at 16 mg/kg/day. Observation of yellow discoloration was also recorded in juvenile rats (see below) and in the monkey dosed ≥1 mg/kg/day, which was not recovered.

Administration site

Administration site findings in both rat and monkey were characterized by mild to moderate fibrosis, minimal to marked chronic-active inflammation, minimal to marked vasculopathy, necrosis of endothelium with fibrin deposition, minimal to moderate subacute muscle inflammation, muscle degeneration, and/or muscle regeneration.

GI findings

In dog at ≥12 mg/kg/day, degeneration of the mucosa involving one or more segments of the small and large intestine, often accompanied by congestion and occasionally haemorrhage and sometimes by ulceration were noticed. Similarly, in monkey at ≥4 mg/kg/day histopathologic changes of mucosal atrophy in the small intestine (duodenum, jejunum, ileum) and large intestine (caecum, colon, rectum) were recorded. The findings in monkey were reversible after recovery.

Additional findings

The liver was identified as an additional organ for toxicity. This was manifested by decreased weight and hepatocyte vacuolation in rat, dog and monkey.

Also, cardiac atrial haemorrhage and necrosis (dog), acute inflammation in the kidneys (monkey), cervical epithelial atrophy (monkey) and decreased pancreatic zymogen granules (monkey) were recorded.

In rat females administered 40 mg/kg/day, a decreased uterus weight was recorded.

In addition, statistically significant organ weight differences compared to controls were present in the 20- and/or 40-mg/kg/day male rats (decreased heart, kidney, pituitary, salivary gland) and in the recovery of the 20- and 40-mg/kg/day males (decreased liver) and 40-mg/kg/day males (increased spleen). However, these organ weight changes were not correlated with any histopathological changes.

Toxicokinetics

The NOAELs initially proposed in the application have in general been lowered during the CHMP assessment. Consequently the margins to patients are smaller than those proposed by the applicant, being close to the clinical exposure (1.7 to 3.5 time clinical exposure). The applicant was asked to clarify how the clinical AUC used for the calculation of exposure margins was derived. The applicant stated that the nonclinical exposure margins was calculated using the AUC and Cmax values (i.e. calculated AUC0-24 = 13.5 µg*h/mL and Cmax= 1.53 µg/mL) derived from the population pharmacokinetics (popPK), using patient data from clinical phase III studies (TETR-CSC-106) analysis. Consequently, the applicant has updated the exposure margins, which are reflected in the Xerava SmPC section 5.3.

Genotoxicity

Eravacycline was not genotoxic in any of the studies performed (Ames assay, mouse lymphoma assay, human peripheral lymphocyte chromosomal aberration assay and a rat bone marrow micronucleus study). Exposure in the *in vivo* chromosomal aberration study is considered sufficient (up to 176 times the clinical based on Cmax) and distribution to the bone marrow was previously confirmed by the administration of radioactive eravacycline. The concentrations used in the *in vitro* studies were in some cases limited by cytotoxicity.

Carcinogenicity

No carcinogenicity studies were performed for this application. CHMP considered this acceptable, in view of the short clinical duration of treatment (up to 14 days).

Reproduction Toxicity

Fertility and early embryonic development

Fertility and early embryonic development were assessed in male and female rats.

In the male fertility study, rats were administered i.v. bolus injections at dose levels of 0, 1, 4, 12, and 16 mg/kg/day eravacycline beginning 70 days before cohabitation, during the cohabitation period, and continuing to the day before euthanasia or recovery. Effects on male fertility were observed at 12 mg/kg/day (NOAEL 4 mg/kg/day). When male rats administered 12 mg/kg/day and higher were cohabited with females immediately after the treatment ended, the number of pregnancies was significantly reduced (number of pregnant females/number of mated females in 12 mg/kg/day: 1/24 and 16 mg/kg/day: 0/24). Decreased sperm counts (cauda epididymal sperm count 178 in control and 37 in 16 mg/kg/day), abnormal sperm morphology, and reduced sperm motility (vas deferens sperm

motility in percent in control 92% and 30% in 16 mg/kg/day) were also observed, and testicular effects included abnormal retention of spermatids with Sertoli cells associated with a reduced presence of residual bodies within the cytoplasm of the Sertoli cells. These findings were reversible following a 70-day (10-week) recovery period, equivalent to a spermatogenic cycle in the rat. The male toxicity and fertility NOAELs were 4 mg/kg/day eravacycline which gives a ~2 times human plasma exposure based on AUC. Toxicity to the male reproductive organs was also recorded in the repeat-dose toxicity studies in rat.

In contrast to male rats, there were no adverse effects on mating or fertility in female rats at any dose level (0, 4, 8, and 20 mg/kg/day). The 20-mg/kg/day dose was associated with reduced body weight gains during the first 2 weeks of dosing and during the gestation dosing period (GD 0 to GD 7). The reproductive toxicity NOAEL was >20 mg/kg/day. Plasma exposure based on AUC after 20 mg/kg/day is approximately 23 times the human plasma exposure. NOAEL for general toxicity was 8 mg/kg/day due to similar findings as discussed previously (swollen snout, limb and/or paws and reduced body weight).

Embryo-foetal development

The embryo-foetal developmental study in rats was conducted at 0, 3, 5, and 10 mg/kg/day. In addition, the metabolite TP6208 was included and administered at 3.5 mg/kg/day together with eravacycline. Maternal findings in the group administered 5 mg/kg/day eravacycline and 3.5 mg/kg/day of the metabolite TP-6208 included reduced body weight and food consumption and observations of swollen snout, limbs/paws. Foetal body weight was reduced in the groups administered 5 and 10 mg/kg/day eravacycline (5.61/5.28 g and 5.26/4.99 g M/F compared with the control group 5.85/5.59 g). At this dose levels there was also a delay in skeletal ossification. NOAEL for both maternal and developmental toxicity was 3 mg/kg/day, with the addition of TP6208 3.5 mg/kg/day. The NOAEL dose corresponds to about two times the clinical exposure based on AUC.

The embryo-foetal developmental study in rabbits was conducted at 0,1 ,2, and 4 mg/kg/day, with the dose-range study conducted at 0, 1, 3, 6, 12 mg/kg/day. One female at 4 mg/kg/day aborted a litter of dead conceptues. Decreases in body weight and food consumption, ungroomed coat and pale heart and liver were noted in the does at 4 mg/kg/day. A 100% post-implantation loss was observed at 12 mg/kg/day. The developmental toxicity in the 4 mg/kg/day group included an increased number of late resorptions (post-implantation loss 2.0% in control and 10.2% in 4 mg/kg/day), 1 dead foetus, reduced foetal body weight (-6.7% in 4 mg/kg/day group) and reduced number of ossified phalanges (ossification site averages in forelimb phalanges 13.89 in control and 13.72 in 4 mg/kg/day). Administration of 12 mg/kg/day in the dosage range finding study was associated with 100 % post-implantation loss. The NOAEL for both maternal and developmental toxicity in this study was set at 2 mg/kg/day (approximately 3.7 fold the clinical exposure based on AUC).

Pre- and postnatal development

The potential effects of eravacycline on development, growth, behaviour, reproductive performance, and fertility of F1 generation were evaluated in rats after administration of 0, 3, 5, or 10 mg/kg/day to F0 females from gestation day 7 through Day 20 postpartum. Furthermore the F1 pups were investigated for cohabitation on post-natal day 90. The NOAEL for general toxicity in the F0 generation was 5 mg/kg/day, the NOAEL for the reproductive toxicity was 10 mg/kg/day. The NOAEL for toxicity and reproduction in the F1 generation and the F2 foetuses was 10 mg/kg/day.

On lactation day 15, eravacycline and the metabolites TP-498 and TP-6208 were measured in pooled milk. The concentration of TP-434 from the dose groups 3, 5, and 10 mg/kg/day was 11.5, 13.5, and 32.8 µg/mL.

Juvenile toxicity studies

The potential toxicity of eravacycline was assessed in two studies in juvenile rats. In the first study (a dosage range finding study), eravacycline was administered during 14 days, starting at 21 days of age. In the other study, eravacycline was administered for 50 days, starting at 21 days of age. In the second study the animals were followed post-dose (males approximately 100 days and females 48 days). The reproductive toxicity previously discussed in male animals was also observed in this study. The fertility index in the male animals was reduced, and remained after a 4-weeks recovery period but recovered after 10 weeks.

It was not possible to establish a NOAEL in juvenile rats in this study. At the low dose (4 mg/kg/h) histopathological findings such as reduced lymphoid cellularity and number and size of germinal centres in the mandibular and mesenteric lymph nodes, hepatocellular vacuolation, and inflammation at the injection site was observed. At higher doses, histopathologic effects were also observed in testes, epididymides, spleen, and thymus. Alterations were also observed on some other investigated parameters.

Yellow discoloration of the calvaria and/or femurs, was observed in the ≥20 mg/kg/day group. The colouring did not resolve during the recovery period. This effect is a known class effect of tetracyclines and should be taken into consideration when children are treated and also in respect when breast-feeding women are going to be treated since eravacycline is transported to the milk in rats.

Summary/discussion

The applicant has presented a complete developmental and reproductive toxicology (DART) programme, including juvenile toxicity studies. The effects on the male reproductive system and bone discoloration were also observed in the repeat dose toxicity studies. In general, no new toxicity was detected in the juvenile toxicity in comparison to the data generated in adult animals. Since no NOAEL could be established in juvenile rats, it could be speculated that juvenile animals may be more prone for eravacycline induced toxicity, but a definite comparison is hard to perform on the available data.

Local Tolerance

In a dedicated local tolerance study, there were no differences in inflammatory changes at the injection site that were related to the concentration or rate of infusion of eravacycline.

Local tolerance was also evaluated in the pivotal repeat-dose i.v. toxicity studies by both gross and microscopic assessment of the injection sites. Injection site findings were observed following i.v. administration, specifically at higher concentrations of eravacycline, when a catheter or vascular access port was not utilised for the administration procedures (i.e., in the rat and shorter duration non-rodent studies).

Other toxicity studies

Immunotoxicity

Immunotoxic effects have been observed in both the KLH study and in the repeat-dose toxicity studies in rats, dogs and monkeys. A decrease in anti-KLH IgG antibody was observed in the 8-mg/kg/day males and females. The decrease in anti-KLH IgG antibody levels correlated microscopically with lymphoid depletion in the spleen, mandibular lymph nodes, and mesenteric lymph nodes. Findings seen in repeat-dose studies in rats, dogs and monkeys included decreased white blood cell parameter indices that correlated with changes in spleen and/or thymus organ weights and the microscopic

finding of bone marrow and/or lymphoid tissue atrophy. At the end of the recovery period, all immune-toxic effects had resolved in rats, but not in dogs and monkeys, where some of the immune parameters had only partially recovered (white blood cell count and immune organ weight).

The applicant argued that there was no evidence of immune-toxic effects (leukopenia, neutropenia, lymphopenia, haematology values) in the clinical development programme in eravacycline-treated subjects, and that the lymphoid findings can be monitored in the clinic and are generally reversible. The safety margins calculated across species and repeat dose toxicity studies are low (0.84-14, AUC_{0-24}); this was considered acceptable by CHMP, considering that any findings can be monitored in the clinic and that they are in general reversible. The applicant also clarified that no immunotoxic effects have been observed in the clinical trial programme and the safety of potentially vulnerable patients is considered taken care of.

Phototoxicity

In an *in vivo* study in pigmented rats, repeated i.v. administrations of 40 mg/kg/day eravacycline were not phototoxic.

Effect on mitochondrial protein synthesis

Several antibiotics, such as linezolid, have showed toxicity related to impaired eukaryotic mitochondrial protein synthesis linked mechanistically to mitochondrial protein synthesis (MPS) inhibition. The mechanism of action of eravacycline involves the disruption of bacterial protein synthesis. The potential effect of eravacycline on mitochondrial protein synthesis was therefore investigated in a mitochondrial toxicity specific assay using tetracycline and linezolid as comparators.

In this assay, eravacycline was found to inhibit mitochondrial protein synthesis with an IC50 value of 1.4 µM. Eravacycline was more potent than tetracycline and linezolid with IC50 values of > 10 and 10 µM, respectively. According to the applicant, the relevance of inhibition of mitochondrial protein synthesis is uncertain, since there are no clear signs of mitochondrial toxicity in the non-clinical and clinical studies. Six cardinal recognised toxicities were according to the applicant attributed to mitochondrial dysfunction (1. hepatitis and steatosis, 2. cardiomyopathy, 3. skeletal muscle injury, 4. peripheral neuropathy, retinal toxicity and ototoxicity, 5. lipodystrophy, 6. renal tubular failure). No recognised mitochondrial toxicities were discovered in the animal studies or in the clinical studies with eravacycline.

Metabolites

The three human major metabolites of eravacycline TP-498 (also present as a specified impurity), TP-6208, and TP-034 (also present as a specified impurity) were qualified through their presence in the eravacycline batches used for the general toxicity, genotoxicity, or reproductive and developmental toxicity studies, or through specific studies (in vitro and/or in vivo) with the individual compounds.

In general the data generated by the applicant on the exposure of the various metabolites in patients in relation to the exposure of the same metabolites in the non-clinical safety studies (both eravacycline and dedicated metabolite studies) do not indicate any additional risks associated with metabolite exposure at or above clinical exposure. Consequently the major human metabolites are considered to the qualified from a non-clinical point of view.

Impurities

An assessment regarding the qualification of impurities TP-498, TP-034, TP-630, TP-5799, TP-6773 and TP-4705, TP-9944 and TP-4308 (process impurities, degradation products, intermediates, or starting materials) has been conducted based on their presence in the eravacycline batches used for

the general toxicity, genotoxicity, or reproductive and developmental toxicity studies, or through specific studies (*in vitro* or *in vivo*). In addition, computational risk assessments have been completed for the same impurities. CHMP agreed that in essence the impurities can be considered as safe and qualified up to the set specifications.

2.3.5. Ecotoxicity / environmental risk assessment

A Phase I exposure assessment indicated the $PEC_{SURFACEWATER}$ exceeded the action limit of 0.01 µg/L. Therefore, a Phase II Tier A assessment was triggered.

The octanol-water partition coefficient (log D_{OW}) of eravacycline at pH 4-9 ranged from -1.395 to 1.33. At physiological pH, the log DOW is below 3, therefore the screening criterion for classification for bioaccumulation is not met. Eravacycline is not considered as PBT substance.

The $PEC/PNEC_{SW}$ ratio (0.7/0.0413 µg/L) for aquatic organisms was above the threshold of 1, thus indicating a potential risk of eravacycline to the aquatic compartment. The applicant was therefore asked to refine the PEC_{SW} value or else this concern for the product should lead to information in the Xerava SmPC on how to dispose of the medicine to protect the environment. The applicant suggested to revise the PEC_{SW} based on the treatment regime and re-calculated the maximum daily dose over a total treatment duration of 14 days in one year (i.e. total 1960 mg in 14 days / 365 days = 5.37 mg/day). This strategy to revise the $PECS_W$ was not considered acceptable by CHMP, as refinement of data in Phase I should take in consideration the worst-case treatment regime and worst-case number of treatment days per year. Therefore, information relating to the possible effects of eravacycline in the aquatic environment was included in sections 5.3 and 6.6 of the Xerava SmPC and correspondingly in the PL.

The PEC/PNEC ratio for groundwater was below the threshold of 1.

The PEC/PNEC ratio for micro-organisms was below the threshold of 0.1.

The preliminary RCR calculated for surface water was based on a PNEC from a study conducted using *P. subcapitata* as test species. According to Question 11 in the EMA ERA Questions & Answers document (EMA/CHMP/SWP/44609/2010 Rev. 1), blue-green algae is the recommended test species for testing antimicrobials on algae. Thus, a repeat study for the algae (blue-green) growth inhibition test (OECD 201) has been reported.

Further testing of the environmental fate of eravacycline (ready biodegradability, adsorption/desorption and aerobic degradation in surface water systems) is also currently being planned. The data from these studies as well as the ecotoxicological data will be used to update the aquatic risk assessment presented in this report. The refinement of the exposure of surface water species will be proposed which could include further testing and/or using a statistical extrapolation technique (Species Sensitivity Distributions - SSD) to derive a refined PNEC (which in this case is the concentration at which 95% of the species theoretically are protected (HC5)) and/or modelling the fate of eravacycline in a sewage treatment plant using the Simple Treat Model.

With regard to the risk to sewage sludge micro-organisms, the data could not be fully assessed. The NOEC for the most sensitive endpoint heterotrophic respiration could not be established, as the value was lower than 0.5 mg/L. Furthermore, the EC_{50} of 3 mg/L of the reference substance was outside the acceptable range of 5 mg/L to 40 mg/L and hence, the initial study was considered as non-valid. Therefore, the applicant has provided a new respiration inhibition test according to OECD 209.

Furthermore, the applicant was initially asked to discuss potential explanations for the strong decrease of test substance concentration during the ecotoxicological tests, despite the suspected stability and moderate logKOW of eravacycline.

The PNECs for algae and daphnids stated in the ERA were miscalculated by a factor of 10. For the RQ calculation, the correct values were applied.

The OECD 210 was conducted in vessels of inadequate size and the measured test concentrations exceeded the nominal by up to 292 %, leading to highly variable exposure. In addition, the test was conducted with embryos that were too far developed, and therefore the embryos were possibly not exposed to the test substance. Due to animal welfare reasons and since algae reacted with much higher sensitivity than fish, CHMP decided not to ask for a new study on fish.

Summary of main study results for eravacyline

Substance (INN/Invented Name): Eravacycline					
CAS-Number (if available): 1207283-85-9 (free base)					
PBT screening	**Method**	**Result**			**Conclusion**
Bioaccumulation potential log D_{Ow}	OECD 107	log D_{OW} = -2.033 (pH 5) log D_{OW} = -0.288 (pH 7) log D_{OW} = -1.035 (pH 9)			Potential PBT (N)
PBT-statement :	Eravacycline is not considered as PBT based on OECD 107 method				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{SURFACE\ WATER}$, default	0.70	µg/L			>0.01 threshold (Y)
$PEC_{SURFACE\ WATER}$, refined	0.027	µg/L			>0.01 threshold (Y) The refined PECSW value is not considered acceptable.
Other concerns (e.g. chemical class)	None				
Phase II Physical-chemical properties and fate					
Study type	**Protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Study initiated; draft results; report due July 2018			K_F and K_d <3,700 L/kg K_{OC} and K_{FOC} <10,000 L/kg No Phase II Tier B terrestrial studies triggered
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Study initiated; report due July 2018			OECD 218 sediment-water chironomid toxicity may be triggered
Phase II Effect studies					
Study type	**Protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test	OECD 201	NOEC	0.0063	mg/L	*Pseudokirchneriella subcapitata*
Algae, Growth Inhibition Test	OECD 201	NOEC	0.000413	mg/L	*Anabaena flos-aquae*; used to calculate $PNEC_{SUEFACE\ WATER}$
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.0833	mg/L	*Daphnia magna*; used to calculate $PNEC_{GROUND\ WATER}$
Fish, Early Life Stage Toxicity Test	OECD 210	NOEC	0.242	mg/L	*Pimephales promelas*

Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	0.5	mg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{10}	0.479	mg/L	Used to calculate $PNEC_{MICRO-ORGANISM}$
$PNEC_{SURFACE\ WATER}$ $PEC/PNEC_{SURFACE\ WATER,\ default}$ $PEC/PNEC_{SURFACE\ WATER,\ refined}$	0.0413 16.9 0.65			µg/L	Ratio > 1, therefore further information in SmPC 5.3/6.6 is necessary. The refined PEC value is not considered acceptable.
$PEC_{GROUND\ WATER}$ $PNEC_{GROUND\ WATER}$ $PEC/PNEC_{GROUND\ WATER}$	0.007 8.33 0.0008			µg/L	Ratio <1, therefore no further assessment is necessary
$PNEC_{MICRO-ORGANISM}$ $PEC/PNEC_{MICRO-ORGANISM}$	47.9 0.00056			µg/L	Ratio <0.1, therefore no further assessment is necessary

Conclusion

The ERA is not finalised and will be re-assessed upon submission of the above mentioned ongoing studies (OECD 106 and OECD 308). These two study reports should be finalised by the end of Q3 2018. Pending the outcome of the study of aerobic / anaerobic transformation in aquatic sediment systems (OECD 308), a further sediment-water chironomid toxicity study (OECD 218) may be needed. A final ERA report, including the report for the potential OECD 218 study (if triggered) should be submitted by the end of Q3 2019. Adequate wording pertaining to the measures for disposal of the medicinal product to protect the environment was included in sections 5.3 and 6.6 of the Xerava SmPC document and correspondingly in the Patient Leaflet.

Table 1. Summary of main study results

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …		Potential PBT (Y/N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT		

Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)		µg/L			> 0.01 threshold (Y/N)
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	K_{oc} =			List all values
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**valu e**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC		µg/L	species
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/ kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/ kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/ kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/ kg	
Sediment dwelling organism		NOEC		mg/ kg	species

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the above mentioned outstanding ERA measures to be addressed.

2.3.6. Discussion on non-clinical aspects

Pharmacology

Eravacycline belongs to the tetracycline class of antibiotics and has an *in vitro* activity against several bacterial organisms. Eravacycline differs from other tetracyclines based on modifications at C-7 (fluorine atom) and C-9 (pyrrolidinoacetamido group) on the phenyl ring. These modifications confer increased activity and stability against tetracycline-specific efflux and resistance due to ribosomal protection proteins (RPP). The *in vitro* primary pharmacodynamics studies are presented and assessed in more detail in the clinical section of the assessment report.

Safety pharmacology

The potential of eravacycline to alter cardiovascular, respiratory system and CNS was examined as part of the safety pharmacology dossier provided by the applicant. The administration of eravacycline 15 and 30 mg/kg caused increases in heart rate and blood pressure associated with quantitative changes in ECG intervals, namely shortenings of the PR and QT intervals in dog. The symptoms were suggested to be associated with acute histamine-release, which in turn have been suggested to be more pronounced in rats and dogs than in humans. Consequently, it was not possible to conclude from this study whether eravacycline can cause a QT prolongation. A dose-dependent increase in respiratory rate was observed during the dosing and 30-60 min after the infusion. Clinical observations of laboured breathing, swelling, and skin erythema and changes in CNS activity and excitability (including reduction in rearing counts and activity/arousal and instances of muscle fasciculation) and effects on the ANS, sensorimotor system, neuromuscular system (including ataxia and gait pattern abnormalities), and decreased body temperature were noticed.

In the safety pharmacology and toxicology studies, indications on an altered thermoregulation were observed. In the off-target pharmacology study inhibitory effects of eravacycline on acetylcholinesterase were observed. Regulation of body temperature has been shown to be affected by inhibition of acetylcholine esterase. Thus, it is not possible to conclude that the observed fluctuations in body temperature are indirectly due to histamine effects, as claimed by the applicant. However, in the clinical safety data base there are no indications on thermoregulatory effects of eravacycline at clinically relevant doses. Consequently, while a thermoregulative effect of eravacycline cannot be ruled out, the clinical relevance is however considered limited by CHMP.

Pharmacokinetics

Following intravenous injection, exposure (C_{max} and AUC) to eravacycline increased with increasing doses. This increase was generally greater than proportional to the increase in dose, and systemic clearance and volume of distribution decreased with increasing doses in rats, dogs, and cynomolgus monkeys.

Eravacycline has an atypical form of protein binding in the plasma of all tested species, where the free fraction of eravacycline has been shown *in vitro* to decrease with increasing concentration of the active substance. In addition, the free fraction of eravacycline vary significantly between species *in vitro*, ranging from 49% in mice to 5.3% in cynomolgus monkeys when using a concentration of 0.1 µg/ml. The applicant was asked by CHMP to discuss the mechanisms for the variable protein binding of eravacycline when using different pools of human plasma. The atypical nonlinear protein binding behaviour of several of the tetracyclines, including eravacycline and doxycycline, may be related to a complex interaction between the agent, metal ions and plasma proteins, but is currently not understood. Due to this lack of knowledge the applicant cannot point to a particular reason for the high variability in protein binding between the different lots of pooled human plasma, and a clear

mechanism could not be presented. However, since this is a class effect that is manageable in the clinic, the response was considered sufficient by CHMP.

The distribution of radiolabelled eravacycline was rapid, widespread and concentrated in the trachea, adrenal gland, liver, and aorta. Radioactivity was generally BLQ 21 days post-dose, with the exception of the uveal tract, bone (including teeth and tracheal hyaline cartilage), thyroid, aorta, bone marrow and pigmented fur. Distribution to melanin-containing structures had high exposure to radiolabelled material and a slow elimination. Given the lack of ocular adverse effects in the non-clinical toxicology studies or in the clinic, the binding of eravacycline to melanin does not appear to be associated with any obvious risk for ocular toxicity in patients. Eravacycline passed the placental barrier in rats and rabbits. Foetal plasma concentrations were in the same range of maternal drug plasma concentrations.

Unchanged eravacycline is the major drug-related component in rat, dog and human plasma and urine after a single IV dose. Qualitatively similar metabolites are found in the plasma of humans, rats and dogs. The metabolic turnover of eravacycline is, however, very slow, with negligible loss. The metabolites of eravacycline were identified in plasma from rat, dog, cynomolgus monkey, and human. The exposure to metabolites (especially TP-6208 and TP-034) was low in animals compared to humans. In order to reach adequate plasma concentrations in the toxicology studies, the human metabolites TP-6208 and TP-034, were dosed to animals in some of the toxicology studies in order to qualify them adequately.

Eravacycline has faecal and/or biliary elimination and a somewhat smaller fraction is eliminated into urine.

Toxicology

The following target organs of toxicity have been identified: cardiovascular (increase in heart rate and blood pressure, and cardiac atrial haemorrhage and necrosis), lymphoid and bone marrow systems, the male reproductive system (including a decrease in fertility), bone, administration site and GI systems. In general the applicant claims that many of these effects (GI, haematopoietic, reproductive, immunological and cardiovascular systems) are due to histamine release (which was not measured in any of the i.v. studies performed by the applicant) in rat and dog, which is a known class effect of tetracyclines and that this toxicity is not relevant to humans. To substantiate this claim, the applicant mainly refers to the approved medicine tigecycline, which it claims has a very similar toxicity profile. In general, tetracycline class effects are expected also for eravacycline and even though no mechanistic explanation as to why histamine-release seems to be induced only in non-human species, any safety concerns in regard to histamine-release were considered by CHMP to be irrelevant to humans.

Male fertility was decreased in rat after administration of eravacycline. Eravacycline did also induce maternal and foetal toxicity in rat. In mothers eravacycline administration gave reduced body weights and food consumption. In the foetal offspring eravacycline exposure resulted in reduced body weight and a delay in skeletal ossification. Also in rabbit similar maternal and foetal toxicity was observed.

In general, no new toxicity was detected in the juvenile toxicity in comparison to the data generated in adult animals. However, since no NOAEL could be established in juvenile rat it could be speculated that juvenile animals are more prone for eravacycline induced toxicity, but a definite comparison is hard to perform on the available data.

The ERA is not finalised and will be re-assessed upon submission of the ongoing studies OECD 106 and OECD 308.

2.3.7. Conclusion on the non-clinical aspects

CHMP agreed that there are no major objections to the approval of Xerava from a non-clinical point of view. CHMP noted that the ERA is not yet finalised. The additional data/studies and an updated ERA should be submitted as one post authorization commitment not later than the end of the third quarter of 2019. Adequate wording pertaining to the measures for disposal of the medicinal product to protect the environment was included in sections 5.3 and 6.6 of the Xerava SmPC and correspondingly in the PL.

The CHMP considers the following measures necessary to address the non-clinical issues:

The additional ERA data/studies and an updated ERA should be submitted as one post authorization commitment not later than the end of the third quarter of 2019.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The applicant claimed that clinical trials were performed in accordance with GCP.

A GCP inspection at two clinical investigator sites located in Latvia and Ukraine and the Sponsor Tetraphase Pharmaceuticals Inc in USA were conducted during December 2017-January 2019 in connection with the conduct of pivotal trial with protocol number TP-434-008. The outcome of the inspection carried out was issued on 12 March 2018.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Report or Study Number	**Report or Study Title**
Single and Multiple Intravenous Dose Pharmacokinetic Studies in Healthy Subjects	
Study TP-434-P1-SAD-1	Randomised, Placebo-Controlled, Double-Blind Study to Evaluate the Safety and PK of Single Ascending Doses
Study TP-434-P1-MAD-1	Randomised, Placebo-Controlled, Double-Blind Study to Evaluate the Safety and PK of Multiple Ascending Doses
Mass Balance, Distribution, and *In vivo* Metabolism Studies	
Study TP-434-012	An Open-Label, Single Dose Study Designed to Assess the Mass Balance Recovery, Metabolite Profile and Identification of Metabolite Structure for [^{14}C]-Eravacycline in Healthy Male Subjects after Oral and IV Dosing
Study TP-434-006	A Phase 1, Open-Label, Safety and PK Study to Assess Bronchopulmonary Disposition of Intravenous eravacycline in Healthy Men and Women.
***In vivo* Drug-Drug Interaction Studies**	
Study TP-434-016	A Phase 1 Open-Label Clinical Study to Assess the Impact of Itraconazole on Eravacycline PK in Healthy Subjects
Study TP-434-020	A Phase 1, Open-Label Clinical Study to Assess the Impact of Rifampin on Eravacycline PK in Healthy Subjects
Special Population and Safety Studies	
Study TP-434-013	A Phase I, Open-Label Study to Assess the Single-Dose Pharmacokinetics of Eravacycline in Subjects with Impaired Hepatic Function and Healthy Subjects
Study TP-434-014	A Phase I, Open-Label Study to Assess the Single-Dose Pharmacokinetics of Eravacycline in Subjects with End Stage Renal Disease and Healthy Subjects

Report or Study Number	Report or Study Title
Study TP-434-004	A randomised, placebo and positive-controlled, three way, crossover study to evaluate the effects of intravenous infusion of eravacycline on cardiac repolarisation in healthy male and female subjects: A thorough QT/QTc study
Phase 2/Phase 3 Efficacy and Safety Studies	
Study TP-434-P2-cIAI-1	Phase 2 Study to Assess the Efficacy, Safety, and Pharmacokinetics of 2 Dose Regiments of TP-434 Compared to Ertapenem in Adults with Community-Acquired Complicated Intraabdominal Infections
Study TP-434-008	A Phase 3, Randomised Double-blind, Double-dummy, Multicenter Prospective Study to Assess the Efficacy and Safety of Eravacycline Compared with Ertapenem in Complicated Intra-abdominal Infections
Study TP-434-025	A Phase 3, Randomised Double-blind, Double-dummy, Multicenter Prospective Study to Assess the Efficacy and Safety of Eravacycline Compared with Meropenem in Complicated Intra-abdominal Infections

2.4.2. Pharmacokinetics

Eravacycline is a new chemical entity and therefore a full pharmacokinetic documentation was required and was submitted by the applicant for CHMP assessment. The clinical pharmacology has been investigated in both healthy volunteers and in patients.

The clinical pharmacology package consists of 9 clinical studies, as per the previous table. In addition, approximately 20 *in vitro* studies using human biomaterial were submitted. PK and PK/PD was investigated in phase II/III studies and were reported separately.

- **Analytical methods**

The bioanalytical methods for the measurement of eravacycline and metabolites (TP-6208, TP-498 and TP-034) concentrations in human plasma and urine were based on deuterium labelled internal standards and LC/MS/MS. The sample preparation was protein precipitation or solid phase extraction. All methods were validated.

- **Pharmacokinetic data analysis**

Standard statistical methods and non-compartmental methods were used to characterise the pharmacokinetics. Population PK analysis was characterised by non-linear mixed effects modelling.

Absorption

Not applicable, as Xerava is administered intravenously as a 60 min infusion.

Distribution

Eravacycline is moderately bound to plasma proteins and is concentration-dependent based on *in vitro* data. Using equilibrium dialysis the unbound fraction were 32%, 27%, 25%, 23% and 13% at 0.1, 0.5, 1, 5, and 10 µg/mL, respectively. The mean whole blood-to-plasma concentration ratio was approximately 1. In the population PK analysis in patients for a typical subject Vc and Vss were 39 L and 226 L, respectively.

Elimination

For eravacycline, from the population PK analysis the CL for a typical patient was 15 L/hr, and elimination half-life was calculated to be 15 h. In healthy subjects, calculated using non-compartmental analysis, the CL was similar to that in patients. The plasma concentration after end of infusion declined in a multiphasic manner (see Figure PK2) and the terminal half-life at steady state was approximately 30 h. The difference in terminal half-lives between patients and healthy subjects is likely due to different sampling schemes and is generally less precise in patients due to sparse plasma sampling scheme.

- **Excretion**

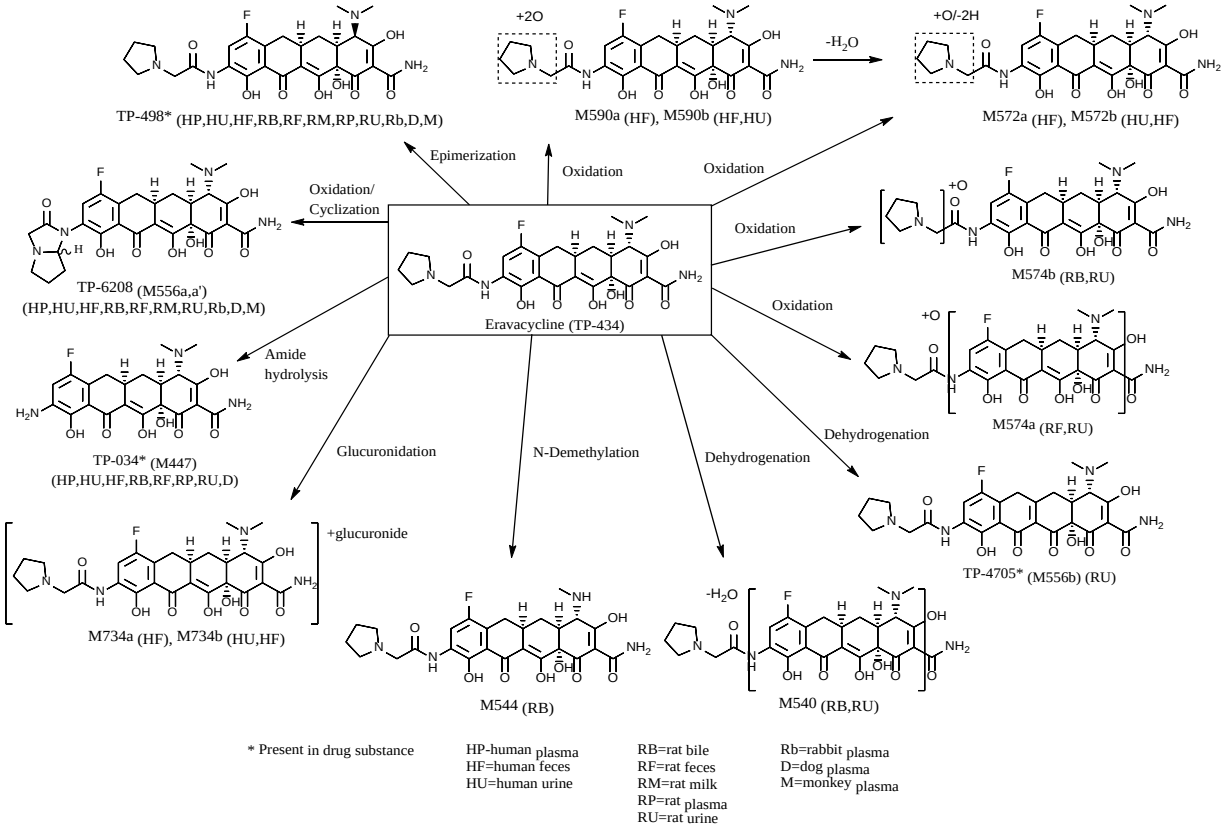
In the human mass balance study following a single IV dose of [^{14}C]Eravacycline of 60 mg, the mean cumulative urinary and faecal recovery was 83%. The mean recovery of radioactivity in faeces and urine was 48 % and 35%, respectively. Parent compound was the major compound found in faeces and urine, accounting for on average 40% (~20% in each excreta) of the administered dose. Based on the human mass balance study the major elimination pathway was excretion of parent compound via kidney, bile and most likely also via direct intestinal secretion.

- **Metabolism**

Eravacycline was relatively stable when incubated in human hepatocytes. In the human ADME study most (60-70%) of the total circulating radioactivity (AUC_{0-24}) in pooled plasma samples was attributed to [^{14}C]eravacycline. Three metabolites were identified in plasma (for structures see following figure); TP-6208 accounted for ~18% of total radioactivity (AUC_{0-24}) in plasma. Both *in vitro* and *in vivo* DDI data support that CYP3A4 is responsible for the formation of TP-6208. Other circulating metabolites in plasma TP-498 and TP-034 were minor (<10% each).

Several metabolites were identified in urine and in faeces; the main metabolites were TP-6208 (initial N-oxidation in the pyrrolidine ring followed by a cyclisation to form a bicyclic ring system) and TP-498 (epimer at carbon-4). TP-6208/TP-498 co-eluted and accounted for ~13% of dose. Oxidation in the pyrrolidine ring formed additional metabolites (M572a/b, M590a/b, ~12% of dose in excreta). Minor metabolites were conjugation with glucuronic acid (M734a/b, ~2% of dose) and formation of TP-034 (~3% of dose, for structures see following figure).

Figure PK1. Eravacycline scheme of metabolic pathways in humans and animals

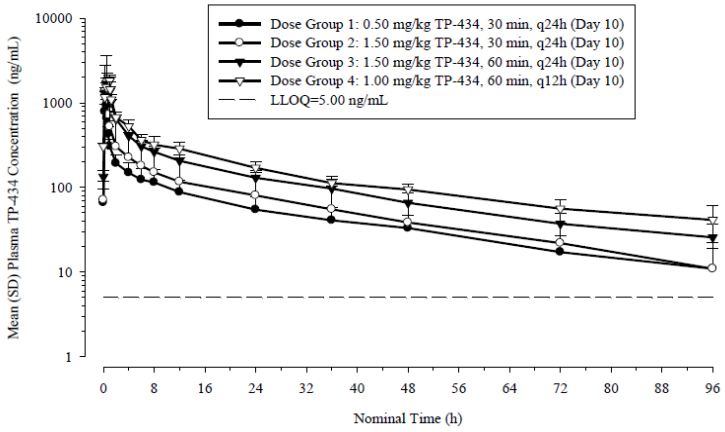


Dose proportionality and time dependencies

Dose proportionality was studied in healthy subjects. At steady state the exposure in terms of AUC_{0-24} and C_{max} increased approximately in a dose proportional manner over the 0.5 to 1.5 mg/kg range.

Steady state was generally reached at day 5 and the accumulation ratio (AUC_{Tau} day 10 /AUC_{inf} day1) was 1.6 (1.0 mg/kg every 12 hours). The following figure shows the mean plasma profiles of eravacycline.

Figure PK2. Mean plasma eravacycline concentrations at Day 10 in healthy subjects after different dosing regimens



- **Population PK analysis**

The population PK model includes a wide range of PK data from 15 clinical studies, including seven Phase 1 studies in healthy volunteers, one study in subjects with hepatic impairment, one study in subjects with ESRD, two DDI studies, one Phase 2 study and two Phase 3 studies in patients with cIAI, and one phase 3 study in patients with cUTI. The population PK model is considered adequate by CHMP to describe data and simulation of AUC.

- **Pharmacokinetic in target population**

The model derived PK parameters for phase 3 is shown in the following table:

Table PK1 Summary of steady state PK parameters in patients with cIAI in pahse 3 studies based on body weight

	Adults non-obese (n=292)	Adults obese (n=58)	Elderly non-obese (n=137)	Elderly obese (n=15)	Overall (n=502)
Cmin (ng/mL)					
Mean (SD)	318 (169)	389 (140)	423 (158)	478 (196)	360 (171)
Median [Min, Max]	286 [25.7, 1150]	374 [123, 781]	398 [95.0, 1010]	547 [133, 842]	329 [25.7, 1150]
Cmax (ng/mL)					
Mean (SD)	1450 (732)	1670 (490)	1620 (466)	1730 (687)	1530 (648)
Median [Min, Max]	1300 [650, 9900]	1530 [1020, 3360]	1540 [799, 3200]	1630 [862, 3100]	1400 [650, 9900]
AUC_{0-12} (ng.h/mL)					
Mean (SD)	6150 (2770)	7300 (2130)	7610 (2350)	8500 (3110)	6750 (2700)
Median [Min, Max]	5670 [1460, 23600]	6960 [3220, 13600]	7150 [2740, 15400]	9310 [2990, 14700]	6310 [1460, 23600]

AUC_{0-12}= area under the concentration-time curve from 0 to 12 hours; C_{max}= maximum concentration; C_{min}= mininum concentration; Max= maximum; Min=minimum; n= number of subjects; SD= standard error
Note: Obese are defined as weight greater or equal at 100 kg; Elderly patients are those of 65 years old and greater

Special populations

- **Hepatic impairment**

Single dose (1.5 mg/kg during 60 min infusion) PK of eravacycline was investigated in subjects with mild, moderate and severe hepatic impairment (HI) compared to subjects with normal hepatic function. For the total plasma concentration, the systemic exposure (AUC) of eravacycline was slightly increased in subjects with mild or moderate hepatic impairment (point estimate 123% and 138%, respectively and 90% CI (84, 180) and (96, 198)) compared to healthy subjects. In severe hepatically impaired subjects the increase was ca. 2-fold (PE 210 90% CI (149-297). C_{max} was in general unaffected in all degrees of hepatic impairment. The half-life was prolonged in subjects with HI (21-26 h) compared to healthy subjects (16 h).

- **Renal impairment**

The pharmacokinetics of eravacycline was studied after a single dose (1.5 mg/kg during 60 min infusion) in subjects with end stage renal disease (ESRD) compared to subjects with normal renal function. For subjects with ESRD eravacycline was given on a day when the subject did not receive dialysis. The exposure (AUC and C_{max}) of eravacycline was approximately similar in the subjects with ESRD as compared to subjects with normal renal function.

Age, sex, race

Sex was included as a covariate in the updated population PK model, but age, sex and race are not expected to have a clinically relevant effect on eravacycline PK.

- **Body weight**

Body weight based allometric scaling on clearance and volume was included in the updated population PK model. Eravacycline dosing regimen is body weight based and this has been shown to be adequate. No patients above 137 kg have been studied.

Pharmacokinetic interaction studies

Effects of other medical products on the pharmacokinetics of eravacycline

In vitro data indicate that eravacycline is a substrate of CYP3A4 and this was confirmed *in vivo* as the major metabolic pathway forming TP-6208. No other CYP enzyme was indicated to be involved in the metabolism. Other enzymes were investigated *in vitro* and flavin monooxygenases (FMO-1, -3, -5) was shown to form TP-6208, while aldehyde oxidase (AO) and monoamine oxidases (MAO-A, MAO-B) were not involved in the metabolism of eravacycline.

An *in vivo* study with itraconazole (strong CYP3A4 and P-gp inhibitor) showed an increase of eravacycline exposure in terms of AUC_{0-inf} when co-administrated with itraconazole (point estimate 1.45) while C_{max} was unchanged. The epimer TP-498 behaved in a similar manner as parent compound, while TP-6208 and TP-034 decreased considerably, a decrease by 60-70% for both AUC_{0-t} and C_{max} was observed. When co-administrating with a strong inducer (rifampicin) the exposure in terms of AUC decreased by ca. 30% while C_{max} was unchanged. The epimer TP-498 behaved in a similar manner as parent compound, while TP-6208 and TP-034 increased considerably; C_{max} approx. 2-fold and AUC_{0-t} ca 1.4-1.5-fold for both metabolites.

In vitro, eravacycline was shown to be a P-gp, OATP1B1 and OATP1B3, but not a BCRP substrate.

Effect of eravacycline on the PK of other medical products

The potential of eravacycline and its metabolites TP-6208, TP-498 and TP-034 to inhibit CYP enzymes have been investigated *in vitro* in a clinically relevant concentration range. No signal of direct or time

dependent CYP inhibition (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4) was observed. The potential of eravacycline and its metabolite TP-6208 to induce CYP enzymes was investigated *in vitro* and no signal of CYP induction was detected.

In vitro, eravacycline and its metabolites TP-6208, TP-498 and TP-034 did not inhibit P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1 or MATE2-K transporters.

The risk of clinically relevant DDIs caused by eravacycline or its metabolites TP-6208, TP-498 and TP-034 is considered to be low.

2.4.3. Pharmacodynamics

Mechanism of action

Eravacycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit, thus preventing the incorporation of amino acid residues into elongating peptide chains.

Primary and Secondary pharmacology

In vitro activity

The following table summarises the *in vitro* activity of eravacycline against selected species from preclinical studies.

Table PD1. Eravacycline spectrum of activity from preclinical studies

Organism	N	Range	MIC_{50}	MIC_{90}
S. aureus (MSSA)	124	0.03 – 0.25	0.06 – 0.25	0.12 – 0.25
S. aureus (MRSA)	219	<0.015 - 1	0.03 – 0.12	0.03 – 0.12
S. epidermidis (MSSE)	52	0.06 - 1	0.12	0.5
S. epidermidis (MRSE)	54	0.06 - 1	0.06	0.5
CoNS (methicillin-S)	35	<0.015 - 1	0.06	0.25
CoNS (methicillin-R)	19	0.03 - 2	0.12	2
S. haemolyticus	149	0.03 - 1	0.12	0.5
E. faecalis (VSE)	81	0.03 – 0.12	0.06 – 0.12	0.12
E. faecalis (VRE)	66	0.03 – 0.12	0.06	0.12
E. faecium (VSE)	80	0.03 – 0.5	0.03 – 0.06	0.06 – 0.12
E. faecium (VRE)	67	0.03 – 0.25	0.06	0.06
S. pneumoniae	182	<0.008 – 0.03	<0.008 – 0.015	0.015 – 0.03
S. pyogenes	74	0.015-0.12	0.015 – 0.03	0.03
S. agalactiae	121	0.015 – 0.06	0.03 – 0.06	0.03 – 0.06
S. anginosus	20	<0.008 – 0.03	0.015	0.015

S. intermedius	30	<0.015 – 0.06	0.015	0.06
S. mitis	29	0.015 – 0.06	0.015	0.06
S. sanguis	18	<0.008 – 0.06	0.015	0.03
Viridans Group Strep.	46	<0.008 – 0.25	0.03	0.25
C. freundii	100	0.06 - 2	0.25 – 0.5	0.5 - 2
E. cloacae	305	0.03 - 4	0.5	1
E. aerogenes	167	0.125 - 2	0.25	0.25 - 1
E. coli	3056	<0.015 - 4	0.125 – 0.25	0.25 – 0.5
K. pneumoniae	1098	0.06 - 8	0.25 – 0.5	1 -2
K. oxytoca	30	0.25 - 2	0.25	1
P. mirabilis	150	0.25 - 4	1 - 2	1 - 4
P. vulgaris	54	0.25 - 2	0.5 - 1	1 - 2
P. stuartii	100	0.12 - 8	0.5 - 1	2
M. morganii	30	0.5 – 2	1	2
Salmonella spp.	30	0.12 – 0.5	0.25	0.25
Shigella spp.	30	0.06 - 1	0.12	0.5
S. marcescens	112	0.25 - 8	0.5 - 1	1 - 2
A. baumanii	303	<0.015 - 8	0.12 - 1	1 - 4
A. lwoffi	29	0.03 – 0.25	0.125	0.25
P. aeruginosa	102	1 - >64	8	16
S. maltophilia	54	0.06 - 4	0.25 – 0.5	1
H. influenzae	101	<0.015 – 0.5	0.12	0.12 - 0.25
M. catarrhalis	78	<0.15 – 0.06	0.03	0.06
N. gonorrhoeae	200	<0.015 – 0.5	0.125	0.25
L. pneumophila	70	0.016 - 2	1	2
B. fragilis	40	0.12 - 2	0.25 – 0.5	0.5 - 1
B. vulgatus	10	0.12 - 1	0.25	0.25
B. thetaiotaomicron	10	0.12 - 4	1	4
B. ovatus	10	0.015 - 8	1	4
Prevotella spp.	60	0.03 - 1	0.06 - 1	0.125 - 1
C. difficile	10	0.03 – 0.12	0.06	0.12

C. perfringens	10	0.06 - 4	1	2

Eravacycline surveillance studies have been conducted in the US, Europe, and Canada for a large number of clinical isolates. The $MIC_{50/90}$ values for eravacycline for clinically important pathogens are summarised in the following table:

Table PD2. Eravacycline activity for clinically-important isolates during 2014-2015

Organism	**N**	**MIC_{50}**	**MIC_{90}**
E. coli	2155	0.25	0.5
– $ESBL^+$	222	0.25	0.5
– CRE	96	0.25	1
K. pneumoniae	1185	0.5	1
– $ESBL^+$	335	0.5	2
– CRE	216	0.5	2
K. oxytoca	556	0.25	0.5
– $ESBL^+$	20	0.25	2
– CRE	2	NA	NA
Enterobacter cloacae	808	0.5	1
– $ESBL^+$	41	1	2
– CRE	38	1	2
C. freundii	387	0.25	0.5
– $ESBL^+$	29	0.25	0.5
– CRE	28	0.25	0.5
A. baumannii all	1152	0.5	1
– CRAB	424	0.5	1
S. aureus	1512	0.06	0.125
Enterococcus faecalis	597	0.06	0.06
Enterococcus faecium	338	0.03	0.06
B. fragilis	199	0.25	2

There was no evidence of cross-resistance with other evaluated agents, based on the lack of isolates with elevated eravacycline MICs observed during surveillance and consistent activity by MIC_{50} and MIC_{90} against isolates resistant to other classes of agents relative to susceptible isolates.

Based on MBC and time-kill studies eravacycline was bacteriostatic against the majority of evaluated pathogens.

Antimicrobial activity of metabolites

Of the primary metabolites, TP-6208 was inactive against Gram-positive and Gram-negative isolates tested (MICs > 32 mg/L). TP-498 and TP-034 were active, though the activity observed was generally less than that of eravacycline.

Resistance

Resistance to tetracyclines is usually attributed to the acquisition of mobile genetic elements carrying tetracycline-specific resistance genes, mutations within the ribosomal binding site, and/or chromosomal mutations leading to increased expression of intrinsic resistance mechanisms (e.g. multidrug efflux pumps).

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 µg/mL in *E. coli* expressing *tet*(X). 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), suggesting differences in strain background and the existence of other antibiotic resistance determinants likely impact susceptibility to eravacycline in these organisms. 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 antibiotics.

Similar to many other antibiotics of different classes, susceptibility to eravacycline is reduced by intrinsic MDR mechanisms regulated by *ramA* in *K. pneumoniae.* Eravacycline appears to be a substrate for the AdeAB pump in *A. baumannii,* several Mex pumps in *P. aeruginosa,* and is a poorer substrate for MepA in *S. aureus*. The activities of eravacycline and other tetracyclines are also impacted by target-based mutations in 16S rRNA and mutations in *rpsJ,* encoding amino acid variations in 30S ribosomal protein S10 near the tetracycline-binding site.

Laboratory selection of resistance

Eravacycline resistance development was evaluated *in vitro* using both spontaneous mutation frequency and serial passage methods with *E. coli*, *K. pneumoniae*, *C. freundii*, *A. baumannii*, *Bacteroides spp*., *Enterococcus faecalis*, *Streptococcus pyogenes*, and *S. aureus*. Laboratory-derived eravacycline mutants underwent broth microdilution susceptibility testing for a variety of antimicrobial agents and were genetically characterised to provide insight into the mechanism of resistance and potential cross-resistance.

Spontaneous mutation frequency values for eravacycline were low and comparable to tigecycline for most of the Gram-positive and Gram-negative isolates tested. Despite the relatively infrequent isolation of eravacycline mutants among Gram-positive organisms, those that were isolated provided some insight into potential cross-resistance and mechanism of resistance. There was no evidence of cross-resistance to linezolid, vancomycin, ciprofloxacin, or daptomycin for eravacycline-selected mutants. As expected, eravacycline-selected mutants had reduced susceptibility to tigecycline and *vice versa,* showing the potential for cross-resistance between these two agents. Cross-resistance for other members of the tetracycline class (doxycycline, minocycline, tetracycline) was also common in instances where the parent isolate was susceptible and cross-resistance to these agents could be evaluated.

MIC data from the eravacycline mutants of *K. pneumoniae*, *C. freundii* and *A. baumannii* showed cross-resistance to tigecycline and other members of the tetracycline class (doxycycline, minocycline, tetracycline) in instances where the parent isolate was susceptible and cross-resistance to these agents could be evaluated. Cross-resistance observed with the eravacycline-selected mutants for other agents varied. There was apparent cross-resistance to ciprofloxacin (*K. pneumoniae* and *A. baumannii*), and to gentamicin for select mutants of *A. baumannii*.

Eravacycline and multiple comparator agents were evaluated for resistance development following 15 to 20 serial transfers in sub-inhibitory concentrations of each test agent. There was no significant increase in MICs for either eravacycline or tigecycline for the Gram-positive organisms *S. aureus* (2 strains), *Enterococcus faecalis* or *Streptococcus pyogenes*. Significant increases in eravacycline MIC values were observed 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 MIC values increased during serial passage but the increase in MIC was not confirmed by broth microdilution MIC testing, indicating no true emergence of resistance for eravacycline and *B. fragilis*.

The genetic characterisation data showed that the primary mechanism of resistance among the 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.

Post-antibiotic effect

A post-antibiotic effect was noted and ranged from 1 to 4 hours for Gram-positive bacteria and 1 to 2 hours for Gram-negative bacteria, depending on the species and on the extent of exposure (2x to 10x the MIC).

Effects of human body fluids on susceptibility to eravacycline

The *in vitro* activity of eravacycline and tigecycline in the presence and absence of 5% and 10% pooled normal human serum and urine was evaluated.

With the exception of *Enterococcus faecalis* ATCC 29212, where eravacycline MICs were 4-fold higher in medium containing 5% to 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 in the absence of serum.

Eravacycline and tigecycline MICs were typically 2- to 8-fold higher in urine relative to broth for both *E. coli* and *K. pneumoniae*. The MICs of both agents were typically 2- to 4-fold higher when testing in broth or urine adjusted to the same pH and increased with decreasing pH of the test medium. Thus, both pH of test medium and testing in urine have an impact on the *in vitro* activity of eravacycline and tigecycline against *E. coli* and *K. pneumoniae*.

In vivo activity

Eravacycline evaluated in various animal infection models

Eravacycline was evaluated in several non-clinical efficacy models of serious hospital- and community-acquired infections. These experimental infections included systemic lethal infections, kidney infections, thigh infections and lung infections in mice, and a rat intra-abdominal abscess model. These studies evaluated the efficacy of eravacycline against Gram-positive or Gram-negative pathogens including *E. coli* (tetracycline-resistant and ESBL producing strains), *K. pneumoniae* (ESBL strains), *S.*

aureus (methicillin- and tetracycline-resistant strains), *Streptococcus pyogenes*, *Streptococcus pneumoniae* (tetracycline-resistant strain), and *B. fragilis*. One of the experimental infection models, the intra-abdominal abscess, was a polymicrobial infection.

The efficacy of eravacycline was compared with appropriate agents for the relevant clinical indication such as tigecycline, ertapenem or meropenem, levofloxacin, doxycycline, linezolid, and vancomycin.

Non-clinical efficacy evaluations of eravacycline required i.v. or intraperitoneal (i.p.) administration to ensure adequate exposure.

Overall, eravacycline was efficacious in the non-clinical models used, except in the rat intra-abdominal abscess model. Although eravacycline exhibited good potency *in vitro* against the *E. coli* and *B. fragilis* isolates used in the model; 10, 20 and 40 mg/kg BID regimens of eravacycline administered *in vivo* did not show a significant reduction in CFU/abscess *in vivo* when compared to the untreated controls. The applicant has been unable to explain the reason why eravacycline failed to reduce the bacterial burden. A complicating factor for the analysis was that no dosing solution or plasma PK analysis was completed as part of the study. Therefore the exposures associated with treatment in this study are unknown.

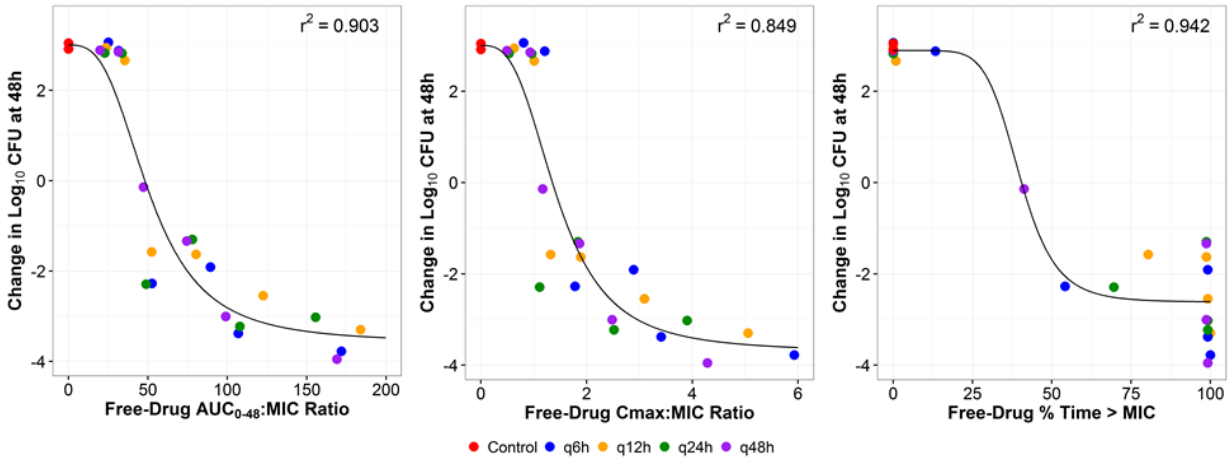
Non-clinical PK/PD of eravacycline

The pharmacokinetics/pharmacodynamics (PK/PD) of eravacycline was investigated in an *in vitro* chemostat system and in murine thigh infection models.

In vitro

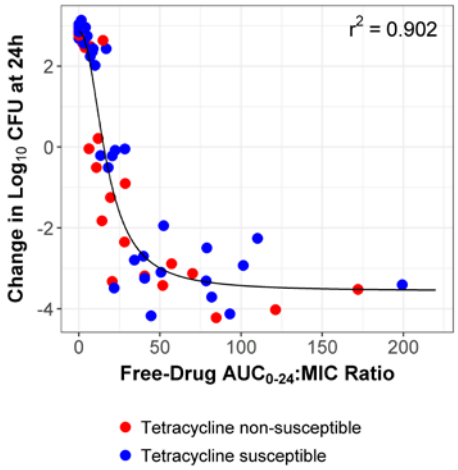
An *in vitro* dynamic chemostat system was utilised to identify the PK/PD index closest associated with efficacy of eravacycline against *E. coli* and to determine the magnitude of the PK/PD index associated with the efficacy of eravacycline using a multiple *E. coli* isolate challenge panel. Eravacycline free-drug AUC_{0-24}:MIC ratio was considered the PK/PD index most associated with the change in bacterial density of *E. coli* based on the coefficient of determination and dispersion of data across the fitted line (see following figure).

Figure PD1. The relationships between change in log_{10} CFU from baseline at 48 h and eravacycline free-drug AUC_{0-48}:MIC ratio, C_{max}:MIC ratio and the %Time > MIC for the reference strain *E. coli* ATCC 25922



Across five *E. coli* challenge isolates including the reference strain above, the magnitude of eravacycline free-drug AUC_{0-24}:MIC ratio associated with net bacterial stasis and 1- and 2-log_{10} CFU reductions from baseline was 15.3, 20.5, and 28.8, respectively (see following figure).

Figure PD2. The relationship between change in log10 CFU from baseline at 24 h and eravacycline free-drug AUC_{0-24}:MIC ratio for five *E. coli* isolates by tetracycline susceptibility



Prevention of the emergence of resistance was observed for three *E. coli* isolates examined for resistance when free-drug AUC_{0-48} ≥192 mg•h/L was achieved.

In vivo

Eight isolates of *Enterobacteriaceae spp*. exhibiting various resistance mechanisms were selected for study in an immunocompetent mouse thigh model. The mean free AUC/MIC magnitudes required for a net static response and a 1-log_{10} reduction for the eight isolates were 2.9 ± 3.1 and 5.6 ± 5.0, respectively.

Table PD3. Free plasma AUC/MIC magnitudes associated with eravacycline efficacy in the immunocompetent murine thigh infection model

Isolate	Genotype	MIC (µg/mL)	Vehicle (Mean±SD)	E_{max}	*f*AUC/MIC magnitude	
					Stasis	1-log reduction
E. coli 315	*tet(*M), ESBL	0.5	1.37±0.31	-1.61	1.47	4.05
*E. cloacae*47	ESBL, CP-R	0.5	1.04±0.82	-0.87	0.69	NR
E. coli 358	FOX-5	0.25	0.83±0.77	-1.69	0.96	2.20
K. pneumoniae 401	CTX-M-2	0.25	1.68±0.23	-0.39	8.37	NR
K. pneumoniae 404	SHV	0.25	0.76±0.62	-0.85	1.27	NR
C. freundii 26	Inducible AmpC	0.125	1.09±0.39	-1.68	0.00	3.23
E. coli 363	ESBL	0.125	2.12±0.29	-1.28	3.35	NR
E. coli C3-14	ESBL, CP-R	0.125	1.88±0.50	-1.73	6.70	12.98
				Mean±SD	**2.9±3.1**	**5.6±5.0**

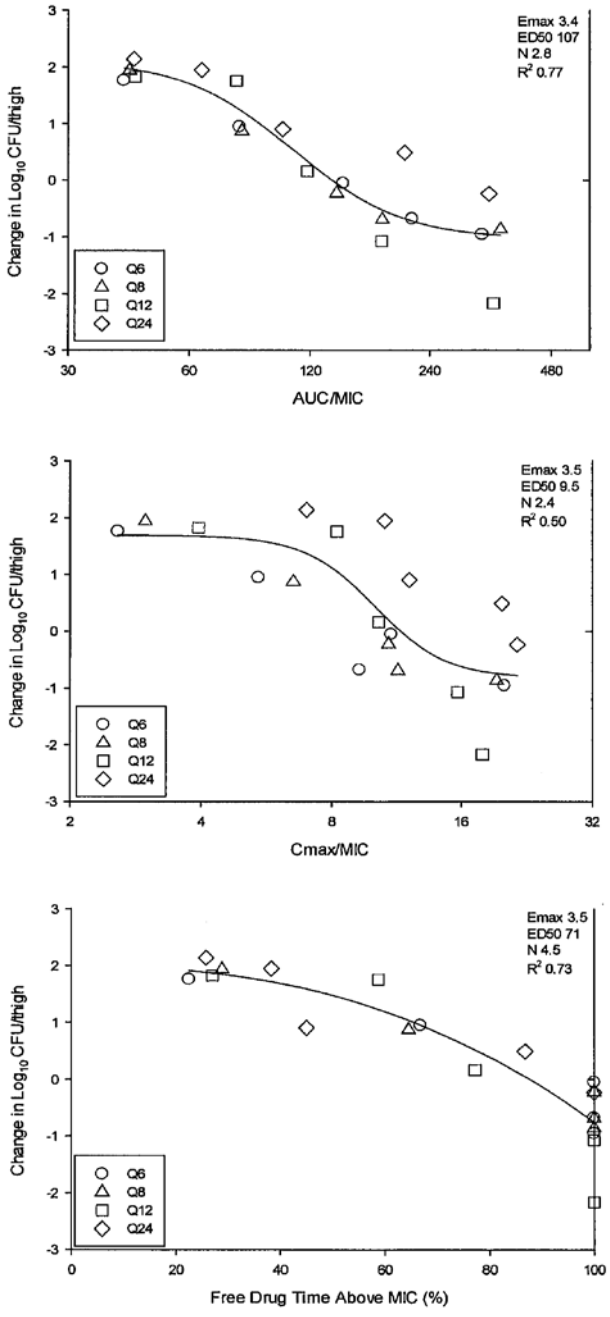
Two separate studies were performed in the neutropenic thigh model with three *E. coli* isolates to assess the *f*AUC/MIC magnitudes associated with efficacy. In the first study, the mean free AUC/MIC magnitudes required for a net static response was 16.1 ± 5.2. In the second study, the same *E.coli* isolates were repeated together with three additional isolates, and eravacycline was administered q12h i.p. starting at 2 h post-infection. The mean free AUC/MIC magnitudes required for a net static response and a 1-$\log_{10}$ reduction for the six isolates were 28.0 ± 8.3 and 32.6 ± 10.8, respectively (following table).

Table PD4. Free plasma AUC/MIC magnitudes associated with eravacycline efficacy in the neutropenic murine thigh infection model following i.p. administration

***E. coli* Isolate**	**Burden**	**Vehicle (Mean±SD)**	**E_{max}**	***f*AUC/MIC magnitude**	
				Stasis	**1-log reduction**
ATCC25922	7.31	2.15±0.14	-2.17	38.6	47.5
355	7.33	2.97±0.16	-0.78	32.2	NR
1135	7.37	2.93±0.08	-1.65	19.1	25.3
1-894-1	7.12	2.98±0.12	-1.74	30.9	37.9
14714-1	7.45	2.19±0.14	-2.13	30.0	32.6
102-94090	7.35	2.61±0.05	-1.61	17.0	19.7
			Mean±SD	**28.0±8.3**	**32.6±10.8**[a]

The correlation between efficacy and the PK/PD indices of AUC/MIC, C_{max}/MIC, and percent of a dosage interval in which the serum drug concentration remains above the MIC (%T>MIC) were determined using a sigmoidal E_{max} model. The analysis showed that AUC/MIC is the PK/PD index best associated with efficacy based upon data fit and the coefficient of determination (R^2) values (see following figure).

Figure PD3. The relationships between change in log_{10} CFU from baseline at 48 h and eravacycline free-drug AUC_{0-48}:MIC ratio, C_{max}:MIC ratio and the %Time > MIC for the reference strain *E. coli* ATCC 25922



Susceptibility testing breakpoints

The applicant has approached the European Committee on Antimicrobial Susceptibility Testing (EUCAST) to set breakpoints.

The final susceptibility testing breakpoints established by the EUCAST are:

Pathogen	MIC Breakpoints (µg/mL)	
	Susceptible (S ≤)	Resistant (R >)
Escherichia coli	0.5	0.5
Staphylococcus aureus	0.25	0.25
Enterococcus spp.	0.125	0.125
Viridans *Streptococcus spp.*	0.125	0.125

It is noted that these data should be considered in relation to the clinical efficacy data. CHMP considered that clinical efficacy has been established for Xerava in cIAI for *E. coli*, viridans *Streptococcus spp.*, *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus aureus* and *Klebsiella pneumoniae*.

Antimicrobial interactions

The antimicrobial interaction of eravacycline with other agents for aerobic Gram-positive and Gram-negative bacteria and for *B. fragilis* was found to be indifferent for nearly all antibiotic combinations and bacteria evaluated in checkerboard titration studies.

Support for dose selection

The proposed eravacycline dose regimen for cIAI is 1.0 mg/kg q12h for 4 to 14 days. Following phase 1 studies with i.v. eravacycline, two dose regimens were selected for evaluation in phase 2 (1.5 mg/kg q24h and 1.0 mg/kg q12h). These doses were selected because they had shown acceptable tolerability as compared to higher doses, at which nausea and vomiting were the main limiting effects.

The selection of the dose regimen for the Phase 3 studies was based on the strength of the clinical response observed in the Phase 2 study in cIAI, on the comparable outcomes obtained with both the 1.0 mg/kg q12h and the 1.5 mg/kg q24h regimens, and on PK/PD analyses of data from the Phase 2 study to determine the likelihood of clinical success and target attainment. The average predicted percentage probability of clinical success was 98.0% across the MIC distribution for all *E. coli* isolates for the 1.0 mg/kg q12h regimen, and 97.3% for the 1.5 mg/kg q24h regimen. Although neither the clinical and microbiological outcomes, nor the safety and tolerability profiles seen in the Phase 2 study clearly differentiated between the two dose regimens of eravacycline used, because clinical cure rates with the 1.0 mg/kg q12h regimen were numerically higher, this dose was selected for the Phase 3 study. Consideration was given to the convenience of the 1.5 mg/kg q24h regimen; however, since it was expected that most cIAI patients would remain in hospital over the therapeutic course, this was not a critical deciding factor. There was also a lower incidence of adverse events (AEs) at the 1.0 mg/kg q12h dose of eravacycline.

The phase 3 studies validated the selection of this dose regimen: eravacycline 1.0 mg/kg q12h was found to produce high clinical cure rates and was shown to be non-inferior to the comparators ertapenem and meropenem for the co-primary endpoints of clinical response in the modified Intent to Treat (MITT) and clinically evaluable (CE) populations.

The microbiological responses for each patient treated with eravacycline in the Phase 3 studies for cIAI were pooled and assessed by pathogen and then by the eravacycline MIC (see following table). With all of the pathogens, there was no trend towards a decrease in a favourable response with increasing eravacycline MIC. For *A. baumannii* and all Enterobacteriaceae with the exception of *E. coli* and K.

pneumoniae, the clinical cut-offs for eravacycline were at the breakpoint initially suggested by the applicant of 1 µg/mL. For *S. aureus*, all streptococci and both species of Enterococcus spp., the clinical cut-offs were ≤ 0.5 µg/mL. The clinical cut-offs for anaerobes included isolates with MIC values up to 4 µg/mL.

Table PD5. Microbiological favourable response at TOC by baseline eravacycline MIC (µg/mL) to key gram-negative aerobic, gram-positive aerobic and anaerobic baseline pathogens for all patients randomised to eravacycline treatment arms in the Phase 3 cIAI studies (Shaded boxes represent isolates that would be categorised as non-susceptible with proposed breakpoint)

MIC (µg/mL)	Number of eradications/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)	
0.12	3/5 (60.0)	1/1 (100)	89/104 (85.6)	6/7 (85.7)	5/5 (100)	1/1 (100)
0.25	11/11 (100)	6/6 (100)	70/76 (92.1)	7/7 (100)	17/17 (100)	6/6 (100)
0.5	4/5 (80.0)	10/13 (76.9)	22/26 (84.6)		8/8 (100)	4/4 (100)
1	1/1 (100)	1/1 (100)	2/2 (100)	1/1 (100)	6/7 (85.7)	2/2 (100)
2			1/1 (100)		1/1 (100)	

MIC (µg/mL)	Number of eradications/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)	
0.12	3/5 (60.0)	1/1 (100)	89/104 (85.6)	6/7 (85.7)	5/5 (100)	1/1 (100)
0.25	11/11 (100)	6/6 (100)	70/76 (92.1)	7/7 (100)	17/17 (100)	6/6 (100)
0.5	4/5 (80.0)	10/13 (76.9)	22/26 (84.6)		8/8 (100)	4/4 (100)
1	1/1 (100)	1/1 (100)	2/2 (100)	1/1 (100)	6/7 (85.7)	2/2 (100)
2			1/1 (100)		1/1 (100)	

MIC (µg/mL)	Number of eradications/number of pathogens at that MIC (% eradication)					
	S. aureus	*E. faecalis*	*E. faecium*	*S. anginosus* group	*S. mitis* group	*S. salivarius* group
≤0.002				5/5 (100)		
0.004				3/3 (100)		
0.008				10/12 (83.3)	3/3 (100)	1/1 (100)
0.015		3/3 (100)	1/2 (50.0)	16/18 (88.9)	13/13 (100)	6/6 (100)
0.03	4/4 (100)	24/27 (88.9)	22/24 (91.7)	30/35 (85.7)	4/5 (80.0)	3/3 (100)
0.06	17/17 (100)	17/22 (77.3)	12/15 (80.0)	13/14 (92.9)	5/5 (100)	
0.12	2/2 (100)	2/2 (100)	3/3 (100)	1/1 (100)	4/4 (100)	
0.25	1/1 (100)				1/1 (100)	
0.5			1/1 (100)			

MIC (µg/mL)	Number of eradications/number of pathogens at that MIC (% eradication)						
	B. caccae	*B. fragilis*	*B. ovatus*	*B. thetaiotaomicron*	*B. vulgatus*	*C. perfringens*	*P. distasonis*
0.015	1/1 (100)		1/1 (100)			3/3 (100)	
0.03		1/1 (100)	1/3 (33.3)	1/1 (100)	6/6 (100)	2/2 (100)	
0.06	1/1 (100)	7/7 (100)	3/4 (75.0)	6/6 (100)	6/6 (100)	3/4 (75.0)	
0.12	7/8 (87.5)	27/30 (90.0)	17/21 (81.0)	17/18 (94.4)	11/13 (84.6)		3/4 (75.0)
0.25	4/6 (66.7)	29/33 (87.9)	6/8 (75.0)	22/24 (91.7)	12/12 (100)	1/1 (100)	3/3 (100)
0.5		5/5 (100)	4/4 (100)	2/2 (100)	1/1 (100)	3/4 (75.0)	11/12 (91.7)
1		2/4 (50.0)	1/1 (100)	2/2 (100)		2/2 (100)	4/4 (100)
2		1/1 (100)		1/1 (100)	1/1 (100)		1/1 (100)
4				1/1 (100)			

Probability of target attainment based on non-clinical PK/PD targets

A population PK model and non-clinical PK/PD targets for efficacy, *in vitro* surveillance data, and Monte Carlo simulations were used to evaluate PK/PD target attainment to provide support for the eravacycline dosing regimen for patients with cIAI and for the interpretive criteria for *in vitro* susceptibility testing of eravacycline against Enterobacteriaceae. Results of these analyses, based on the neutropenic murine thigh-infection model and two approaches for assessing protein binding have shown the following:

- Using free-drug AUC/MIC ratio targets associated with net bacterial stasis and a one-log reduction based on the neutropenic murine thigh-infection model and adjustments for protein binding using microdialysis/ultrafiltration, percentage probabilities of PK/PD target attainment were ≥90% at MICs of 0.015. At the MIC_{90} values of 0.5 and 1 µg/mL for Enterobacteriaceae, percentage probabilities of PK/PD target attainment equalled 0%.
- Using free-drug AUC/MIC ratio targets associated with net bacterial stasis and a one-log reduction based on the neutropenic murine thigh-infection model and adjustments for protein binding using serum activity assessments, percentage probabilities of PK/PD target attainment were ≥90% at MICs of 0.12. At the MIC_{90} values of 0.5 µg/mL percentage probabilities were ~6 and ~3% for net bacterial stasis and a one-log reduction; these percentages fell to 0% at 1 µg/mL.

Percent probabilities of PK/PD target attainment by MIC value on Day 1 based free-drug AUC/MIC ratio targets associated with net bacterial stasis and 1-log10 CFU reductions from baseline for Enterobacteriaceae for simulated patients after the administration of eravacycline 1.0 mg/kg q12h are shown in the following figure and table.

Figure PD4. Percentage probabilities of PK/PD target attainment by MIC for eravacycline 1.0 mg/kg q12h among simulated patients based on protein binding assessed using serum activity evaluations (A) and microdialysis/ultrafiltration (B), overlaid over the MIC distribution for Enterobacteriaceae

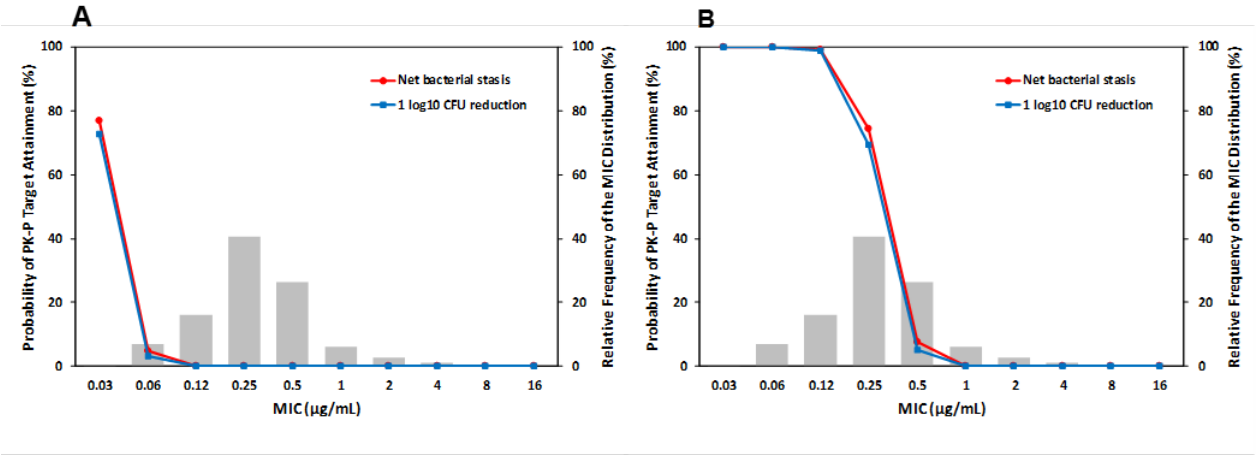


Table PD6. Percentage probability of PK/PD target attainment by MIC based on free-drug AUC/MIC ratio targets for Enterobacteriaceae based on the neutropenic murine infection model and two protein binding methods for simulated patients after administration of eravacycline 1.0 mg/kg q12h

Eravacycline MIC (µg/mL)	Percentage probability of PK/PD target attainment by MIC and protein binding method			
	Microdialysis/Ultrafiltration[b]		Serum activity[c]	
	Net bacterial stasis	1-log_{10} CFU reduction	Net bacterial stasis	1-log_{10} CFU reduction
0.004	100	100	100	100
0.008	100	100	100	100
0.015	99.5	99.2	100	100
0.03	74.8	68.1	100	100
0.06	3.88	1.91	100	99.9
0.12	0	0	99.1	98.5
0.25	0	0	71.7	63.7
0.50	0	0	5.92	3.31
1	0	0	0	0
2	0	0	0	0
4	0	0	0	0
Overall[a]	0.70	0.39	71.7	68.0

The efficacy predictions based on the PTA analysis using non-clinical PK/PD targets from the neutropenic murine thigh infection model are therefore not consistent with the uniformly high rates of microbiologic favourable outcomes in patients with cIAI in the clinical trials up to a breakpoint of ≤1 mg/L, which was initially suggested by the Applicant for Enterobacteriaceae, *A. baumanii* and anaerobes.

Other findings from PK/PD analyses using data from eravacycline-treated patients in the phase 2 and 3 studies

Results for univariable PK-PD analyses for efficacy endpoints failed to demonstrate evidence of relationships between free-drug AUC:MIC ratio and response. The high percentages of successful responses likely hindered the ability to detect PK-PD relationships for efficacy. Evaluation of the distribution of free-drug AUC:MIC ratio relative to non-clinical targets for efficacy did not provide support for the intended eravacycline dosing regimen, suggesting that predictions based on non-clinical PK-PD targets for efficacy may not correlate well with clinical outcomes in patients with cIAI.

PK-PD analyses for fever resolution demonstrated relationships between fever resolution and Day 1 total-drug AUC.

PK-PD analyses for nausea/vomiting demonstrated significant relationships between the probability of nausea/vomiting and total-drug $C_{max.}$

Results of repeated measures multiple linear regression analyses for amylase, lipase, and aPTT showed statistically significant increases in these laboratory measures associated with increases in $C_{min.}$

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

CHMP agreed that basic pharmacokinetic characteristics for eravacycline, such as distribution and elimination, have been sufficiently investigated.

ADME

In the human mass balance study after an IV dose of ^{14}C[eravacycline], 48% and 35% of the radioactivity was recovered in faeces and urine, respectively. In the rat mass balance IV study in both intact and bile cannulated animals, data support that eravacycline is secreted across GI mucosa and that the faecal radioactivity represents both biliary excretion and secretion into the lumen. This is also supported by the rat autoradiography study, where the highest tissue:blood ratio was found in the large and small intestinal contents after an IV dose. Based on the human mass balance study, the major elimination pathway was the excretion of parent compound via kidney, bile and most likely also via direct intestinal secretion (supported by rat data). In total ca. 40% of the dose was excreted unchanged, however none of these pathways was considered to be major (i.e. not >25%). Kidney and bile/intestinal secretion contributing to ca. 20% each and is considered to be equally important elimination pathways. Metabolites that were structurally identified, accounted for approximately 30% of the dose, with TP-6208 being the main metabolite (~10% of the radioactive dose). All other metabolites were considered minor by CHMP.

TP-6208 appears to be a major metabolite accounted in plasma (>10% of total radioactivity in plasma). Both *in vitro* and *in vivo* DDI data support that CYP3A4 is responsible for the formation of TP-6208. Other circulating metabolites in plasma TP-498 and TP-034 appeared to be minor.

In the *in vivo* DDI study, when eravacycline was co-administrated with itraconazole (strong CYP3A4 and P-gp inhibitor), the $AUC_{0\text{-}inf}$ for eravacycline increased by 45%. This suggests that ca. 30% of the elimination of eravacycline is mediated by CYP3A4. A decrease of metabolite TP-6208 exposure was observed, indicating that the formation of TP-6208 is mediated by CYP3A4. This was also supported by *in vitro* CYP identification data and together this suggests that CYP3A4 is the enzyme responsible for the main metabolic pathway to form TP-6208. *In vitro*, TP-6208 was also formed by FMO isoenzymes.

Similarly, the exposure of TP-034 decreased when eravacycline was co-administered with itraconazole. However, this is not in line with the *in vitro* data, where CYP3A4/5 was not indicated to be involved in the formation of TP-034. *In vitro*, TP-034 appeared to be formed directly from eravacycline in an enzymatic- and NADPH-dependent manner, but the enzyme has not been identified. The lack of information was considered acceptable by CHMP, as TP-034 is a minor metabolic pathway.

The epimerization to TP-498 was observed to occur instantaneously and is therefore not likely to involve enzymes. Still when eravacycline is co-administered with itraconazole there was an effect on TP-498 AUC (increased ca. 40%). This may be due to a rapid equilibrium between eravacycline and TP-498.

In summary, the main elimination pathway of eravacycline was excretion of parent compound via kidney, bile and most likely also via direct intestinal secretion. *In vitro*, eravacycline was shown to be a substrate for the transporters P-gp, OATP1B1 and OATP1B3, but not for BCRP. The kidney and bile/intestinal secretion accounted for approximately 20% each route. Metabolism contributed to ca. 30%, with TP-6208 being the major metabolite in excreta (~10% of the radioactive dose). The responsible enzyme for the formation of TP-6208 was CYP3A4 and possibly also FMOs. All other metabolites are considered minor by CHMP.

Population PK

The initially submitted main model TETR-PCS-100 was updated with data from three additional studies. This updated model i.e. TETR-CSC-106 is regarded as the main population PK model from which PK parameters and dose recommendations are derived. It comprises a wide range of PK data from 15 clinical studies, including seven Phase 1 studies in healthy volunteers, one study in subjects with hepatic impairment, one study in subjects with ESRD, two DDI studies, one Phase 2 study and two Phase 3 studies in patients with cIAI, and one phase 3 study in patients with cUTI. Overall, the applicant has adequately clarified their modeling strategy and the model looks adequate to describe AUC for IV infusion administration. Shrinkages for clearance parameters were less than 30%, while shrinkages for volumes parameters were higher (62.8% for V2). Monte Carlo simulations based on the model parameter estimates can be used for illustrating the exposure to eravacycline in terms of *e.g.* AUC and Cmax. However, due to the significant shrinkage in volume parameters, the individual *post hoc* estimates (Empirical Bayes Estimates, EBE) derived from the model should be interpreted with caution. This affects mainly the derived Cmax and Cmin values.

Special populations

The applicant notified that the blood samples for PK analysis in studies TP-434-013 (HI) and TP-434-014 (RI) were collected in the wrong blood collection tubes, i.e. in tubes containing EDTA as the anticoagulant, in contrast to heparin, which was used in other studies. Also, that it is likely that EDTA anticoagulant produced artifactually lower plasma concentrations as it could influence the blood:plasma ratio, as previously shown for tigecycline (Chen et al., Xenobiotica 2008, (38):77-86). However, it may be even more complex in this case compared to the Chen article, as in the HI and RI studies it appears that the QC and standard curves were prepared in heparin plasma and study blood samples in EDTA tubes. Data provided during the assessment have shown that eravacycline concentrations in Na heparin plasma were consistently higher than those in EDTA plasma (average 2.88-fold, range 2.49-3.09). The bioanalysis method appeared to be suitable for quantitation of eravacycline irrespective of the collection tubes (heparin vs. EDTA) used for blood sampling. Lastly, sensitivity analyses were performed to examine the impact of the hepatic and renal study PK data and the derived correction factor 2.88 on the overall population PK model. Based on the presented findings CHMP agreed that

data from the hepatic and renal studies (TP-434-013, TP-434-014) and the population PK model (TETR-CSC-106) could be used to support dosing recommendation in these populations.

Body weight

Body weight based allometric scaling on clearances and volumes were included in the updated population PK model. Eravacycline dosing regimen is body weight based and this has been shown to be adequate in the body weight range studied. No data are available for patients weighing more than 137 kg. The potential influence of severe obesity on exposure of eravacycline has not been studied.

Pharmacodynamics

Eravacycline (TP-434) is a synthetic fluorocycline antibacterial agent that, like other agents of the tetracycline class, inhibits bacterial protein synthesis. Eravacycline is primarily bacteriostatic and has a broad spectrum of *in vitro* activity against a variety of aerobic and anaerobic Gram-negative and Gram-positive bacteria including important pathogens that cause intra-abdominal infections with MIC90 values ranging from lower values up to 1 to 4 mg/L. Also against *A. baumanii* the MIC_{90} values were ranging from 1 to 4 mg/L in different data sets. The poorer activity against *P. aeruginosa* with MIC_{90} values of 16 to 32 mg/L is similar to what has been seen with other agents of the tetracycline class.

The primary metabolites of eravacycline are inactive *in vitro* or have less activity then the parent compound.

Resistance studies indicate that eravacycline generally retains activity against tetracycline-specific resistance mechanisms (RPP and efflux) excluding the tetracycline-inactivating enzyme tet(X) which impacts all tetracyclines. Like many other classes of antibiotics, eravacycline activity is negatively affected by expression of some MDR efflux pumps. In addition, target based mutations in 16S rRNA and the 30S ribosomal protein S10 resulted in decreased susceptibility to eravacycline.

Eravacycline maintained activity against methicillin-resistant staphylococci, vancomycin-resistant enterococci, cephalosporin-resistant/ESBL and carbapenem-resistant Enterobacteriaceae, carbapenem-resistant A. baumannii, and fluoroquinolone-resistant Gram-positive and Gram-negative isolates – i.e. no cross-resistance based on similar mechanisms was apparent.

Spontaneous mutation frequency values for eravacycline were low and comparable to tigecycline for most of the Gram-positive and Gram-negative isolates tested. For *E.coli*, *K. pneumoniae* and *B. fragilis* but not for *S. aureus, S pyogenes* and *E. faecalis* the MIC increased significantly during serial passage experiments demonstrating the ability for resistance to eravacycline to develop. The increase in MIC was however not confirmed for the *B. fragilis* isolate.

Eravacycline was efficacious in various non-clinical models of infection, with the exception of the rat intra-abdominal abscess model (for unknown reasons). The applicant pointed out that no dosing solution or plasma PK analysis was completed as part of the study and therefore a full analysis of the reasons for failure can unfortunately not be done.

In an *in vitro* dynamic chemostat system eravacycline free-drug AUC_{0-24}:MIC ratio was the PK/PD index that was considered most associated with the change in bacterial density of *E. coli,* based on the coefficient of determination and dispersion of data across the fitted line. The *in vivo* PK/PD experiments confirmed these results. It can be noted that the coefficient of determination was however as high (or somewhat higher in the chemostat experiments) for the PK/PD-index fT>MIC. However, for these evaluations the doses chosen were not well adapted because they often resulted in a T>MIC of 100%. Notably, only strains of *E-coli* were evaluated in these experiments.

The magnitude of eravacycline free-drug AUC_{0-24}:MIC ratio associated with net bacterial stasis and 1- and 2-log_{10} CFU reductions from baseline was 15.3, 20.5, and 28.8, respectively in the *in vitro* system.

In an immunocompetent mouse thigh model, the mean free AUC/MIC magnitudes required for a net static response and a 1-log_{10} reduction for the eight isolates of Enterobacteriaceae were 2.9 ± 3.1 and 5.6 ± 5.0, respectively.

In two neutropenic murine thigh model studies, the mean free AUC/MIC magnitudes required for a net static response and a 1-log_{10} reduction in the first study was 16.1 ± 5.2 and 23.8±9.9, respectively and in the second study 28.0 ± 8.3 and 32.6 ± 10.8, respectively. As commented on above, only strains of *E.coli* were evaluated in these experiments.

The neutropenic mouse thigh model is the widely used model to derive effective doses for humans based on the fact that the magnitude of non-clinical targets has been shown to be predictive of human efficacy for several antibacterial agents. However, as can be noted below, the efficacy predictions based on the PTA analysis using nonclinical PK/PD targets from the neutropenic murine thigh infection model are not consistent with the rates of microbiological favourable outcomes in patients with cIAI in the clinical trials up to the breakpoint initially proposed by the Applicant of ≤1 mg/L.

Susceptibility breakpoints were proposed based on clinical efficacy in human clinical studies and on the *in vitro* susceptibility distributions. As already noted, the proposed breakpoints are not supported by probability of target attainment simulations based on magnitudes of non-clinical PK/PD targets. The EUCAST has provided their recommendations to CHMP on the susceptibility testing breakpoints and consulted with CHMP on the species that would be considered to be relevant pathogens.

The antimicrobial interaction of eravacycline with other antibacterial agents for aerobic Gram-positive and Gram-negative bacteria and for *B. fragilis* was found to be indifferent for nearly all antibiotic combinations and bacteria evaluated.

The proposed eravacycline dose regimen for cIAI 1.0 mg/kg q12h for 4 to 14 days was brought from phase 1 through phase 3 based on acceptable tolerability in phase 1 and on expectations that the exposure in relation to *in vitro* susceptibility would result in high clinical cure rates when compared theoretically with tigecycline. High clinical success rates were confirmed in phase 2 and 3 and the proposed dose regimen showed non-inferiority to ertapenem and meropenem for the treatment of complicated intraabdominal infections. The microbiological responses in the Phase 2 and Phase 3 studies were pooled and assessed by pathogen and then by the eravacycline MIC. There was no trend towards a decrease in a favourable response with increasing eravacycline MIC for any of the pathogens. However, it should be noted that the MIC ranges were limited and that for many pathogens the total numbers were low and for all pathogens the numbers were low at the highest MIC values that would be considered treatable based on the proposed breakpoints. Moreover, as the majority of infections were polymicrobial it was difficult to draw conclusions on the actual or major causative pathogen.

The high rates of clinical and microbiological favourable outcomes and non-inferiority to ertapenem and meropenem in the treatment of cIAI could be considered reassuring. However, the PTA analysis using non-clinical PK/PD targets from the murine thigh infection model did not provide support for the proposed dose regimen to cover for the full MIC distribution of the wild-type populations of several clinically relevant pathogens nor did they support the proposed susceptibility breakpoints. The PTA analyses did not reach above 90% for pathogens with an eravacycline MIC above 0.12 mg/L for free drug AUC/MIC targets associated with net bacterial stasis and a 1-log_{10} CFU reduction. The reason for the discrepancy between clinical outcome and PTA based on non-clinical targets is not fully elucidated. The applicant pointed out that the same phenomenon exists for tigecycline. Possible explanations for

the difference seen in the clinical trials and the low predicted target attainment based on non-clinical PK/PD targets include differences in the protein binding relationship for eravacycline in mouse and human serum, differences in the micro environment of the neutropenic mouse thigh versus the human abdomen and the complementary role of surgical intervention in the clinical trials. Nevertheless, data obtained with the chemostat were also considered. Another factor noted by CHMP is that a high proportion of the infections were poly-microbial (~70% in the phase 3 studies), where there is lack of certainty of the actual or major causative pathogen.

Despite the lack of support from non-clinical PK/PD data and the limitations of the clinical microbiology data to support the proposed dose regimen, CHMP however noted that the applicant submitted the results of a second pivotal study during the assessment. Efficacy data from this study and from the previously submitted study show high clinical and microbiological cure rates for patients treated with eravacycline. The dose selection is therefore considered confirmed by CHMP.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacokinetics for eravacycline has been sufficiently characterised. The *in vitro* and *in vivo* activity of eravacycline have been adequately described. PTA simulations did not provide support for the proposed dose regimen to fully cover for pathogens belonging to the wild-type populations. However, efficacy data from two pivotal studies showed high clinical and microbiological cure rates for patients treated with eravacycline and thus CHMP agreed that the dose selection can be considered confirmed.

2.5. Clinical efficacy

2.5.1. Main studies

TP-434-008 (IGNITE 1)

This was a phase 3, randomised, double-blind, double-dummy, multicentre study to evaluate the non-inferiority of eravacycline 1.0 mg/kg i.v. q12h to ertapenem 1.0 g i.v. q24h in subjects with cIAI.

Methods

Study Participants

Inclusion criteria

1. Male or female subject hospitalised for cIAI with one of the following diagnoses:
    a. Intra-abdominal abscess: one or more abscesses surrounding diseased or perforated viscera
    b. Gastric or intestinal perforation associated with diffuse peritonitis
    c. Peritonitis due to perforated viscus or other focus of infection (but not spontaneous bacterial peritonitis associated with cirrhosis and chronic ascites)
    d. Appendicitis with perforation, peritonitis, or abscess
    e. Cholecystitis with perforation or abscess
    f. Intra-abdominal abscess (single or multiple), including hepatic and splenic abscesses
    g. Peritonitis (local or diffuse)
2. At least 18 years of age (and not over the age of 65 for subjects in India)
3. Evidence of a systemic inflammatory response with at least one of the following:

a. Fever (oral, rectal, tympanic, or by temporal artery >100.4°F/38°C) or hypothermia (temperature ≤95.9°F/35.5°C)

b. Elevated white blood cell (WBC) count (> the upper limit of normal [ULN] laboratory range) or proportion of band forms of the WBC differential beyond the ULN laboratory range

c. Increased pulse (heart rate [HR] >90 beats per minute)

d. Increased respiratory rate (>20 breaths per minute)

4. 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; localized or diffuse abdominal wall rigidity; mass; or ileus

5. Able to provide informed consent

6. If male: must agree to use an effective barrier method of contraception during the study and for 30 days following the last dose, if sexually active with a female of childbearing potential.

7. If female:

a. Not pregnant or nursing

b. If of childbearing potential, committed to either:

i. Using at least 2 medically accepted, effective methods of birth control (e.g., condom, oral contraceptive, indwelling intrauterine device, hormonal implant/patch, injections, or approved cervical ring) during study drug dosing and for 30 days following the last study drug dose

ii. Sexual abstinence

And either

8A. Met all inclusion criteria for preoperative enrolment:

Had a sonogram or radiographic imaging result congruent with the diagnosis of cIAI, and acute surgical or percutaneous intervention (open laparotomy, laparoscopic surgery, or percutaneous drainage of an abscess) was foreseen within 48 hours

8B. Met all inclusion criteria for intraoperative/postoperative enrolment:

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)

<u>Exclusion criteria</u>

Subjects must not have met any of the following exclusion criteria:

1. Considered unlikely to survive the 6- to 8-week study period because of the following:

a. Any rapidly progressing disease or immediately life-threatening illness, including acute hepatic failure, respiratory failure, and septic shock

b. Requirement of vasopressors (prior to enrolment) at therapeutic dosages (i.e., dopamine >5 µg/kg/min or any dose of norepinephrine, epinephrine, or phenylephrine) to maintain a systolic blood pressure ≥90 mmHg or a mean arterial pressure ≥70 mmHg following adequate fluid resuscitation

2. Had renal failure defined as:

a. a 3-fold increase of serum creatinine to a known previous value, or

b. a decrease in estimated glomerular filtration rate to <75% of a known previous value, or

c. a urine output of <0.3 mL/kg/h for >24 hours, or

d. anuria for >12 hours, or

e. a serum creatinine level of >4 mg/dL (353.6 µmol/L) with an acute rise of 0.5 mg/dL (42.2 µmol/L) compared with a previous value, or

f. a creatinine clearance <50 mL/min as estimated by the Cockcroft-Gault equation, or eCCrmL/min] = (140 − Age [years]) × Body Weight [kg] × [0.85 if female] 72 × Serum Creatinine [mg/dL]

g. requiring peritoneal dialysis, haemodialysis, or hemofiltration

3. Presence or had possible signs of significant hepatic disease:

a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × ULN; >5 × ULN for subjects with hepatic abscess, or

b. Total bilirubin >3 × ULN, unless isolated hyperbilirubinemia is directly related to the acute process, or

c. Alkaline phosphatase >3 × ULN, or

d. Diagnosis of hepatic failure

4. Had immunocompromised condition, including known human immunodeficiency virus positivity (requiring anti-retroviral therapy or with CD4 count <300 cells per microliter), had Acquired Immune Deficiency Syndrome (AIDS), received organ (bone marrow) transplant, and had haematological malignancy. Subjects who use immunosuppressive therapy, including high-dose corticosteroids (e.g., >40 mg prednisone or equivalent per day for >2 weeks) were also excluded.

5. 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

6. Had participated in any investigational drug or device study within 30 days prior to study entry

7. Had known or suspected current central nervous system disorder that may predispose to seizures or lower seizure threshold (e.g., severe cerebral arteriosclerosis or epilepsy)

8. Had previously received eravacycline in a clinical trial

9. Had antibiotic-related exclusions:

a. Receipt of effective antibacterial drug therapy for cIAI for a continuous duration of >24 hours during the 72 hours preceding enrolment (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. Treatment failure was defined as persistent fever and/or clinical symptoms or the development of a new intra-abdominal abscess after >72 hours of antibiotic therapy)

b. Receipt of ertapenem or any other carbapenem or tigecycline for the current infection

c. Need for concomitant systemic antimicrobial agents other than the study drug

10. Refused mechanical ventilation, dialysis or hemofiltration, cardioversion, or any other resuscitative measures and drug/fluid therapy at the time of consent

11. Had known or suspected inflammatory bowel disease or associated visceral abscess

12. Had anticipated need for systemic antibiotics for a duration of more than 14 days

13. Had systemic malignancy that required chemotherapy, immunotherapy, radiation therapy, or antineoplastic therapy within the previous 3 months or was anticipated to begin prior to the TOC Visit

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

Treatments

The study was of double-blind, double-dummy design. Patients were randomised to:

- eravacycline 1.0 mg/kg (up to a maximum of 150 mg) q12h in (weight ÷ 0.3) ml over 60 min, or
- ertapenem 1.0 g q24h in 60 ml over 30 min

Objectives

The primary objective of this study was to compare the clinical response at the TOC Visit for subjects in the 2 treatment groups. The primary analysis populations were the modified intent-to-treat (MITT) and the clinically evaluable (CE) populations.

The following secondary objectives were examined:

- Compare the clinical response for subjects in the 2 treatment groups in the following populations (for visits not captured in the primary objective):
    - Intent-to-treat (ITT) population
    - MITT population
    - CE population
    - micro-ITT population
    - ME population
- Compare the microbiologic response for subjects in the 2 treatment groups in the following populations (at the End of Treatment [EOT] and TOC visits):
    - micro-ITT population
    - ME population
- Assess the safety and tolerability of eravacycline administration in the safety population
- Explore PK parameters after eravacycline infusion

Outcomes / endpoints

The primary endpoint for efficacy of this study was the clinical response at the TOC Visit for the MITT and CE-EOT populations.

The secondary endpoints for efficacy of the study were as follows:

- Clinical response at the EOT, TOC, and Follow-up (FU) Visits
- Microbiologic response at the EOT and TOC Visits

Sample size

A sample size of approximately 536 randomised subjects provided 89% and 92% power in the MITT and CE-TOC populations, respectively, to show NI assuming an NI margin of 12.5%, a 1-sided alpha of 0.005, and a 95% evaluability rate for the MITT population and 75% for the CE-TOC population. The rates of clinical success were assumed to be 85% in both treatment groups in the MITT population and 90% in both treatment groups in the CE-TOC population based on the results from the phase 2 study.

Randomisation

Subjects were assigned to receive eravacycline or ertapenem in a 1:1 ratio with stratification by primary site of infection (complicated appendicitis versus all other cIAI diagnoses) using dynamic allocation randomisation via an Interactive Web-based Response System (IWRS). No more than approximately 30% of subjects should have complicated appendicitis.

Blinding (masking)

This was a double-blind study. Since both eravacycline and ertapenem, when prepared for infusion, are coloured solutions, require different infusion volumes and, since the dosing interval differed, this study was designed with a double-dummy methodology through the use of matching placebo infusions. All solutions for infusion were to be prepared by an unblinded pharmacist or designee. Except for the responsible study site pharmacist/designee and separate unblinded clinical research associates (CRAs) to monitor drug supply and adherence to study drug blinding and randomisation procedures, all study staff and subjects were to be blinded to treatment assignment.

Statistical methods

This study was designed to show non-inferiority of eravacycline compared to ertapenem. The co-primary efficacy analyses were based on the MITT and CE-TOC populations and examined clinical response at the TOC Visit.

Analysis populations

- **ITT population**: all subjects who were randomised
- **MITT population**: all randomised subjects who received any amount of study drug
- **micro-ITT population**: all randomised subjects who had baseline bacterial pathogens that cause cIAI and against at least one of which the investigational drug has in vitro antibacterial activity. As clinical breakpoints for eravacycline had not been determined at the time of the study, for the purpose of this analysis population, all baseline bacterial pathogens were considered susceptible to eravacycline.
- **CE population**: all subjects who met the definition for the ITT population and had no major protocol deviations. Following criteria are specifically noted:

Subjects must have fulfilled minimal disease criteria (inclusion criteria 1, 3, 4, and 8).

Subjects were excluded from the CE analysis set if they:

- were found to have met exclusion criterion 9
- received any systemic concomitant antibiotic therapy which was potentially effective against the baseline pathogen except if the subject was a clinical failure and received non-study antibiotics for insufficient therapeutic effect of the study drug or received 1 dose as prophylaxis for procedures unrelated to the ongoing infection or received an oral antibiotic with no systemic absorption
- did not have adequate source control
- did not receive at least 3 days of study drug and was at least 80% compliant
    - **ME population**: all subjects who met the definition for the micro-ITT population and had no major protocol deviations (i.e. included in the CE population).

Clinical response

Clinical response was classified by the investigator as clinical cure, clinical failure, indeterminate or missing based on clinical outcomes.

Clinical cure was defined as complete resolution or significant improvement of signs or symptoms of the index infection such that no additional antibacterial therapy, surgical, or radiological intervention (e.g., ultrasound guided drainage) was required.

Subjects were classified as a *clinical failure* based on:

- Death related to cIAI at any time point
- Persistence of clinical symptoms of cIAI
- Unplanned surgical procedures or percutaneous drainage procedures
- Post-surgical wound infections requiring systemic antibiotics
- Initiation of rescue antibacterial drug therapy for cIAI

If the subject's outcome was neither *clinical cure* nor *clinical failure* then the outcome was to be listed as *Indeterminate*. The reason for an "Indeterminate" designation had to be provided.

Subjects who were assessed as a failure at the EOT Visit were to have the failure carried forward to the TOC Visit. Clinical response at TOC (based on Investigator's assessment) was determined as follows from the assessments at the EOT and TOC Visit:

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

A Surgical Adjudication Committee (SAC) was responsible for reviewing all subjects classified as a clinical failure and all subjects classified as a clinical cure at the TOC or FU Visits who underwent a second procedure to determine the adequacy of the source control and for the clinical cures, to assess whether subjects met the criteria of a clinical cure.

Microbiologic evaluation

There were 3 categories of pathogen identification, as follows:

1. Always a pathogen:

- All Enterobacteriaceae (e.g., *E. coli*, *Enterobacter spp.*, *Klebsiella* spp., *Proteus* spp.), *Pseudomonas* spp., *Bacteroides* spp., *Clostridium* spp., *Prevotella* spp., *Peptostreptococcus* spp., *Fusobacterium* spp., *Eubacterium* spp., *Streptococcus* spp., *Enterococcus* spp., and *S. aureus* were always considered pathogens.
- *Acinetobacter* spp. and *Stenotrophomonas* spp.

2. Not considered a pathogen: fungi and coagulase-negative staphylococci

3. Pathogens for Microbiology Review Committee (MRC) review: isolates were reviewed in a blinded manner by the MRC on a case-by-case basis if neither rule 1 nor 2, above, applied.

Analyses of the primary efficacy outcome

The primary efficacy outcome was the percentage of subjects with a clinical cure at the TOC visit. 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.

To test the null hypothesis, an adjusted (for the randomisation stratification factor of primary disease diagnosis) 2-sided 99% CI for the observed difference in primary outcome rates (eravacycline treatment group minus ertapenem treatment group) was calculated for the MITT and CE-TOC populations. The two-sided 99% CI for non-inferiority testing was computed using the method proposed with stratification for the primary disease diagnosis by Miettinen and Nurminen (Miettinen 1985). In the calculation of the CI, Cochran-Mantel-Haenszel weights were used for the stratum weights. If the lower limit of the 99% CI for the difference in clinical cure rates analysis set exceeded -12.5%, then the null hypothesis was rejected and the NI of eravacycline to ertapenem was declared. No adjustment for multiple comparisons was required.

If eravacycline was determined to be non-inferior to ertapenem, superiority of eravacycline to ertapenem was to be assessed and superiority of eravacycline for clinical cure at the TOC Visit to be concluded if the lower bound of the 2-sided 99% CI was shown to be greater than 0.

The Investigator's assessments of clinical response at the TOC Visit (not incorporating the assessment of the SAC) in the micro-ITT population, MITT and CE-TOC populations were presented to support the findings of the primary and secondary efficacy analyses.

The primary efficacy outcome was also assessed across the randomisation stratification factor of primary disease diagnosis, and across geographical region and country by treatment group. For each infection site stratum, geographical region and country, an unadjusted 2-sided 99% CI for the observed difference in the clinical cure rate at the TOC Visit was calculated for the MITT and CE-TOC populations.

Sensitivity analyses of the primary outcome were also conducted. The first analysis was an unadjusted analysis (Miettinen and Nurminen, 1985) for the MITT and CE-TOC populations. The second sensitivity analysis analysed those subjects who were considered indeterminates in the primary analysis as clinical cures including a CI that was calculated using an adjusted method (Miettinen and Nurminen, 1985 adjusted for primary diagnosis at baseline). Additional sensitivity analyses were stratified analyses for the following combinations: primary site of infection and geographic region, primary site of infection and prior antibiotic use, and geographic region and prior antibiotic use. Prior antibiotic use was defined as use of any systemic antibiotic in the 72 hours prior to enrolment. Two-sided 99% CIs were computed for the difference in clinical cure rate at the TOC Visit between the eravacycline and ertapenem treatment groups within each stratum and across strata (Miettinen and Nurminen, 1985).

In secondary efficacy analyses, the number and percentage of subjects in each treatment group with an efficacy outcome of clinical cure, clinical failure and indeterminate/missing were to be presented at additional time-points (for the EOT Visit, the TOC visit and the FU visit) based on the different analysis populations. Two-sided 95% unadjusted CIs were constructed for the observed difference in the clinical cure rates between the treatment groups for descriptive purposes; no conclusion of non-inferiority was made.

There was no formal interim analysis of efficacy for this study. A Data and Safety Monitoring Board (DSMB) was to review safety data by unblinded treatment assignment when approximately 150, 300 and 450 subjects have had their TOC visit.

The final SAP, Statistical Analysis Plan EMA 3.0 (dated 7 January, 2015), was based on protocol version 3.0 dated October 31, 2013.

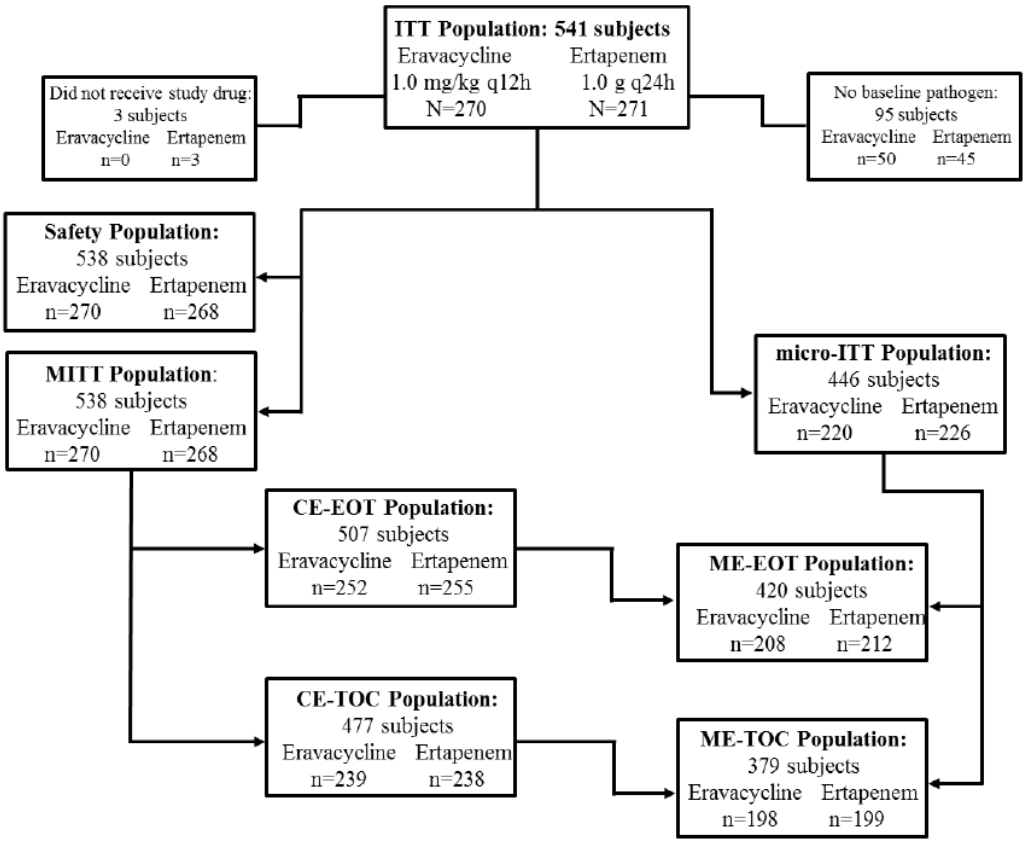
Results

Participant flow

A total of 541 subjects were randomly assigned to the eravacycline group (270 subjects) or the ertapenem group (271 subjects). Three subjects in the ertapenem group did not receive study drug. Two of these subjects withdrew consent prior to study drug administration and 1 subject was randomised in error (screen failure: antibiotic-related exclusion) and did not receive study drug. These 3 subjects were not included in the Safety population or in the MITT population.

The following figure shows the study analysis populations.

Figure E1. Study analysis populations



The following table shows the subject disposition and reasons for both study withdrawal and study drug discontinuation for the ITT population.

Table E1. Subject disposition and reasons for study withdrawal and study drug discontinuation (ITT population)

	Number (%) of subjects	
	Eravacycline	**Ertapenem**
Randomised	270 (100)	271 (100)
Randomised, not treated	0	3 (1.1)
Completed study	246 (91.1)	255 (94.1)
Not completed study	24 (8.9)	16 (5.9)
Reason for early termination		
Lost to follow-up	15 (5.6)	3 (1.1)
Adverse event	3 (1.1)	6 (2.2)
Withdrawal of consent	3 (1.1)	2 (0.7)
Noncompliance	2 (0.7)	3 (1.1)
Other	1 (0.4)	2 (0.7)
Completed treatment	255 (94.4)	255 (94.1)
Premature treatment discontinuation	15 (5.6)	16 (5.9)
Reason for premature treatment discontinuation		
Adverse event	7 (2.6)	6 (2.2)
Insufficient therapeutic effect	4 (1.5)	3 (1.1)
Withdrawal of consent	2 (0.7)	2 (0.7)
Other	2 (0.7)	2 (0.7)
Need for concomitant antibiotic for an infection other than cIAI	0	2 (0.7)
Noncompliance	0	1 (0.4)

Compliance and exposure to study drug

- The mean (±SD) percent compliance was 99.19% ± 2.374 for the eravacycline group and 99.27% ± 2.372 for the ertapenem group.
- All subjects achieved ≥80% compliance.
- The mean duration of treatment was 7.6 days ± 2.77 days in the eravacycline group and 7.6 days ±2.44 days in the ertapenem group.
- The mean number of active doses administered was 14.0 ± 5.47 in the eravacycline group and 7.0 ±2.34 in the ertapenem group, consistent with the planned dosing regimens.

Prior and concomitant exposure to other antibiotics

Approximately half of the subjects in the micro-ITT population used systemic antibacterial medication prior to the first dose of study drug and the incidence was similar between the treatment groups (48.6% vs. 48.7% for eravacycline and ertapenem groups, respectively). Numbers in the CE-TOC population were 49.0% vs. 47.5%, respectively. The most frequently used systemic antibacterial medications prior to the first dose of study drug were imidazole derivatives, combinations of penicillins, second-generation cephalosporins, and third-generation cephalosporins.

Concomitant systemic antibacterial medications use from the first dose of study drug through the TOC Visit in the MITT population was 13.0% of the subjects in the eravacycline treatment group and 8.6% of the subjects in the ertapenem treatment group. The most frequently used systemic antibacterial medications after the first dose of study drug were imidazole derivatives, third-generation cephalosporins, and fluoroquinolones.

Recruitment

The study was conducted between 28 August 2013 and 26 August 2014. The study included 66 clinical sites in 11 countries. The majority of subjects (415 of 541) were enrolled in Eastern Europe. No site enrolled more than 35 subjects.

Conduct of the study

There were 2 global amendments to the original study protocol.

The first was implemented before any subjects were enrolled and documented the following: an increase in the study sample size, inclusion of the micro-ITT population, change in assessment timing, change in microbiological specimen collection, clarification of inclusion and exclusion criteria, refinement of clinical response assessment, and other global administrative changes and clarifications.

The second was implemented after 197 subjects were enrolled and documented the following: the change in primary analysis populations and NI margin for the EMA, revision of the inclusion and exclusion criteria, change in the dose of eravacycline was limited to 1.0 mg/kg, up to a maximum of 150 mg q12h, changes in the restricted concomitant medications, clarification on study drug and placebo preparation, change in the maximum dosage in 24 hours, and other global administrative changes and clarifications. Changes to the protocol were considered to have no negative impact on the safety of subjects already enrolled into the study.

There were also certain country-specific protocol amendments issued that did not affect the overall design or outcome of the study.

Baseline data

The demographics and baseline characteristics are shown in the following table:

Table E2. Demographics and baseline characteristics (ITT-population)

Parameter	Eravacycline n=270	Ertapenem n=271
Gender, n (%)		
Male	156 (57.8)	163 (60.1)
Female	114 (42.2)	108 (39.9)
Race, n (%)		
Caucasian/White	263 (97.4)	260 (95.9)
Other	6 (2.3)	11 (4.1)
Age (y), mean (SD)	54.8 (16.9)	54.8 (16.1)
Age group, n (%)		
<65 years	182 (67.4)	195 (72.0)
65-75 years	62 (23.0)	44 (16.2)
>75 years	26 (9.6)	32 (11.8)
BMI (kg/m^2), mean (SD)	28.0 (5.7)	27.0 (5.0)
APACHE II score, mean (SD)	6.3 (4.1)	6.6 (3.8)
APACHE II score, by numerical category		

Parameter	Eravacycline n=270	Ertapenem n=271
0-10	235 (87.0)	221 (81.5)
11-15	28 (10.4)	40 (14.8)
>15	5 (1.9)	6 (2.2)
Site of infection, n (%)		
Complicated appendicitis	73 (27.0)	74 (27.3)
Other Site of Infection, n (%)[c]	197 (73.0)	197 (72.7)
Peritonitis	78 (32.1)	84 (36.2)
Gastric/duodenal perforation	29 (11.9)	31 (13.4)
Intestinal perforation	28 (11.5)	35 (15.1)
Complicated cholecystitis	55 (22.6)	47 (20.3)
Intra-abdominal abscess	97 (39.9)	90 (38.8)

Baseline microbiology

Approximately 80% of all randomised subjects had at least one baseline bacterial pathogen that was considered to cause cIAI (=micro-ITT population).

Approximately 70% of subjects in each treatment group had poly-microbial infections.

Gram-negative aerobes were isolated from 182 [82.7%] eravacycline vs. 186 [82.3%] ertapenem treated patients, respectively. The corresponding figures for Gram-positive aerobes were 117 [53.2%) vs. 120 [53.1%] and for anaerobes 106 [48.2%] vs. 107 [47.3%].

Pathogens belonging to Enterobacteriaceae were most frequently isolated (168 [76.4%] vs. 171 [75.7%]) with *E. coli* being the most commonly isolated species (127 [57.7%] vs. 132 [58.4%]) for eravacycline and ertapenem patients, respectively.

20 (9.1%) eravacycline vs. 20 (8.8%) ertapenem patients were bacteraemic.

Numbers analysed

A summary of analysis populations and numbers analysed is shown in the following:

Table E3. Analysis populations

Analysis population	Eravacycline, n (%)	Ertapenem, n (%)
ITT	270 (100)	271 (100)
MITT	270 (100)	268 (98.9)
Micro-ITT	220 (81.5)	226 (83.4)
CE-EOT	252 (93.3)	255 (94.1)
CE-TOC	239 (88.5)	238 (87.8)
ME-EOT	208 (77.0)	212 (78.2)
ME-TOC	198 (73.3)	199 (73.4)

Outcomes and estimation

Non-inferiority of eravacycline to ertapenem was shown in the co-primary analyses, see the following table:

Table E4. Primary efficacy analysis: Clinical response at TOC for the MITT and CE populations

Efficacy measure	Eravacycline 1.0 mg/kg q12h n (%)	Ertapenem 1.0 g q24h (n (%)
MITT population	270	268
Clinical cure	235 (87.0)	238 (88.8)
Treatment difference (99% CI)[a]	-1.80 (-9.2, 5.6)	
Clinical failure	19 (7.0)	15 (5.6)
Indeterminate/missing	16 (5.9)	15 (5.6)
CE population	239	238
Clinical cure	222 (92.9)	225 (94.5)
Treatment difference (99% CI) [a]	-1.70 (-7.9, 4.4)	
Clinical failure	17 (7.1)	13 (5.5)

The most frequent reasons for clinical failure were unplanned surgical procedure or percutaneous drainage procedure (MITT: 4.1% for both treatment groups; CE: 3.3% in the eravacycline group and 3.4% in the ertapenem group), initiation of rescue antibacterial therapy for cIAI (MITT: 2.2% for both groups; CE: 2.1% in the eravacycline group and 0.8% in the ertapenem group), persistence of clinical symptoms of cIAI (MITT: 1.9% in the eravacycline group and 2.2% in the ertapenem group; CE: 1.3% in the eravacycline group and 1.7% in the ertapenem group) and post-surgical wound infections requiring systemic antibiotics (MITT: 1.9% in the eravacycline group and 1.1% in the ertapenem group; CE: 2.1% in the eravacycline group and 0.8% in the ertapenem group. There were no deaths due to cIAI.

Sensitivity analyses

The results of the sensitivity analyses (Sensitivity analysis 1#: unadjusted 99% CI; Sensitivity analysis 2#: indeterminate/missing as clinical cure) were supportive of the primary analysis results. The lower bounds of the 99% CI were -9.2, -7.3, -7.9 and -7.9 for the sensitivity analysis 1# and MITT, sensitivity analysis 2# and CE, sensitivity analysis 1# and CE, and sensitivity analysis 2# and CE, respectively.

Clinical response by primary disease diagnosis

There were no meaningful differences in cure rate between the treatment groups in either population (MITT and CE at TOC), regardless of whether the primary site of infection was complicated appendicitis or other cIAI.

Clinical response by geographic region or country

Rates of response between treatment groups in the MITT population were generally similar for geographic region and country, with the highest rates of response occurring in Ukraine, Romania and Latvia. Generally higher overall clinical cure rates were observed in the CE population with between-group differences that were more similar across geographic regions and countries.

The differences in clinical success rates varied by geographic region, but the varying sizes of the geographic subgroups made direct comparisons difficult. In the United States, the larger between-group difference in clinical response was primarily due to a higher rate of indeterminate responses in the ertapenem group. In the CE population, which does not include subjects with indeterminate responses, the between group difference was smaller and was more similar to the differences seen in other geographic regions and countries.

Additional analyses taking into consideration primary disease diagnosis and geographic region, prior antibiotic use and geographic region, and prior antibiotic use and primary disease diagnosis were also conducted. The variable numbers of subjects in any given subgroup makes direct comparisons of these data difficult, but generally the clinical response was similar and consistent between treatment groups in the analyses performed regardless of primary diagnosis, geographic region or prior antibiotic use.

Ancillary analyses

Subgroup analyses by patient and infection characteristics

A series of sub-population analyses of clinical response at the TOC visit by baseline characteristics for the MITT and CE populations was conducted.

- There were no meaningful differences or trends in the clinical cure rates for any **age category** in either population, nor between the eravacycline and ertapenem treatment groups.
- There were no apparent differences in clinical cure by **gender** for either population.
- The majority of subjects in the both treatment groups in both populations were Caucasian. As a consequence of the predominance of one race, examination of the effect of **race** on clinical response was not feasible.
- For the eravacycline-treated MITT population, there was no apparent difference in clinical cure between Europe, EU and non-EU Europe. Clinical cure rates in this analysis population were slightly lower in North America. Clinical cure rates were higher in the ertapenem-treated MITT population in all European subpopulations, but notably lower in North America. These trends were maintained in the CE population by **geographic region.**
- There were no major differences in clinical response by **site of infection** at baseline for either analysis population.
- In the MITT population, cure rates for eravacycline were somewhat lower among subjects who had no **abscesses** at baseline than ertapenem (88.1% compared to 92.5%). This small difference is of no clear clinical significance. There were no differences among subjects who had ≥1 abscess at baseline. There were no trends or differences in clinical response in the CE population.
- In the MITT population, cure rates for eravacycline were somewhat lower among subjects with **APACHE II score** <10 at baseline than for ertapenem (87.1% compared to 91.3%). In the subjects with APACHE II score ≥10 at baseline, cure rates for eravacycline were slightly higher than for ertapenem (86.3% compared to 83.1%). These small differences are of no clear clinical significance. There were no trends or differences in clinical response in the CE population.
- With regard to subjects with **renal function impairment**, in the MITT population, cure rates were lower in the Moderate/Severe group for both treatment groups compared with the Normal/Mild group. Cure rates in the augmented group were similar to those in the Normal/Mild group. The same trends were seen in the CE population. Between-group comparisons were limited by the small sample size in some of the subgroups.
- Clinical cure rates in the MITT population were higher in both treatment groups among subjects who had not received **prior antibiotic treatment** compared with those who had. The same trends were seen in the CE population, although overall cure rates were numerically higher. Potential factors in the lower cure rate among subjects who received prior antibiotics are inclusion of subjects who had already failed prior antibiotic treatment and higher baseline disease severity in this group.

Secondary efficacy analyses

Clinical response was evaluated at the EOT, TOC, and Follow-up Visits in the ITT, MITT, micro-ITT, CE-EOT (or TOC), and ME-EOT (or TOC) populations. The differences in clinical cure rates are summarised in the following table:

Table E5. Difference in clinical cure rates between eravacycline-treated subjects and ertapenem-treated subjects by analysis population by visit

Analysis Population	Study Visit		
	EOT Difference (95% CI)	TOC Difference (95% CI)	FU Difference (95% CI)
ITT	−1.50 (−6.1, 3.0)	−0.80 (−6.5, 4.9)	−4.90 (−11.0, 1.2)
MITT	−2.60 (−7.1, 1.8)	−1.80 (−7.4, 3.8)[a]	−5.80 (−11.9, 0.2)
micro-ITT	−2.00 (−7.2, 3.0)	−0.80 (−7.1, 5.5)[b]	−4.50 (−11.3, 2.3)
CE-EOT	−3.60 (−7.4, −0.3)	N/A	N/A
CE-TOC	N/A	−1.70 (−6.3, 2.8)[a]	−5.00 (−10.3, 0.1)
CE-FU (post hoc)	N/A	N/A	−2.90 (−7.8, 1.8)
ME-EOT	−4.80 (−9.3, −1.1)	N/A	N/A
ME-TOC	N/A	−3.60 (−8.9, 1.5)	−6.60 (−12.6, −0.9)
ME-FU (post hoc)	N/A	N/A	−5.00 (−10.7, 0.2)

Time to defervescence

Nearly 100 subjects in each treatment arm were febrile at baseline. The median time to defervescence as determined by using the Kaplan-Meier method was 5 days for subjects in both the eravacycline and ertapenem treatment groups (interquartile range: 3, 7 days for subjects in the eravacycline treatment group and 2, 7 days for subjects in the ertapenem treatment group).

Microbiological response

Microbiological response was largely derived from the clinical response because, as expected for a cIAI study, very few repeat cultures were performed. A clinical cure was a “presumed eradication” and therefore a favourable microbiological response. For example at the TOC visit all but one (of 192 subjects) in the eravacycline group and all but four (of 202 subjects) in the ertapenem group had a favourable microbiological response derived from clinical cure. The per-subject microbiological response at the TOC visit for the micro-ITT population is presented in the following table:

Table E6. Per-subject microbiological response at the TOC visit (micro-ITT population)

Visit	Per-subject Microbiological Responses	Eravacycline 1.0 mg/kg q12h n (%)		Ertapenem 1.0 g q24h n (%)
TOC	N1	220		226
	Favorable	192 (87.3)		202 (89.4)
	Difference (95% CI)		-2.1 (-8.2,3.9)	
	Eradicated	1 (0.5)		4 (1.8)
	Presumed eradicated	191 (86.8)		198 (87.6)
	Unfavorable	18 (8.2)		9 (4.0)
	Persistence	6 (2.7)		4 (1.8)
	Persistence with Decreased Susceptibility	1 (0.5)		0 (0.0)
	Presumed persistence	11 (5.0)		5 (2.2)
	Indeterminate	10 (4.5)		15 (6.6)

The pathogens present in the instances of persistence responses (TOC visit, ME population) were *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus durans*, *Clostridium perfringens*, *Haemophilus parainfluenzae*, and *Bacteroides ovatus*, and *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, *Streptococcus constellatus*, and *Streptococcus Group F* in the eravacycline and ertapenem groups, respectively.

The per-pathogen microbiological response (at least 10 subjects in either treatment group) is presented in the following table:

Table E7. Microbiological favourable response (at least 10 subjects in either treatment group) at the TOC visit by baseline pathogen (micro-ITT population)

Pathogen Type Pathogen	Eravacycline 1.0 mg/kg q12h (N = 220) n/N1 (%)	Ertapenem 1.0 g q24h (N = 226) n/N1 (%)
Gram-negative aerobes	159/182 (87.4)	166/186 (89.2)
Enterobacteriaceae	144/168 (85.7)	151/171 (88.3)
Escherichia coli	109/127 (85.8)	115/132 (87.1)
Klebsiella pneumoniae	17/18 (94.4)	19/23 (82.6)
Enterobacter cloacae	11/14 (78.6)	18/18 (100.0)
Proteus mirabilis	13/14 (92.9)	10/11 (90.9)
Citrobacter freundii	14/15 (93.3)	7/9 (77.8)
Klebsiella oxytoca	7/7 (100.0)	12/13 (92.3)
Gram-negative aerobes other than Enterobacteriaceae	39/44 (88.6)	33/34 (97.1)
Pseudomonas aeruginosa	15/18 (83.3)	19/20 (95.0)
Gram-positive aerobes	106/117 (90.6)	107/120 (89.2)
Streptococcus spp.	61/65 (93.8)	56/64 (87.5)
Streptococcus anginosus	26/29 (89.7)	10/12 (83.3)
Streptococcus constellatus	15/15 (100.0)	11/14 (78.6)
Streptococcus mitis	7/7 (100.0)	17/17 (100.0)
Enterococcus faecalis	16/23 (69.6)	22/26 (84.6)
Enterococcus faecium	13/16 (81.3)	26/30 (86.7)
Anaerobes	93/106 (87.7)	101/107 (94.4)
Bacteroides spp.	76/87 (87.4)	79/84 (94.0)
Bacteroides fragilis	40/44 (90.9)	41/42 (97.6)
Bacteroides thetaiotaomicron	25/26 (96.2)	17/20 (85.0)
Bacteroides ovatus	14/19 (73.7)	16/17 (94.1)
Bacteroides vulgatus	11/12 (91.7)	15/17 (88.2)

As can be noted, the percentage of favourable responses was relatively similar between treatment groups for most pathogens. The baseline pathogens in subjects where the incidence of favourable responses was >10% greater in the eravacycline treatment group compared to the ertapenem treatment group included *Streptococcus constellatus*, *C. freundii*, *K. pneumoniae*, and *B. thetaiotaomicron*. The baseline pathogens in subjects where the incidence of favourable responses was >10% less in the eravacycline treatment group compared to the ertapenem treatment group included *Enterobacter cloacae*, *B. ovatus*, *Enterococcus faecalis*, and *P. aeruginosa*.

The applicant stresses that a 100% favourable response was noted in subjects with baseline *Acinetobacter baumannii* in both treatment groups (8/8 and 5/5 in the eravacycline and ertapenem groups, respectively) at the TOC Visit. However, CHMP noted that the number was low and the role for

a specific pathogen in the individual case is difficult to judge since the majority of infections were polymicrobial and the outcome is not only dependent on antimicrobial chemotherapy but also surgery.

Subject	Pathogen at screening (intra-abdominal source unless otherwise commented)
1	*E. coli, P. aeruginosa, A. baumanii complex, B thetaiotoamicron*
2	*A. baumanii complex, S. aureus*
3	*A. baumanii complex*
4	*P. aeruginosa, A. baumanii complex, E. coli*
5	*E. coli, K.pneumoniae, A. baumanii complex, S. epidermidis, B. vulgatus*
6	*A. baumanii complex, E. faecalis*
7	*P. aeruginosa* (intra-abdominal and blood), *A. baumanii complex, E. faecalis*
8	*A. baumanii complex, E. faecium*

Subjects with bacteraemia at baseline had a high microbiological favourable response rate. There was one patient with an unfavourable response in each treatment group that both had *E. coli* isolated from the blood.

Favourable microbiological response rates by MIC to study drug received were also analysed in the micro-ITT population for the most frequently isolated pathogens. Overall, over the range of MICs observed, eravacycline had a high level of activity against the most frequently isolated pathogens.

The incidence of superinfection or new infection was low (3 or fewer subjects in each treatment group) and similar for the treatment groups in the micro-ITT population.

In subjects whose outcomes were classified as clinical failures and who underwent a second surgical procedure that allowed for repeated culture, the susceptibility to eravacycline of the pathogens isolated at the follow-up procedure was compared with the susceptibility of the original baseline pathogens.

Only one subject exhibited decreasing susceptibility. One subject was enrolled in the study with a diagnosis of a perforated intestine with intra-abdominal abscess. Baseline cultures grew *B. ovatus*, *B. vulgatus*, *Clostridium perfringens*, *E. coli* and *P. aeruginosa*. The patient was treated with 9 dose cycles of eravacycline with improvement. However, on study Day 7, the patient was diagnosed with a wound infection and dehiscence. The patient was assessed as a treatment failure, study drug was discontinued, and the patient underwent revision of the surgical wound. Repeat cultures grew *B. ovatus*, *Enterococcus faecalis* and *P. aeruginosa*. MICs to eravacycline for *B. ovatus* and *P. aeruginosa* increased from 0.03 at baseline to 0.12 µg/mL post-baseline and 2 at baseline to 8 µg/mL post-baseline, respectively. Tobramycin and amikacin were started. The patient subsequently had complete resolution of her cIAI and wound infection signs and symptoms.

Study TP-434-025 (IGNITE 4)

Methods

This was a phase 3, randomised, double-blind, double-dummy, multicentre study to evaluate the NI of eravacycline 1.0 mg/kg i.v. q12h to meropenem 1.0 g i.v. q8h in subjects with cIAI.

Study Participants

The inclusion and exclusion criteria used in study TP-434-025 were similar to those used in study TP-434-008.

The randomisation of patients with complicated appendicitis was capped to 50 % as compared to 30% in the previous study. CHMP noted that this was not in line with the antibacterial Addendum which states that the percentage of patients with complicated appendicitis should be limited to 30%. The percentage of patients having cIAI originating from complicated appendicitis is stated in Section 4.4 of the SmPC.

Treatments

Patients were randomized to receive either:

- Eravacycline 1.0 mg/kg, q12h or
- meropenem 1 mg, q8h (minimum four 24 hour dosing cycles).

As the efficacy of IV eravacycline for the treatment of cIAI was demonstrated in TP-434-008 study, the eravacycline 1.0 mg/kg every 12-hour dose (with no maximum dose) was selected for this study.

Objectives

The primary objective and secondary objectives are identical to those in Study TP-434-008.

Outcomes/endpoints

The primary endpoint was clinical response at TOC for the MITT and CE populations.

Secondary endpoints were Clinical response at the EOT, TOC and FU visits, and Microbiological response at the EOT and TOC visits.

Objectives and endpoints for efficacy are in line with what would be expected for a comparative study in patients with cIAI. The endpoints are identical to those in Study TP-434-008. The time points for the EOT, TOC and FU visits, were similar to the time points for the corresponding visits in Study TP-434-008.

Sample size

The sample size was based on the assumptions of clinical cure rates of 84% in the eravacycline group and 85% in the meropenem group in the MITT population and 89% in the eravacycline group and 90% in the meropenem group in the CE-TOC population, an NI margin of -12.5%, a one-sided alpha of 0.025, evaluability rates of 95% for the MITT population and 85% for the CE-TOC population, and the methodology of Farrington and Manning, there was more than 90% power in both the MITT population and the CE population to show non-inferiority with a sample size of 466 enrolled subjects (increased from 400 based on a pre-specified assessment of the actual number of subjects in the micro-ITT population following completion of the 250th subject using data blinded to treatment).

Randomisation

Subjects were assigned to receive eravacycline or meropenem in a 1:1 ratio with stratification by primary site of infection (complicated appendicitis versus all other cIAI diagnoses) via an Interactive Web-based Response System (IWRS). In Study TP-434-008, randomisation of subjects with complicated appendicitis was capped at 30%. This was increased to 50% in Study TP-434-025 as the results from Study TP-434-008 showed similar clinical cure rates in the eravacycline arm for subjects in the complicated appendicitis stratum and the "Other cIAI" stratum.

As it turned out (Study TP-434-025); the proportion of subjects diagnosed with complicated appendicitis was approximately 40% and (as expected) similar in both arms (see baseline characteristics below). In study TP-434-008 the corresponding proportion was approximately 27%. A percentage of 40% diagnosed with complicated appendicitis is not in line with the CHMP guideline where a cut-off of 30% for these infection types is recommended. Still, this patient population reflects what is commonly observed in clinical studies with cIAI, namely a dominance of patients with mild to moderately severe infections mainly originating from the appendix.

Blinding (masking)

This was a double-blind study. The two drugs required different infusion volumes and the dosing interval differed. The study was therefore designed using double-dummy methodology with eravacycline-matched placebo and meropenem-matched placebo to consist of sterile normal saline (0.9% NaCl). Both eravacycline and meropenem, when prepared for infusion, are coloured solutions, therefore coloured tubing and bag covers were also used. All solutions for infusion were to be prepared by an unblinded pharmacist or designee.

Statistical methods

For an overview of the analysis populations and categories of pathogens for the microbiological evaluation as well as the methods and analysis approach used, please see the Methods section in study TP-434-008.

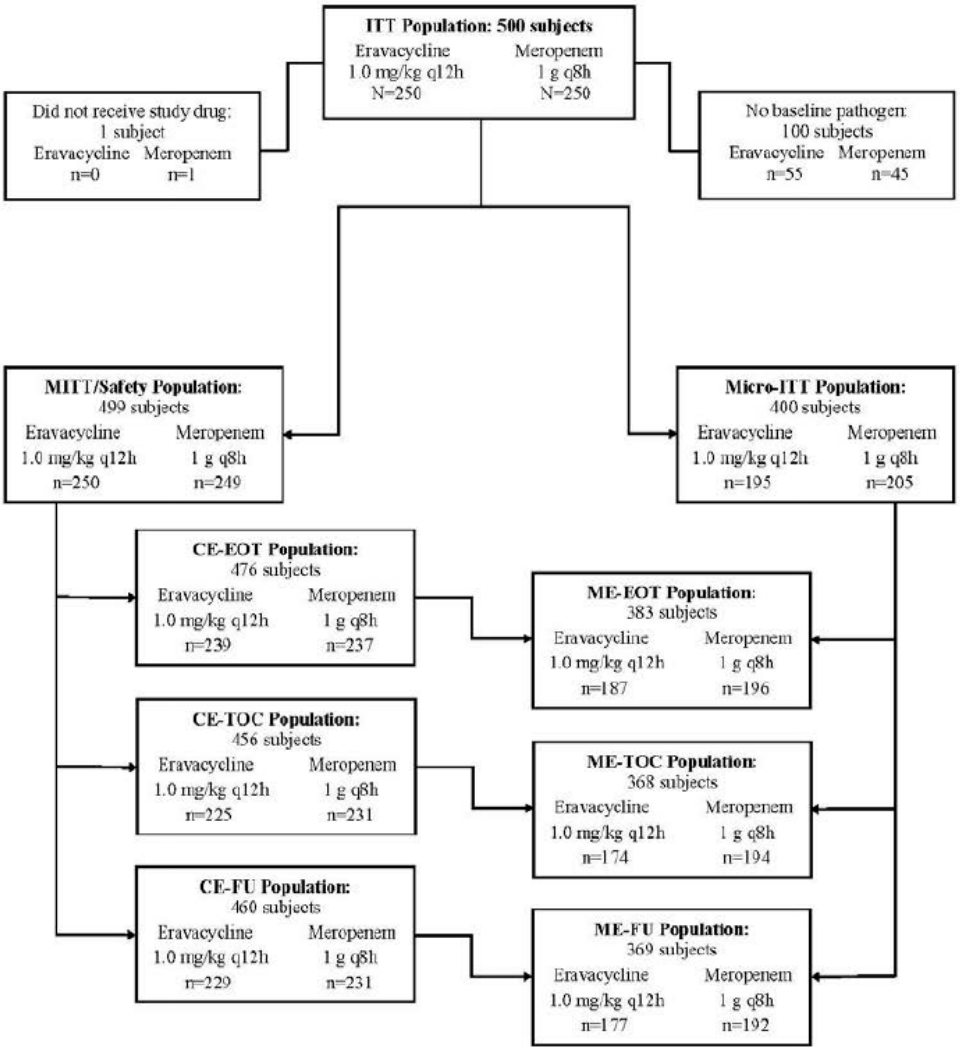
Results

Participant flow

A total of 500 subjects were randomly assigned to the eravacycline group (250 subjects) or the meropenem group (250 subjects). One subject in the meropenem group did not receive study drug because the subject withdrew from the study. This subject was not included in the Safety population or the MITT population.

The following figure shows the study analysis populations.

Fugure E2: Study analysis populations



Abbreviations: CE=clinically evaluable; EOT=End of Treatment; FU=Follow-up; ITT=intent-to-treat; ME=microbiologically evaluable; micro-ITT=microbiological intent-to-treat; MITT=modified intent-to-tre N=number of subjects in the ITT population; n=number of subjects in the subgroup or treatment group; q12h=every 12 hours; q8h=every 8 hours; TOC=Test of Cure.
Note: The Safety and MITT populations were identical.

The following table shows the subject disposition and reasons for both study withdrawal and study drug discontinuation for the ITT population.

Table E8 Subject disposition and reasons for study withdrawal and study drug discontinuation (ITT population)

	Number (%) of subjects	
	Eravacycline	**Meropenem**
Randomised	250 (100)	250 (100)
Randomised, not treated	0	1 (0.4)
Completed study	237 (94.8)	241 (96.4)

Not completed study	13 (5.2)	9 (3.6)
Reason for early termination		
Lost to follow-up	6 (2.4)	4 (1.6)
Adverse event	4 (1.6)	2 (0.8)
Withdrawal of consent	1 (0.4)	3 (1.2)
Noncompliance	2 (0.8)	0
Premature treatment discontinuation	10 (4.0)	8 (3.2)
Reason for premature treatment discontinuation		
Adverse event	3 (1.2)	5 (2.0)
Lack of efficacy	1 (0.4)	0
Noncompliance	1 (0.4)	0
Withdrawal of consent	2 (0.8)	3 (1.2)
Investigator request	2 (0.8)	0
Other	1 (0.4)	0

Compliance and exposure to study drugs

- The mean (±SD) percent compliance was 99.82 % ± 1.460 for the eravacycline group and 99.87% ± 1.057 for the meropenem group.
- All subjects achieved ≥80% compliance.
- The mean duration of treatment was 7.2 days ± 2.74 days in the eravacycline group and 7.5 days ±2.95 days in the meropenem group.
- The mean number of active doses administered was 12.7 ± 5.35 in the eravacycline group and 19.8 ±8.57 in the meropenem group, consistent with the planned dosing regimens.

Prior and concomitant exposure to other antibiotics

Approximately half of the subjects in the micro-ITT population used systemic antibacterial medication prior to the first dose of study drug and the incidence was similar between the treatment groups (54.4% vs. 49.3% for eravacycline and meropenem groups, respectively). The most frequently used systemic antibacterial medications prior to the first dose of study drug were imidazole derivatives, combinations of penicillins and third-generation cephalosporins.

Concomitant systemic antibacterial medications use from the first dose of study drug through the TOC Visit in the MITT population was 8.0% of subjects in the eravacycline treatment group and 21 8.4% of subjects in the meropenem treatment group.

The most frequently used systemic antibacterial medications after the first dose of study drug were imidazole derivatives, combinations of penicillin including beta-lactamase inhibitors and carbapenems.

Recruitment

The study was conducted between 13 October 2016 and 19 May 2017. The study included 65 clinical sites in 11 countries. The majority of subjects (348 of 500) were enrolled in Eastern Europe. No site enrolled more than 35 subjects.

Conduct of the study

There was one amendment to the original study protocol. Changes to the protocol included two clarification letters regarding the inclusion criterion one and the increase in planned enrolment for the study. Further administrative changes and clarifications were introduced.

There were 161 [64%] subjects in the eravacycline treatment group and 143 [57%] subjects in the meropenem treatment group who had at least 1 *protocol deviation*. The most frequently reported major protocol deviation in either group was incomplete or out-of-window subject visit (11 [4%] subjects in the eravacycline treatment group and 10 [4%] subjects in the meropenem treatment group). The number of patients having major protocol deviations was, in general, similar between the two treatment groups and is considered not to have had any major influence on the overall conclusion on benefit-risk of eravacycline.

Baseline data

The demographics and baseline characteristics in the MITT population are shown in the following table:

Table E9 Demographics and baseline characteristics (MITT-population)

Parameter	**Eravacycline n=250**	**Meropenem n=249**
Gender, n (%)		
Male	139 (55.6)	129 (51.8)
Female	111 (44.4)	120 (48.2)
Race, n (%)		
Caucasian/White	249 (99.6)	249 (100.0)
Other	1 (0.4)	0
Age (y), mean (SD)	52.1 (17.7)	52.8(18.2)
Age group, n (%)		
<65 years	180 (72.0)	174 (69.9)
65-75 years	50 (20.0)	48 (19.3)
>75 years	20 (8.0)	27 (10.8)
BMI (kg/m^2), mean (SD)	27.6 (5.5)	27.1 (4.9)
APACHE II score, mean (SD)	6.6 (3.6)	6.5 (4.1)
APACHE II score, by numerical category		
0-10	220 (88.0)	210 (84.3)
11-15	27 (10.8)	31 (12.4)
>15	3 (1.2)	8 (3.2)
Site of infection, n (%)(randomization)		
Complicated appendicitis	100 (40.0)	99 (39.8)
Other cIAI	150 (60.0)	150 (60.2)
Diagnosed intra-/postop n (%)	240 (96.0)	238 (95.6)
Intra-abdominal abscess	154 (64.2)	136 (57.1)
Complicated appendicitis	98 (40.8)	100 (42.0)
Intestinal perforation	16 (6.7)	19 (7.9)
Gastric/duodenal perforation	25 (10.4)	26 (10.9)
Peritonitis	125 (52.1)	116 (48.7)
Complicated cholecystitis	61 (25.4))	58 (24.4)

In general there were no major differences between groups with concern to baseline characteristics. However, in the meropenem treated group there was a slightly larger proportion of patients > 75 years (n=20 (10.8%) vs. n= 27 (8.0%) and with APACHE II score >15 (n=8 (3.2%) vs. n=3 (1.2%). The number of patients in each group having baseline blood culture that grew at least one pathogen known

to cause cIAI were similar to what was seen in Study TP-434-008 (16 [8.2%] subjects in the eravacycline group and 15 [7.3%] subjects in the meropenem group, respectively).

Approximately 40% in both groups had complicated appendicitis (capped at 50%) with other dominating diagnoses being intra-abdominal abscess and peritonitis.

Baseline microbiology

All subjects in the micro-ITT population had a baseline intra-abdominal specimen, and all but one subject had baseline blood culture samples. The majority of the intra-abdominal specimens had confirmed bacterial growth on culture (>99% of subjects in both treatment groups).

In the eravacycline group there were 75 % of subjects with polymicrobial infections. The corresponding figure in the meropenem treatment group was 65 %.

Gram-negative aerobes were isolated from 158 [81.0%] eravacycline vs. 166 [81.0%] meropenem treated patients, respectively. The corresponding figures for Gram-positive aerobes were 122 [62.6%) vs. 107 [52.2%] and for anaerobes 110 [56.4%] vs. 111 [44.1%].

Pathogens belonging to Enterobacteriaceae were most frequently isolated (146 [74.9%] vs. 154 [75.1%]) with *E. coli* being the most commonly isolated species (126 [64.6%] vs. 134 [65.4%]) for eravacycline and meropenem patients, respectively.

Approximately 17% of the blood cultures in the eravacycline group and 15% in the meropenem group had confirmed growth. The pathogens isolated from blood were similar to those isolated from intra-/extra-abdominal cultures.

Numbers analysed

A summary of analysis populations and numbers analysed is shown below:

Table E10 Analysis populations

Analysis population	Eravacycline, n (%)	Meropenem, n (%)
ITT	250 (100)	250 (100)
MITT	250 (100)	249 (99.6)
Micro-ITT	195 (78.0)	205 (82.0)
CE-EOT	239 (95.6)	237 (94.8)
CE-TOC	225 (90.0)	231 (92.4)
ME-EOT	187 (74.8)	196 (78.4)
ME-TOC	174 (69.6)	194 (77.6)

Outcomes and estimation

Table E11 Primary efficacy analysis: Clinical response at TOC for the MITT and CE populations

Efficacy measure	Eravacycline 1.0 mg/kg q12h n (%)	Meropenem 1.0 g q8h (n (%)
MITT population	250	249
Clinical cure	231 (92.4)	228 (91.6)
Treatment difference (95% CI)	0.8 (-4.1, 5.8)	
Clinical failure	7 (2.8)	9 (3.6)
Indeterminate/missing	12 (4.8)	12 (4.8)
CE population	225	231

Efficacy measure	Eravacycline 1.0 mg/kg q12h n (%)	Meropenem 1.0 g q8h (n (%)
Clinical cure	218 (96.9)	222 (96.1)
Treatment difference (95% CI)	0.8 (-2.9, 4.5)	
Clinical failure	7 (3.1)	9 (3.9)

The most frequent reasons for clinical failure in both populations and in both treatment groups were initiation of rescue antibacterial therapy for cIAI and unplanned surgical procedure or percutaneous drainage procedure.

The primary analysis show statistical non-inferiority of eravacycline as compared with meropenem in the treatment of cIAI in both the MITT and the CE populations at the TOC visit.

Secondary Efficacy analysis- Clinical response

Clinical response was evaluated at the EOT, TOC, and Follow-up Visits in the ITT, MITT, micro-ITT, CE-EOT (or TOC), and ME-EOT (or TOC) populations. The differences in clinical cure rates are summarised in the following table.

Table E12 Difference in Clinical Cure Rates Between Eravacycline-treated Subjects and Meropenem-treated Subjects by Analysis Population by Visit

Analysis Population	Study Visit		
	EOT Difference (95% CI)[a]	TOC Difference (95% CI)	FU Difference (95% CI)[a]
ITT	0.4 (-4.0, 4.8)	1.2 (-3.7, 6.2)[a]	-0.8 (-6.2, 4.6)
MITT	0.0 (-4.3, 4.4)	0.8 (-4.1, 5.8)[b]	-1.2 (-6.5, 4.2)
Micro-ITT	-1.3 (-6.5, 3.7)	-0.5 (-6.3, 5.3)[a]	-3.1 (-9.5, 3.2)
CE-EOT	-1.7 (-4.8, 1.1)	NA	NA
CE-TOC	NA	0.8 (-2.9, 4.5)[b]	NA
CE-FU	NA	NA	0.4 (-3.5, 4.3)
ME-EOT	-2.2 (-6.2, 1.2)	NA	NA
ME-TOC	NA	-0.4 (-4.9, 3.8)[a]	NA
ME-FU	NA	NA	-0.9 (-5.7, 3.6)

CE = clinically evaluable; CI = confidence interval; EMA = European Medicines Agency; EOT = End of Treatment; FDA = Food and Drug Administration; FU = Follow-up; ITT = intent-to-treat; ME = microbiologically evaluable; micro-ITT = microbiological intent-to-treat; MITT = modified intent-to-treat; NA = not applicable; SAC = Surgical Adjudication Committee; TOC = test of cure.

Notes: Difference = difference in clinical success rates (eravacycline minus meropenem).

a. CIs were calculated using the unadjusted Miettinen-Nurminen method (Miettinen and Nurminen, 1985).

b. CIs were calculated using the adjusted Miettinen-Nurminen method.

Clinical response was based on the SAC assessment (if available). The primary endpoint was assessed in the micro-ITT population for the FDA and the co-primary endpoints were assessed in the MITT and CE-TOC populations for the EMA.

The results of the secondary analyses were supportive of the primary analysis in that non-inferiority is shown at EOT, TOC and FU visits in the populations analysed.

Secondary Efficacy Analysis-Microbiological response

At the EOT visit, 183 (93.8%) of subjects in the eravacycline treatment group and 192 (93.7%) of meropenem subjects in the micro-ITT population had favorable per-subject microbiological responses. Of the subjects in the micro-ITT population with favorable responses, 179 (91.8%) subjects in the eravacycline group and 187 (91.2%) subjects in the meropenem group had presumed eradicated responses. The 5 (2.6%) subjects in the eravacycline group and the 6 (2.9%) subjects in the meropenem group with unfavorable microbiological responses had responses of persistence. Seven subjects in each treatment group had an indeterminate microbiological response.

Table E13 Per-Subject Microbiological Response at the EOT and TOC Visits (Micro-ITT Population)

Visit	Per-Subject Microbiological Response	1.0 mg/kg q12h n (%)		1 g q8h n (%)
EOT	N1	195		205
	Favorable	183 (93.8)		192 (93.7)
	Difference (95% CI) [1]		0.2 (-4.9, 5.2)	
	Eradicated	4 (2.1)		5 (2.4)
	Presumed eradicated	179 (91.8)		187 (91.2)
	Unfavorable	5 (2.6)		6 (2.9)
	Persistence	3 (1.5)		3 (1.5)
	Persistence with decreased susceptibility	0		0
	Presumed persistence	2 (1.0)		3 (1.5)
	Indeterminate	7 (3.6)		7 (3.4)
TOC	N1	195		205
	Favorable	179 (91.8)		189 (92.2)
	Difference (95% CI) [1]		-0.4 (-6.0, 5.1)	
	Eradicated	4 (2.1)		6 (2.9)
	Presumed eradicated	175 (89.7)		183 (89.3)
	Unfavorable	6 (3.1)		7 (3.4)
	Persistence	3 (1.5)		4 (2.0)
	Persistence with decreased susceptibility	1 (0.5)		0
	Presumed persistence	2 (1.0)		3 (1.5)
	Indeterminate	10 (5.1)		9 (4.4)

Note: N1 = Number of subjects in the Micro-ITT population. n = Number of subjects in specific category. Percentages calculated as 100x(n/N1).
Difference = Difference in Microbiological favorable response rates (Eravacycline minus Meropenem). TOC = Test of Cure.
EOT = End of Therapy.
[1] Confidence interval is calculated using the unadjusted Miettenin-Nurminen method.

Table E14 Microbiological Favorable Response (At Least 10 Subjects in Either Treatment Group) at the TOC Visit by Baseline Pathogen, micro-ITT Population

Pathogen Type Pathogen	Eravacycline 1.0 mg/kg q12h (N = 195) n/N1 (%)	Meropenem 1 g q8h (N = 205) n/N1 (%)
Gram-negative aerobes	145/158 (91.8)	156/166 (94.0)
Enterobacteriaceae	133/146 (91.1)	145/154 (94.2)
Escherichia coli	114/126 (90.5)	128/134 (95.5)
Klebsiella pneumoniae	21/21 (100.0)	24/27 (88.9)
Non-Enterobacteriaceae	37/38 (97.4)	29/30 (96.7)
Pseudomonas aeruginosa	18/19 (94.7)	19/20 (95.0)
Gram-positive aerobes	109/122 (89.3)	101/107 (94.4)
Enterococcus avium	10/11 (90.9)	9/10 (90.0)
Enterococcus faecalis	29/31 (93.5)	27/28 (96.4)
Enterococcus faecium	26/29 (89.7)	22/23 (95.7)
Staphylococcus aureus	16/16 (100.0)	8/8 (100.0)
MSSA	15/15 (100.0)	8/8 (100.0)
Streptococcus spp	52/60 (86.7)	47/50 (94.0)
Streptococcus viridans group	50/57 (87.7)	41/44 (93.2)
Streptococcus anginosus group	39/45 (86.7)	32/33 (97.0)
Streptococcus anginosus	25/29 (86.2)	22/22 (100.0)
Streptococcus constellatus	13/15 (86.7)	10/11 (90.9)
Streptococcus mitis group	13/14 (92.9)	11/12 (91.7)
Anaerobes	100/110 (90.9)	105/111 (94.6)
Bacteroides spp	84/94 (89.4)	83/88 (94.3)
Bacteroides fragilis	34/40 (85.0)	36/38 (94.7)
Bacteroides ovatus	19/24 (79.2)	28/28 (100.0)
Bacteroides thetaiotaomicron	28/30 (93.3)	30/33 (90.9)
Bacteroides uniformis	14/16 (87.5)	14/14 (100.0)
Bacteroides vulgatus	27/28 (96.4)	23/23 (100.0)
Clostridium perfringens	7/7 (100.0)	12/12 (100.0)
*Parabacteroides (*previously *Bacteroides) distasonis*	16/16 (100.0)	9/9 (100.0)

Abbreviations: micro-ITT=microbiological intent-to-treat; MRSA=methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-susceptible *Staphylococcus aureus*; N=number of subjects in the micro-ITT population; N1=number of subjects with the specified baseline pathogen; n=number of subjects within a specific category; q12h=every 12 hours; q8h=every 8 hours; TOC=Test of Cure.

Notes: Percentages were calculated as 100 × (n/N1). Subjects with the same pathogen from more than 1 specimen were counted only once for that pathogen. Subjects were counted only once in the overall tabulation of Gram-negative aerobes, Gram-positive aerobes, and Gram-positive anaerobes. Subjects were counted only once for the overall tabulation of Enterobacteriaceae, non-Enterobacteriaceae, *Streptococcus* spp, within each subcategory of *Streptococcus* spp, and within each subcategory of anaerobic species. Subjects with both MRSA and MSSA were counted once in the overall tabulation for *Staphylococcus aureus*.

The percentage of favourable responses was generally similar between treatment groups for most pathogens. It is noted that in the previous Study TP-434-008, the response rate was particularly low in the eravacycline group for *Enterococcus faecalis* (69.6%), while in the current study the response rate was > 90%.

The baseline pathogens in subjects where the incidence of favourable responses was >10% greater in the eravacycline treatment group compared to the meropenem treatment group included *Klebsiella pneumoniae.* The baseline pathogens in subjects where the incidence of favourable responses was >10% less in the eravacycline treatment group compared to the meropenem treatment group included *Streptococcus anginosus* group, *Bacteroides ovatus* and *Bacteroides uniformis.*

The response rate in subjects with baseline *A. baumannii* was 100% in both treatment groups (5/5 and 2/2 in the eravacycline and meropenem groups, respectively) at the TOC visit. However, the numbers of *Acinetobacter baumannii* included in the clinical trials were too low to convincingly claim efficacy against this microbe.

Subjects with bacteraemia at baseline had high microbiological favourable response rates in both treatment groups. All subjects in the eravacycline group and all but one subject in the meropenem group had a favourable microbiological response at the TOC Visit.

Microbiologic favourable response rates by MIC were analysed in the micro-ITT population for the most frequently isolated pathogens. Overall, over the range of MIC values observed, eravacycline had a high level of activity against the most frequently isolated pathogens.

The incidences of superinfection and decreasing susceptibility were low. One subject had superinfection and one subject had decreasing susceptibility at the TOC Visit; both subjects were in the eravacycline group. No subjects reported a new infection.

As also observed in Study TP-434-008, the portion of cIAI patients being infected by multidrug resistant pathogens such as ESBL, AmpC β-lactamase- and carbapenemase-producing gram-negative aerobic pathogens were too low in both treatment groups to be able to draw any conclusions.

Sensitivity analyses

Sensitivity analyses of the primary outcome were conducted for the MITT population. The results of the sensitivity analyses were supportive of the primary analysis results.

Clinical response by primary disease diagnosis

Clinical response at the TOC Visit for subjects in the MITT and CE populations were analysed by primary disease diagnosis. Clinical response was observed to a similar extent in subgroups with complicated appendicitis or other cIAI.

Clinical response by geographic region or country

The differences in clinical success rates varied by geographic region, but the varying sizes of the geographic subgroups made direct comparisons difficult.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Title: A phase 3, randomised, double-blind, double-dummy, multicentre prospective study to assess the efficacy and safety of eravacycline compared with ertapenem in complicated intra-abdominal infections			
Study identifier	TP-434-008 EUDRA CT number: 2013-001913-34		
Design	This was a Phase 3, randomised, double-blind, double-dummy, multicenter, prospective study to assess the efficacy, safety, and PK of eravacycline compared with ertapenem in adults with complicated intra-abdominal infections (cIAIs). Qualified subjects enrolled in the study were randomised to 1 of 2 treatment groups, eravacycline 1.0 mg/kg every 12 hours (q12h), or ertapenem 1 g every 24 hours (q24h), in a 1:1 ratio. Randomisation was stratified based on the primary site of infection (complicated appendicitis versus all other diagnoses).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Day 1 to day 50 including treatment phase, EOT visit, TOC visit (day 25-31)and FU visit (day 38-50) Not applicable Not applicable
Hypothesis	Non-inferiority		
Treatments groups	Eravacycline		Eravacycline 1.0 mg/kg q12h for a maximum of 14 days, 270 subjects randomised
	Ertapenem		Ertapenem 1.0 g q24h for a maximum of 14 days, 271 subjects randomised
Endpoints and definitions	Co-Primary endpoints	Clinical response in the MITT and CE populations at the TOC Visit	The primary objective was to compare clinical response between the eravacycline and ertapenem arms at the TOC Visit in the modified ITT (MITT) and clinically evaluable (CE) populations.

Results and Analysis

Analysis description	**Co-Primary Analysis – Clinical response (MITT)**		
Analysis population and time point description	Modified Intent to treat population = all randomised subjects who received any amount of study drug TOC-visit = day 25-31		
Descriptive statistics and estimate variability	Treatment group	Eravacycline	Ertapenem
	Number of subject	270	268
	Clinical cure, n (%)	235 (87.0)	238 (88.8)
	Treatment difference (99% CI)	-1.80 (-9.2, 5.6)	
	Clinical failure, n (%)	19 (7.0)	15 (5.6)
	Indeterminate/missing, n (%)	16 (5.9)	15 (5.6)

Analysis description	**Co-Primary Analysis – Clinical response (CE)**		
Analysis population and time point description	CE population = all subjects who met the definition for the ITT population and had no major protocol deviations TOC-visit = day 25-31		
Descriptive statistics and estimate variability	Treatment group	Eravacycline	Ertapenem
	Number of subject	239	238
	Clinical cure, n (%)	222 (92.9)	225 (94.5)
	Treatment difference (99% CI)	-1.70 (-7.9, 4.4)	
	Clinical failure, n (%)	17 (7.1)	13 (5.5)
Notes			

Title: A phase 3, randomised, double-blind, double-dummy, multicentre prospective study to assess the efficacy and safety of eravacycline compared with meropenem in complicated intra-abdominal infections			
Study identifier	TP-434-025 EUDRA CT number: 2016-002208-21		
Design	This was a Phase 3, randomised, double-blind, double-dummy, multicenter, prospective study to assess the efficacy, safety, and PK of eravacycline compared with meropenem in adults with complicated intra-abdominal infections (cIAIs). Qualified subjects enrolled in the study were randomised to 1 of 2 treatment groups, eravacycline 1.0 mg/kg every 12 hours (q12h), or meropenem 1 g every 8 hours (q8h), in a 1:1 ratio. Randomization was stratified based on primary site of infection (ie, complicated appendicitis versus all other cIAI diagnoses).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Day 1 to day 50 including treatment phase, EOT visit, TOC visit (day 25-31)and FU visit (day 38-50) Not applicable Not applicable
Hypothesis	Non-inferiority		
Treatments groups	Eravacycline		Eravacycline 1.0 mg/kg q12h for a maximum of 14 days, 250 subjects randomised
	Meropenem		Meropenem 1.0 g q8h for a maximum of 14 days, 250 subjects randomised
Endpoints and definitions	Co-Primary endpoints	Clinical response in the MITT and CE populations at the TOC Visit	The primary objective was to compare clinical response between the eravacycline and meropenem arms at the TOC Visit in the modified ITT (MITT) and clinically evaluable (CE) populations.
Results and Analysis			

Analysis description	**Co-Primary Analysis – Clinical response (MITT)**		
Analysis population and time point description	Modified Intent to treat population = all randomised subjects who received any amount of study drug TOC-visit = day 25-31		
Descriptive statistics and estimate variability	Treatment group	Eravacycline	Meropenem
	Number of subject	250	249
	Clinical cure, n (%)	231 (92.4)	228 (91.6)
	Treatment difference (95% CI)	0.8 (-4.1, 5.8)	
	Clinical failure, n (%)	7 (2.8)	9 (3.6)
	Indeterminate/missing, n (%)	12 (4.8)	12 (4.8)
Analysis description	**Co-Primary Analysis – Clinical response (CE)**		
Analysis population and time point description	CE population = all subjects who met the definition for the ITT population and had no major protocol deviations TOC-visit = day 25-31		
Descriptive statistics and estimate variability	Treatment group	Eravacycline	Meropenem
	Number of subject	225	231
	Clinical cure, n (%)	218 (96.9)	222 (96.1)
	Treatment difference (95% CI)	0.8 (-2.9, 4.5)	
	Clinical failure, n (%)	7 (3.1)	9 (3.9)

Analysis performed across trials (pooled analyses and meta-analysis)

Table E15 Clinical Response at the Test of Cure Visit – Pivotal Phase 3 Studies and Pooled Analysis, MITT and CE Populations (EMA Co-Primary Endpoints)

Efficacy Measure	TP-434-008		TP-434-025		Pooled	
	ERV 1.0 mg/kg q12h n (%)	ERT 1 g q24h n (%)	ERV 1.0 mg/kg q12h n (%)	MER 1 g q8h n (%)	ERV 1.0 mg/kg q12h n (%)	Comparators n (%)
MITT population	270	268	250	249	520	517
Clinical cure	235 (87.0)	238 (88.8)	231 (92.4)	228 (91.6)	466 (89.6)	466 (90.1)
Treatment Difference (CI)[a]	-1.8 (-7.4, 3.8)		0.8 (-4.1, 5.8)		-0.5 (-4.2, 3.2)	
Clinical failure	19 (7.0)	15 (5.6)	7 (2.8)	9 (3.6)	26 (5.0)	24 (4.6)
Indeterminate/missing	16 (5.9)	15 (5.6)	12 (4.8)	12 (4.8)	28 (5.4)	27 (5.2)
CE population	239	238	225	231	464	469
Clinical cure	222 (92.9)	225 (94.5)	218 (96.9)	222 (96.1)	440 (94.8)	447 (95.3)
Treatment Difference (CI)[a]	-1.7 (-6.3, 2.8)		0.8 (-2.9, 4.5)		-0.5 (-3.4, 2.4)	
Clinical failure	17 (7.1)	13 (5.5)	7 (3.1)	9 (3.9)	24 (5.2)	22 (4.7)

CE = all subjects who met the definition for the ITT population and had no major protocol deviations as defined in the Statistical Analysis Plan; CI = confidence interval; EMA = European Medicines Agency; ERV = eravacycline; ETP = ertapenem; MER = meropenem; MITT = all randomised subjects who received any amount of study drug; n = number of subjects with the specific response; q8h = every 8 hours; q12h = every 12 hours; q24h = every 24 hours.

Percentages are calculated as 100 x (n/N). Clinical response is based on the Surgical Adjudication Committee assessment (if available).

a. Difference = Difference in clinical cure rates (Eravacycline minus Comparator). 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 studies in special populations

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Active Controlled Trials	200/1184	117/1184	11/1184
Placebo Controlled Trials	1/424	0/424	0/424
Non Controlled trials	0/20	0/20	0/20

Supportive study

TP-434-P2-cIAI-1

This was a phase 2, randomised (2:2:1), double-blind, double-dummy, multicentre study comparing two regimens of eravacycline (1.5 mg/kg q24h and 1.0 mg/kg i.v. q12h) with ertapenem (1.0 g i.v. q24h) in subjects with community-acquired cIAI. Randomisation was stratified based on primary site of infection (complicated appendicitis vs. other sites of cIAI). There was an enrolment cap of 50% complicated appendicitis.

The study population included men and women 18 to 75 years of age. Eligible subjects had a diagnosis of CA-cIAI requiring urgent surgical or percutaneous intervention and not expected to require antibacterial therapy for longer than 14 days. Patients with pathogens resistant to one of the studied drugs, with APACHE score >25, or renal failure were excluded from the study.

Subjects were treated for 4 to a maximum of 14 days and remained hospitalised for the complete course of the treatment. TOC evaluations occurred 10 to 14 days after the last dose and a follow-up visit occurred 28 to 42 days after the last dose.

The primary endpoint was clinical response at the TOC visit in the microbiologically evaluable (ME) population. Clinical response at the TOC visit in the MITT and CE populations were evaluated as secondary endpoints.

A total of 143 subjects from 40 sites in six countries (four countries in Eastern Europe, India and the US) were enrolled and included in the analyses.

Table E16. Subject disposition (ITT population)

Parameter	ERV 1.5 mg/kg q24h N (%)	ERV 1.0 mg/kg q12h N (%)	Ertapenem N (%)
Sample Size	56	57	30
Did not receive study drug	2	1	1
Completer Status			
Completed treatment[a]	52 (96.3)	53 (94.6)	27 (93.1)
Discontinued treatment prematurely[a]	2 (3.7)	3 (5.4)	2 (6.9)
Completed the study[a,b]	44 (81.5)	49 (87.5)	26 (89.7)
Did not complete the study[a,b]	10 (18.5)	7 (12.5)	3 (10.3)
Primary Reason for Discontinuing Study Drug Prematurely[a]			
Adverse Event	2 (3.7)	0	2 (6.9)
Withdrawal of Consent	0	3 (5.4)	0
Primary Reason for Early Study Termination[a]			
Lost to Follow-up	5 (9.3)	3 (5.4)	2 (6.9)
Withdrawal of Consent	0	4 (7.1)	0
Physician decision	1 (1.9)	0	1 (3.4)
Other[c]	4 (7.5)	0	0
Subject Stratification by Diagnosis at Entry			
Complicated appendicitis	30 (53.5)	31 (54.4)	15 (50.0)
Other diagnosis[d]	26 (46.4)	26 (45.6)	14 (46.7)

Parameter	ERV 1.5 mg/kg q24h N (%)	ERV 1.0 mg/kg q12h N (%)	Ertapenem N (%)
Missing	0	0	1 (3.3)

The mean duration of treatment was 6.7, 6.3 and 6.2 days, respectively.

Demographic and baseline characteristics were generally similar across the 3 treatment groups. The majority of subjects were male (72.0%) and Caucasian (68.5%). The overall mean (standard deviation [SD]) age was 42.6 (17.64) years, with the majority of subjects (86.7%) under 65 years of age. Median body weight was 70.0 kg for all 3 treatment groups.

A total of 119 subjects in the m-MITT population had at least one intra-abdominal pathogen identified at baseline; a total of 212 baseline isolates were collected. Gram-negative aerobes were identified at baseline in 84.0% of subjects, Gram positive aerobes in 36.1%, Gram-negative anaerobes in 10.9%, and Gram-positive anaerobes in 4.2%. The most frequently isolated Gram-negative pathogen was *E. coli* (65.5% of subjects). *Enterococcus faecalis* (6.7% of subjects) was the most frequently identified Gram-positive aerobe, while *B. fragilis* (5.0% of subjects) was the most frequently isolated Gram-negative anaerobe.

The clinical response at the TOC visit in the ME (primary analysis population), CE and MITT (secondary analysis populations) populations are shown in the following table.

Table E17. Clinical response at the TOC visit ME, CE and ITT populations

Clinical Response	Eravacycline 1.5 mg/kg q24h	Eravacycline 1.0 mg/kg q12h	Ertapenem 1.0 g q24h
ME population			
Overall n	42	41	26
Cure n (%)	39 (92.9)	41 (100)	24 (92.3)
Failure n (%)	3 (7.1)	0	2 (7.7)
CE population			
Overall n	49	48	28
Cure n (%)	46 (93.9)	47 (97.9)	26 (92.9)
Failure n (%)	3 (6.1)	1 (2.1)	2 (7.1)
MITT population			
Overall n	54	56	29
Cure n (%)	46 (85.2)	47 (83.9)	26 (89.7)
Failure n (%)	3 (5.6)	1 (1.8)	2 (6.9)
Indeterminate n (%)	5 (9.3)	8 (14.3)	1 (3.4)

The clinical cure rate was comparable for all treatment arms and analysis populations. The number of clinical failures was low. Reasons for the response of failure included persisting or recurrent infection, concomitant antibacterial therapy, and postsurgical wound infection in the eravacycline groups, and concomitant antibacterial therapy and persisting or recurrent infection in the ertapenem group. In the MITT population the number with a clinical response of indeterminate was higher in the eravacycline groups. Reasons for the response of indeterminate included assessment not available, prophylactic antibiotics, consent withdrawn, response imputed, and death not due to IAI.

The microbiological response followed the results of the clinical response. For the subjects with unfavourable microbiological response the outcome was deemed presumed persistence.

2.5.2. Discussion on clinical efficacy

The efficacy of eravacycline in the treatment of adults with cIAI has been assessed in one Phase 2 study (TP-434-P2-cIAI-1) comparing two i.v. regimens of eravacycline with ertapenem and in two Phase 3 studies (TP-434-008 and TP-434-025) comparing one i.v. regimen of eravacycline with ertapenem or meropenem, respectively.

Design and conduct of clinical studies

The main studies (TP-434-008 [IGNITE 1] and TP-434-025 [IGNITE 4) were randomised, double-blind, double-dummy, multicentre studies to evaluate the NI of eravacycline 1.0 mg/kg i.v. q12h to ertapenem 1.0 g i.v. q24h or meropenem 1g i.v. q8h in subjects with cIAI. Adult patients hospitalised with cIAI including intraabdominal abscess or peritonitis in the need for acute surgical or percutaneous intervention and at least one symptom of systemic inflammatory response were included. Subjects with most severe infections including those with septic shock were excluded from the studies. Patients with renal failure, significant hepatic disease or immunocompromised patients were furthermore excluded. The inclusion/exclusion criteria were considered acceptable by CHMP. However, CHMP agreed that the important limitations of the clinical data are presented in section 4.4 of the Xerava product information. Patients with creatinine clearance < 30 ml/min were initially excluded, however, the study protocol for study TP-434-008 was amended in 2013 to exclude only patients with creatinine clearance < 50 ml/min. Considering that for many acute severe infections, GFR will be low secondary to sepsis and hypovolemia, excluding patients with CrCl < 50 ml/min will lead to a selection of less ill patients. The applicant has clarified that the exclusion criteria: creatinine clearance cut-off was raised from 30 ml/min to 50 mL/min due to the lack of eravacycline PK data in subjects with renal impairment. By the time these data became available, it was considered that the enrolment of patients with creatinine clearance cut-off of 50 ml/min would be almost finalised before a protocol amendment would be approved, which is considered acceptable. Creatinine clearance < 50 ml/min was used as an exclusion criterion in study TP-434-025.

With regard to patients with severe renal impairment, data is limited and the limitation is reflected in the Xerava SmPC section 5.2.

It should be noted that ertapenem is not recommended for patients with severe renal impairment because of lack of data. Although the study could include severe cases of cIAI the majority of patients had low APACHE II scores and ertapenem and therapy resulted in a high clinical success rate. Therefore the choice of ertapenem as comparator is considered acceptable by CHMP. In the second pivotal study TP-343-025, meropenem was used as the comparator with dosing in accordance with recommendations. Meropenem is recommended for the treatment of more severe cases and cases of health-care associated infections. Meropenem is considered an appropriate comparator by CHMP, although also in this study the majority of patients had low APACHE II scores.

The dose of eravacycline chosen for the phase 3 study is discussed in the pharmacodynamics section of this report, and some questions were raised on the sufficiency to cover the range of target pathogens. However, CHMP considered that data from the two pivotal studies showed high clinical and microbiological cure rates for patients treated with eravacycline with the proposed dose.

The primary objective of the pivotal studies was to compare the clinical response at the TOC Visit for subjects in the two treatment groups. The primary endpoint for efficacy was the clinical response at

the TOC Visit for the MITT and CE-EOT populations. CHMP agreed that objectives and endpoints for efficacy are in line with what would be expected for a comparative study in patients with cIAI.

Sample size considerations were deemed adequate. The studies were of non-inferiority design with a NI margin of -12.5%, which is in accordance with recommendations in the CHMP guideline. Study TP-343-008 was designed using a 1-sided alpha of 0.005, in line with CHMP expectations for cIAI studies when a single pivotal study is conducted (i.e. two-sided 0.01). The second cIAI study (i.e. TP-343-025) was designed using a conventional significance level (i.e. when non-inferiority and one-sided; 0.025).

Subjects were randomised to eravacycline or ertapenem or to eravacycline or meropenem in a 1:1 ratio, with stratification by primary site of infection (complicated appendicitis versus all other cIAI diagnoses). Initially an enrolment cap of approximately 50% complicated appendicitis was planned for study TP-434-008, but this was changed to 30% before any subjects were enrolled (Amendment 1.0, Final Protocol Version 2.0 dated 20 June 2013). As the results from study TP-434-008 showed similar cure rates irrespective of primary site of infection, for study TP-434-025 the cap for appendicitis was increased to 50%. Approximately 40 % of subjects in study TP-434-025 in both treatment arms had complicated appendicitis. The percentage of patients having cIAI originating from the appendix is stated in section 4.4 of the Xerava SmPC.

Both studies were double-blind using the double-dummy technique. The methodology used and the procedures planned to mask the study treatments were deemed adequate by CHMP.

The final version of the EMA SAP (version 3.0) for Study TP-343-008 was dated 7 January, 2015 and according to the submitted Data Management Plan the database lock was expected to be on 23 January, 2015. The actual date was not found, hence, the date for database lock and code break needed to be confirmed. As clear from the applicant's response, the database lock, unblinding of the statistician and the primary analysis were performed during December 2014. While being ahead of the date for the final SAP, no concern was raised, since the primary analysis was nonetheless performed according to what was later to be updated in the SAP with the major updates claimed to be due to errors in the SAP.

Study TP-434-008 and study TP-434-025 were designed to address both EMA and US FDA regulatory requirements; separate strategies for the statistical analyses were pre-defined and there were two different versions of the SAP. The EMA SAP was considered overall appropriate. The definition of the analysis populations and definition of clinical response was acceptable. Subjects were classified as a clinical failure based on, among other things, "persistence of clinical symptoms of cIAI". Recurrences of clinical symptoms of cIAI were classified as clinical failure.

The pathogen identification was adequate, although there is an inherent uncertainty on the major causative agent(s) in cIAI because findings are often poly-microbial. The NI margin of -12.5%, the co-primary efficacy analysis based on the MITT and CE-TOC analysis populations and, for Study TP-343-008, 2-sided 99% CI (instead of standard 2-sided 95% CI, when at the time performed was to serve as a single pivotal study) were in line with CHMP expectations for NI studies in cIAI. In the primary analysis based on the MITT population, subjects with missing data were displayed as indeterminate/missing and contributed to the analysis as non-responders. Subjects who were assessed as a failure at the EOT Visit were to have the failure carried forward to the TOC Visit. In the (co-primary) CE-TOC population, subjects with missing/indeterminate response were by definition excluded. In both studies sensitivity analyses were planned.

For study TP-434-008, a total of 541 subjects were randomised to the eravacycline group (270 subjects) or the ertapenem group (271 subjects). Approximately 94% in each treatment group completed treatment and 91% and 94% completed the study in the eravacycline and ertapenem

groups, respectively. The difference between the groups was mainly due to a higher number of patients lost to follow-up in the eravacycline group.

For study TP-434-025, there were 250 subjects randomised to the eravacycline and meropenem groups, respectively. Approximately 96% in each treatment group completed treatment and 95% and 96% completed the study in the eravacycline and meropenem groups, respectively.

Other reasons for early termination or premature treatment discontinuation were evenly distributed in the two treatment arms in both studies.

The applicant has submitted a detailed description of the major protocol deviations reported in the two treatment groups for both the pivotal clinical studies. CHMP considered that the identified major protocol deviations in the TP-434-008 study and the TP-434-025 study did not have any major influence on the overall conclusion on the benefit-risk assessment of eravacycline.

The mean duration of the study drug was 7.6 days and compliance was over 80% in all subjects, with the mean value being over 99% in both treatment arms in study TP-434-008. Equal figures were observed in study TP-434-025 for compliance and the mean duration of treatment was 7.2 days.

There were differences between treatment arms with regards to prior and concomitant antibacterial treatment in favour of the eravacycline group. The proportion of subjects that had received antibacterial medications prior to the first dose in the CE-TOC population was 49.0% vs. 47.5% for the eravacycline and ertapenem groups, respectively in study TP-434-008 and 54.4% and 49.3% for the eravacycline and meropenem groups, respectively in study TP-434-025. Concomitant systemic antibacterial medications use from the first dose of study drug through the TOC Visit in the MITT population was 13.0% of the subjects in the eravacycline treatment group and 8.6% of the subjects in the ertapenem treatment group in study TP-434-008. In the MITT population in study TP-434-025 the corresponding figures were 8.0% and 8.4% in the eravacycline and meropenem groups, respectively. According to the protocol patients could receive up to 24 hours of effective antibiotics prior to randomisation without being excluded. Thereafter concomitant antimicrobial treatment was not accepted, with the exception of cases with failure, prophylaxis for unrelated procedures and for agents with no systemic exposure. Prior antibacterial treatment in the MITT population has been presented. From these data it is observed that the majority of patients received short-term antibacterial treatment prior to first dose of study drugs while a limited number received longer antimicrobial treatment for AEs and prophylaxis.

Baseline demographic characteristics were comparable between treatment groups. In study TP-434-008, the typical subject was a male Caucasian aged 55 years. Only 10% of the subjects were above 75 years old. Approximately 27% had complicated appendicitis (below the cap of 30%) and 73% had other site of infection of which nearly 40% had intraabdominal abscess, ~30% peritonitis, ~20% complicated cholecystitis and ~10% to ~15% each of gastric/duodenal perforation or intestinal perforation. The baseline characteristics were similar in study TP-434-025, with the exception of the site of infections. Approximately 40% in both treatment groups had complicated appendicitis (capped at 50%), with other dominating diagnoses being intra-abdominal abscess and peritonitis.

Based on APACHE II score, the severity of infections was low, with 10-15% of subjects having scores above 10 and only a few patients having scores above 15. Also less than 10% in each treatment arm were bacteraemic. The fact that the majority of patients included in the study had mild to moderate cIAIs, could question the representativeness of the current patient population in regards to patients with more severe cIAI. The limitations of the studied populations are described in the Xerava SmPC

section 4.4. Also the number of patients with infections originating from the appendix from the two clinical studies is included.

Approximately 80% of all randomised subjects had at least one baseline bacterial pathogen that was considered to cause cIAI and, as would be expected for cIAI, 70% of subjects in each treatment group had polymicrobial infections. Gram-negative aerobes, Gram-positive aerobes and anaerobes were isolated from ~80%, ~50% and ~50% of subjects, respectively. Pathogens belonging to Enterobacteriaceae were most frequently isolated, with *E. coli* being the most commonly isolated species.

The number of subjects in each analysis population was similar between treatment groups. Close to 100% of randomised patients were included in the MITT populations and nearly 90% were included in the CE populations confirming reasonable compliance to the study protocol. As noted above, approx. 80% had at least one baseline bacterial pathogen considered to cause cIAI (micro-ITT population).

Efficacy data and additional analyses

Clinical cure in the MITT population at TOC in study TP-434-008 were 87.0% in the eravacycline group and 88.8% in the ertapenem group. The corresponding figures in the CE population were 92.9% and 94.5%, respectively. In study TP-434-025 clinical cure was approximately 92 % and 96-97% in both arms in the MITT population and CE populations, respectively.

The results of the sensitivity analyses were supportive of the primary analyses results. Without being very conservative, no additional analysis of the primary endpoint is considered necessary based on the definition of the primary endpoint (implying failure imputation), the high clinical response rates (in both treatment arms), the fact that the conclusion of non-inferiority was shown in both the MITT and the CE-TOC analysis in combination with the seemingly high both study and treatment compliance.

There was a trend of higher clinical cure rate in patients with 0-1 sign of systemic infection observed in both treatment groups in both populations. The only exception was the cure rate for patients in the eravacycline group (MITT population) in study TP-434-008, which was lower in patients with 0-1 sign of systemic infection (86.1%) compared to patients with ≥ 2 signs of systemic infection (88.2%). The lower limit of the 95% CI for the difference between the eravacycline and ertapenem group did not exceed -12.5% (-5.9 [-13.4, 1.4]). This was, however, not seen for the corresponding patient and treatment group in the CE-TOC population.

In sub-population analyses (including age, gender, race, geographic region, site of infection, abscess/no abscess, APACHE II score, renal function, and prior antibacterial treatment) no major clinically meaningful differences were detected. The response rates were similar, but lower in patients with renal impairment.

When clinical response was evaluated at the EOT, TOC, and Follow-up Visits in the ITT, MITT, micro-ITT, CE-EOT (or TOC), and ME-EOT (or TOC) populations in study TP-434-008, it was noted that the difference in clinical cure rates between the eravacycline and ertapenem treatment groups increased from TOC to FU for all analysis populations. In the MITT and CE-TOC populations, the difference was mainly explained by the addition of 12 and 9 subjects with an indeterminate outcome, respectively in the eravacycline treatment arm and a lower number of additional indeterminates for the ertapenem treatment group (2 additional cases for each analysis population). There was only one additional failure in the eravacycline treatment arm, whereas there were no additional failures in the ertapenem treatment arm. Here, a 95% CI was used instead of a 99% CI and it did not seem unreasonable that the lower limit of a 99% CI would have been below the NI margin. Considering that it is of utmost

importance that the treatment effect remains at later time-points and since the application at the time of initial assessments relied on a single pivotal study the applicant was requested to recalculate the differences in clinical cure rates for the MITT and CE populations at the different visits using adjusted 99% CIs and discuss the reasons for the lower response rate at the later visit. The reason for the higher number of indeterminates in the eravacycline arm was moreover to be discussed. A comparison to the corresponding results in the now completed IGNITE4 study (TP-434-025) was further asked for. In its response, the applicant did not present clinical cure rates with, as initially requested, 99% CIs. This was justified by the applicant by the fact that the results of two pivotal studies had now been submitted. The use of 95% CIs is accepted by CHMP. It can be noted that the same trend to a lower response over time was found in the completed cUTI study (TP-434-010). The applicant has argued that the lower response detected in that study could be the lower exposure secondary to oral administration after IV to oral switch.

Favourable per-subject microbiological response at the TOC visit for the micro-ITT population was in the same range as the favourable clinical response in the MITT population for eravacycline and ertapenem/meropenem groups. This is not surprising because of the overall high favourable clinical response rate and that the favourable microbiological response was derived from clinical success in almost all cases.

Favourable per pathogen microbiological response ranged from 85% to 100% in all treatment groups for the majority of pathogens in both studies.

Also subjects with bacteraemia at baseline had a high microbiological favourable response rate, however, in general < 10% of the patients in both treatment groups in both studies had diagnosed bacteraemia.

The applicant has proposed a list of pathogens for inclusion in the SmPC section 5.1. The incidence of pathogens in baseline samples and in literature reports has been summarized. Microbiologically favourable response at TOC by baseline pathogen has also been presented for pooled data from the pivotal studies and from mono-microbial and poly-microbial infections in the studies.

CHMP was of the view that the list should be rationalised with regard to the pathogens considered relevant to cIAI, for which antibiotic activity has been established *in vitro* and for which clinical efficacy is established.

The difficulty of establishing the relevance of specific pathogens for cIAI, which often yields poly-microbial cultures (approximately 70% of cases in the clinical programme for Xerava), is acknowledged. This is further complicated by the unclear impact of surgery on clinical outcome.

CHMP considered that clinical efficacy has been established in cIAI for *Escherichia coli*, viridans *Streptococcus spp.*, *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus aureus* and *Klebsiella pneumoniae*.

Concerning the section 'Antibacterial activity against other relevant pathogens', CHMP agreed that the only relevant information to be included in the SmPC is about the fact that *in vitro* data indicate that *Pseudomonas* aeruginosa is not susceptible to eravacycline.

In a supportive study of community acquired cIAI two regimens of eravacycline (1.5 mg/kg q24h and 1.0 mg/kg i.v. q12h) were compared with ertapenem (1.0 g i.v. q24h). The clinical cure rates at the TOC visit were high and generally comparable between treatment arms for the primary analysis population (ME population) and secondary analysis populations (MITT and CE populations). The microbiological response was similar to the clinical response.

2.5.3. Conclusions on the clinical efficacy

PTA simulations based on preclinical PK/PD targets and human PK data did not provide support for the proposed dose regimen to fully cover for pathogens belonging to the wild-type populations.

Still eravacycline showed non-inferiority to ertapenem and meropenem for the treatment of complicated intra-abdominal infections in two pivotal studies. For both studies similar clinical and microbiological cure rates were achieved and in general similar results in important sub-populations were observed. Therefore CHMP considered that in the setting of cIAI, as an adjunct to surgical management, the efficacy of eravacycline has been sufficiently established to infer clinical benefit.

2.6. Clinical safety

Earlier investigations - safety pool:

The safety and efficacy of i.v. eravacycline in subjects with cIAI were initially evaluated in a single phase 2 and a single phase 3 study.

It should be noted that eravacycline was also developed for the treatment of complicated urinary tract infection (cUTI), including pyelonephritis. A phase 3 study evaluating i.v. with transition to oral (p.o.) eravacycline in subjects with cUTI, including pyelonephritis, has been completed. The applicant informed that the primary endpoint was not met and the development program for cUTI was ongoing. The safety data from the cUTI study are included, where appropriate, in addition to data from studies for cIAI.

The safety data were derived from 19 clinical studies according to three analysis pools (Table S1). The analysis pools were composed as following:

1) All Phase 1 pool - integrated pool of all Phase 1 healthy volunteers who received eravacycline, regardless of dose or route of administration

2) All Phase 2/Phase 3 pool – integrated pool of Phase 2 and Phase 3 subjects with cIAI or cUTI who received eravacycline, regardless of dose or route of administration

3) cIAI Only Phase 2/Phase 3 pool – Phase 2 and Phase 3 subjects with cIAI by dose of eravacycline received (i.v. only)

Clinical studies pooled in the cIAI only group tested in case of one study, two different dose regimens of eravacycline i.v. and compared the outcome against ertapenem:

Table S1. Data Pooling Strategy for the Eravacycline Summary of Clinical Safety

Analysis pool	Safety data analysis set
All Phase 1	**integrated pool of all Phase 1 healthy volunteers who *received eravacycline, regardless of dose or route of administration***
	5 iv single dose studies
	TP-434-P1-SAD-1-MAD-Oral (double-blind, placebo controlled)
	TP-434-004 (TP-434 kinetics study)
	TP-434-012 (double-blind, placebo controlled)
	TP-434-013 (open-label, eravacycline kinetics study)
	TP-434-014 (open-label, eravacycline kinetics study)
	2 oral single dose studies
	TP-434-Oral-P1-SAD-1 (double-blind, placebo controlled)
	P-434-012a (open-label, metabolic study)
	12 iv multiple dose studies
	TP-434-006 (open-label, Tp-343 kinetics study)
	TP-434-P1-MAD-1 (placebo-controlled, double-blind)
	TP-434-016 (open-label, itraconazole interaction study)
	TP-434-020 (open-label, rifampicin interaction study)
	TP-434-002-P1-MAD-Oral (placebo-controlled, double-blind)
	TP-434-003 (TP-434 kinetics study)
	TP-434-007 (double-blind, placebo controlled)
	TP-434-009 (pharmacokinetics study of two different oral formulation of eravacycline)
	TP-434-015 (phase 1, multiple-dose, open-label, eravacycline-digoxin interaction study)
	TP-434-016 (phase 1, open label, itraconazole – eravacycline interaction study)
	TP-434-017 (open-label, partial crossover-study, bioavailability study of different oral eravacycline formulations)
	TP-434-020 phase1, open-label, eravacycline-rifampicin interaction study
All Phase 2/ Phase 3	**integrated pool of Phase 2 and Phase 3 subjects with cIAI or cUTI who received eravacycline, regardless of dose or route of administration**
	3 iv multiple dose studies
	TP-434-P2-cIAI-1 (double-dummy, double-blind, comp. w. ertapenem)
	TP-434-008 (double blind, double dummy, comp. w. ertapenem)
	TP-434-010 (double blind, double dummy, comp. w. levofloxacin; this study applied eravacycline both i.v. and oral to each participant)
cIAI Only Phase 2/Phase 3 pool	**Phase 2 and Phase 3 subjects with cIAI by dose of eravacycline received (i.v. only)**

	TP-434-P2-cIAI-1 (double blind, double dummy, comp. w. ertapenem) During each 24-hour dosing cycle, subjects received three infusions: •Eravacycline 1.5 mg/kg every 24 hours (q24h) group: eravacycline 1.5 mg/kg (1 infusion) and placebo (2 infusions) •Eravacycline 1.0 mg/kg every 12 hours (q12h) eravacycline 1.0 mg/kg q12h (2 infusions) and placebo (1 infusion) •Ertapenem group: ertapenem 1.0 g q24h (1 infusion) and placebo (2 infusions). TP-434-008 (double blind, double dummy, comp. w. ertapenem) During each 24-hour dosing cycle, subjects received 3 infusions: •Eravacycline group: eravacycline 1.0 mg/kg q12h (2 infusions) and placebo (1 infusion) •Ertapenem group: ertapenem 1.0 g q24h (1 infusion) and placebo (2 infusions)

Updated investigations – new study study TP-434-025 and new integrated safety 2/3 pool:

The applicant has studied and presented the results for study TP-434-025 and has additionally performed a novel pooled analysis obtaining a new integrated phase 2/3 pool. The safety pool of the additionally submitted study TP-434-025 is composed of the MITT population, which has received any dosage of study drug.

New study results are evaluated in the following in comparison to the safety results obtained in the former safety phase 2/ 3 pool, named as safety pool 1 in the updated evaluations and in comparison to the integrated phase 2/3 safety pool composed of the current study and safety pool 1, named as integrated safety pool in the evaluations below.

Patient exposure

Earlier investigations – old phase 2/3 pools (referred to as safety pool 1 when comparing with the new integrated safety pool in the following):

Overall, 1284 subjects have been exposed to eravacycline in completed studies, thereof 926, who obtained at least 1.5mg/kg q24 in a multiple i.v. dose setup. The mean duration of exposure was consistent and approximately 7 days across the Phase 2/Phase 3 studies.

Table S2. Extent of exposure in the Phase 2/3 program with eravacycline

	All Phase 1	All Phase 2/Phase 3		cIAI Only Phase 2/Phase 3		
Parameter	Eravac.	Eravac.	all Comp.	Eravac. 1.0mg/kg q12h	Eravac. 1.5 mg/kg q24h	Ertapenem 1.0 mg q24h
N enrolled	385	993	826	357	63	314
N treated	358	926	796	326	53	298
% completing	92.5	92.8	96.2	90.5	81.1	94.6
prematurely withdrawn, n (%)	27 (7.5)	67 (7.2)	30 (3.8)	31 (9.5)	10 (18.9)	16 (5.4)
prematurely withdrawn due to AE, n (%)	14 (3.9)	2 (0.2)	1 (0.1)	0	0	0
prematurely discontinuing drug due to AE, n (%)	-	28 (3.0)	19 (2.4)	7 (2.1)	2 (3.8)	8 (2.7)
Average daily dose, mg (range)	173.9 (6.3-675)	203.2 (60-403.4)	804.2 (1-1000)	158.6 (72-245.8)	101.4 (60-144)	899.4 (1000-1000)
Mean duration of treatment, days (range)	4.7 (1-17)	7.0 (1-15)	7.1 (1-15)	7.4 (2-15)	6.7 (2-8)	7.4 (1-15)

Table S3a and b. Subject disposition in the Phase 2 / 3 program with eravacycline (safety population)

Table S3a. **Phase 2 / 3 program – cIAI and cUTI population**

		cIAI			cUTI	
	Statistic	ERV 1.0 mg/kg q12h IV	ERV 1.5 mg/kg q24h IV	ERT 1.0 g q24 IV	ERV 1.5 mg/kg q24 h IV + 200/250 mg PO q12h	Levofloxacin 750 mg q24h IV + 750 mg PO q24h
Number of Subjects Treated	n	326	53	298	547	498
Number of Subjects Prematurely Withdrawing from Study	n (%)	31 (9.5)	10 (18.9)	16 (5.4)	26 (4.8)	14 (2.8)
Reason for Premature Withdrawal from Study						
Adverse Event	n (%)	3 (0.9)	0	6 (2.0)	3 (0.5)	1 (0.2)
Investigator's Decision	n (%)	0	1 (1.9)	1 (0.3)	1 (0.2)	0
Subject's Decision	n (%)	7 (2.1)	0	0	8 (1.5)	3 (0.6)
Non-Compliance with Study Drug	n (%)	2 (0.6)	0	3 (1.0)	1 (0.2)	1 (0.2)
Lost to Follow-up	n (%)	18 (5.5)	5 (9.4)	5 (1.7)	13 (2.4)	7 (1.4)
Other	n (%)	1 (0.3)	4 (7.5)	1 (0.3)	0	2 (0.4)
Number of Subjects Prematurely Discontinuing Study Drug	n (%)	18 (5.5)	2 (3.8)	15 (5.0)	42 (7.7)	26 (5.2)
Reason for Premature Discontinuation of Study Drug						
Adverse Event	n (%)	7 (2.1)	2 (3.8)	8 (2.7)	19 (3.5)	11 (2.2)
Investigator's Decision	n (%)	0	0	0	1 (0.2)	0
Subject's Decision	n (%)	5 (1.5)	0	0	10 (1.8)	3 (0.6)
Non-Compliance with Study Drug	n (%)	0	0	1 (0.3)	0	0
Insufficient Therapeutic Effect	n (%)	4 (1.2)	0	5 (1.7)	4 (0.7)	5 (1.0)
Lost to Follow-up	n (%)	0	0	0	0	0
Other	n (%)	2 (0.6)	0	1 (0.3)	8 (1.5)	7 (1.4)

Table S3b. **Phase 2 / 3 program – All phase 2 / 3 population**

		Integrated Phase 2 & 3 Studies	
	Statistic	All ERV	All Comparator
Number of Subjects Treated	n	926	796
Number of Subjects Prematurely Withdrawing from Study	n (%)	67 (7.2)	30 (3.8)
Reason for Premature Withdrawal from Study			
Adverse Event	n (%)	6 (0.6)	7 (0.9)
Investigator's Decision	n (%)	2 (0.2)	1 (0.1)
Subject's Decision	n (%)	15 (1.6)	3 (0.4)
Non-Compliance with Study Drug	n (%)	3 (0.3)	4 (0.5)
Lost to Follow-up	n (%)	36 (3.9)	12 (1.5)
Other	n (%)	5 (0.5)	3 (0.4)
Number of Subjects Prematurely Discontinuing Study Drug	n (%)	62 (6.7)	41 (5.2)
Reason for Premature Discontinuation of Study Drug			
Adverse Event	n (%)	28 (3.0)	19 (2.4)
Investigator's Decision	n (%)	1 (0.1)	0
Subject's Decision	n (%)	15 (1.6)	3 (0.4)
Non-Compliance with Study Drug	n (%)	0	1 (0.1)
Insufficient Therapeutic Effect	n (%)	8 (0.9)	10 (1.3)
Lost to Follow-up	n (%)	0	0
Other	n (%)	10 (1.1)	8 (1.0)

Updated exposure – study TP-434-025 and the integrated phase 2/3 safety pool

In the safety pool of TP-434-025 250 individuals obtained eravacycline 1.0 mg/kg q12h and 249 received 1g q 8h meropenem. The integrated phase 2/3 safety pool is composed of 1176 who received eravacycline and 1045 individuals receiving comparator treatment.

Adverse events

Earlier observations:

Table S4. Overview of Treatment-Emergent Adverse Events – All Phase 2/Phase 3 Pool

TEAE category (n, %)	All Phase 1	All Phase 2/Phase 3		cIAI Only Phase 2/Phase 3		
	Eravacycline	Eravacycline	All comparator	Eravacycline 1.0 mg/kg q12h	Eravacycline 1.5 mg/kg q24h	Ertapenem 1.0 g q24h
No. treated	**358**	**926**	**796**	**326**	**53**	**298**
≥1 TEAE	185 (51.7)	358 (38.7)	192 (24.1)	128 (39.3)	19 (35.8)	79 (26.5)
≥1 severe TEAE	2 (0.6)	39 (4.2)	24 (3.0)	16 (4.9)	4 (7.5)	18 (6.0)
≥1 related TEAE	**143 (39.9)**	**196 (21.2)**	**63 (7.9)**	**43 (13.2)**	**2 (3.8)**	**7 (2.3)**
≥1 TEAE leading to study drug discontinuation	**17 (4.7)**	**25 (2.7)**	**18 (2.3)**	**5 (1.5)**	**2 (3.8)**	**7 (2.3)**
≥1 serious TEAE	0	33 (3.6)	24 (3.0)	18 (5.5)	6 (11.3)	17 (5.7)
≥1 serious related TEAE	**0**	**0**	**1 (0.1)**	**0**	**0**	**0**
≥1 TEAE leading to death	0	7 (0.8)	6 (0.8)	3 (0.9)	3 (5.7)	6 (2.0)

Table S5. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Occurring in ≥2 Eravacycline-Treated Subjects – All Phase 2/Phase 3 Pool

System Organ Class and Preferred Term	All Eravacycline n (%)	All Comparator n (%)
Total Exposed (N)	**926**	**796**
Any Treatment-Emergent Adverse Event	358 (38.7)	192 (24.1)
Gastrointestinal disorders	**187 (20.2)**	**66 (8.3)**
Nausea	126 (13.6)	20 (2.5)
Vomiting	61 (6.6)	15 (1.9)
Diarrhoea	21 (2.3)	19 (2.4)
Dyspepsia	13 (1.4)	2 (0.3)
Abdominal pain upper	11 (1.2)	3 (0.4)
Constipation	6 (0.6)	5 (0.6)
Abdominal pain	5 (0.5)	3 (0.4)
Ileus	3 (0.3)	0
Duodenal ulcer haemorrhage	2 (0.2)	1 (0.1)
Intestinal fistula	2 (0.2)	1 (0.1)
Salivary hypersecretion	2 (0.2)	0
General disorders and administration site conditions	**62 (6.7)**	**30 (3.8)**
Pyrexia	12 (1.3)	9 (1.1)
Infusion site phlebitis	10 (1.1)	2 (0.3)
Infusion site erythema	6 (0.6)	2 (0.3)
Infusion site thrombosis	4 (0.4)	0
Oedema peripheral	4 (0.4)	5 (0.6)
Asthenia	3 (0.3)	2 (0.3)
Vessel puncture site reaction	3 (0.3)	0
Catheter site pain	2 (0.2)	0
Chest pain	2 (0.2)	0
Fatigue	2 (0.2)	1 (0.1)
Infusion site irritation	2 (0.2)	0
Infusion site pain	2 (0.2)	1 (0.1)
Infusion site reaction	2 (0.2)	0
Infections and infestations	**45 (4.9)**	**36 (4.5)**
Wound infection	8 (0.9)	2 (0.3)
Influenza	4 (0.4)	2 (0.3)
Postoperative wound infection	4 (0.4)	1 (0.1)
Vulvovaginal candidiasis	4 (0.4)	1 (0.1)
Pneumonia	3 (0.3)	5 (0.6)
Urinary tract infection	3 (0.3)	1 (0.1)
Abdominal abscess	2 (0.2)	6 (0.8)
Candidiasis	2 (0.2)	0
Liver abscess	2 (0.2)	1 (0.1)
Lobar pneumonia	2 (0.2)	0
Nasopharyngitis	2 (0.2)	2 (0.3)
Vascular disorders	**43 (4.6)**	**15 (1.9)**
Hypertension	15 (1.6)	9 (1.1)
Phlebitis	8 (0.9)	1 (0.1)
Thrombophlebitis	6 (0.6)	1 (0.1)
Hypotension	5 (0.5)	1 (0.1)
Deep vein thrombosis	4 (0.4)	0
Phlebitis superficial	3 (0.3)	0
Thrombophlebitis superficial	2 (0.2)	0
Nervous system disorders	**36 (3.9)**	**14 (1.8)**
Headache	20 (2.2)	7 (0.9)
Dizziness	6 (0.6)	3 (0.4)
Dysgeusia	7 (0.8)	1 (0.1)
Investigations	**30 (3.2)**	**28 (3.5)**
Lipase increased	9 (1.0)	2 (0.3)
Amylase increased	7 (0.8)	1 (0.1)
Activated partial thromboplastin time prolonged	3 (0.3)	0
Blood pressure increased	3 (0.3)	6 (0.8)
Blood creatine phosphokinase increased	2 (0.2)	4 (0.5)
Blood potassium increased	2 (0.2)	1 (0.1)
Haemoglobin decreased	2 (0.2)	0

System Organ Class and Preferred Term	All Eravacycline n (%)	All Comparator n (%)
Oxygen saturation decreased	2 (0.2)	1 (0.1)
Prothrombin time prolonged	2 (0.2)	0
Injury, poisoning and procedural complications	**25 (2.7)**	**6 (0.8)**
Wound dehiscence	5 (0.5)	1 (0.1)
Inflammation of wound	2 (0.2)	0
Seroma	2 (0.2)	0
Subcutaneous haematoma	2 (0.2)	0
Respiratory, thoracic and mediastinal disorders	**20 (2.2)**	**18 (2.3)**
Dyspnoea	5 (0.5)	2 (0.3)
Pleural effusion	4 (0.4)	2 (0.3)
Cough	2 (0.2)	3 (0.4)
Hydrothorax	2 (0.2)	1 (0.1)
Tachypnoea	2 (0.2)	0
Metabolism and nutrition disorders	**16 (1.7)**	**18 (2.3)**
Hypocalcaemia	3 (0.3)	1 (0.1)
Hypoglycaemia	3 (0.3)	1 (0.1)
Hypokalaemia	3 (0.3)	4 (0.5)
Decreased appetite	2 (0.2)	0
Hyperglycaemia	2 (0.2)	3 (0.4)
Hyperkalaemia	2 (0.2)	0
Psychiatric disorders	**15 (1.6)**	**6 (0.8)**
Anxiety	6 (0.6)	2 (0.3)
Insomnia	3 (0.3)	4 (0.5)
Blood and lymphatic system disorders	**14 (1.5)**	**17 (2.1)**
Anaemia	6 (0.6)	8 (1.0)
Leukocytosis	3 (0.3)	3 (0.4)
Leukopenia	2 (0.2)	2 (0.3)
Renal and urinary disorders	**13 (1.4)**	**13 (1.6)**
Dysuria	5 (0.5)	2 (0.3)
Calculus bladder	2 (0.2)	0
Renal colic	2 (0.2)	2 (0.3)
Cardiac disorders	**12 (1.3)**	**12 (1.5)**
Palpitations	3 (0.3)	1 (0.1)
Angina pectoris	2 (0.2)	1 (0.1)
Atrial fibrillation	2 (0.2)	2 (0.3)
Skin and subcutaneous tissue disorders	**10 (1.1)**	**8 (1.0)**
Hyperhidrosis	3 (0.3)	0
Rash	2 (0.2)	1 (0.1)
Musculoskeletal and connective tissue disorders	**5 (0.5)**	**11 (1.4)**
Back pain	2 (0.2)	2 (0.3)
Immune system disorders	**2 (0.2)**	**2 (0.3)**
Hypersensitivity	2 (0.2)	2 (0.3)
Surgical and medical procedures	**2 (0.2)**	**0**
Biliary drainage	2 (0.2)	0

Table S6. Most Commonly Reported Treatment-Emergent Adverse Events by Preferred Term (≥2% Subjects in any treatment group) – cIAI Only Phase 2/Phase 3 Pool (extract from table S6)

TEAE Preferred Term	cIAI Phase 2/Phase 3		
	Eravacycline 1.0 mg/kg i.v. q12h n (%)	Eravacycline 1.5 mg/kg i.v. q24h n (%)	Ertapenem 1.0 g i.v. q24h n (%)
Total exposed (N)	**326**	**53**	**298**
Any TEAE	**128 (39.3)**	**19 (35.8)**	**79 (26.5)**
Nausea	28 (8.6)	1 (1.9)	4 (1.3)
Vomiting	12 (3.7)	3 (5.7)	8 (2.7)
Phlebitis	8 (2.5)	0	1 (0.3)
Diarrhoea	7 (2.1)	0	5 (1.7)

Pyrexia	7 (2.1)	1 (1.9)	8 (2.7)
Wound infection	7 (2.1)	1 (1.9)	2 (0.7)
Anaemia	5 (1.5)	1 (1.9)	6 (2.0)
Lipase increased	4 (1.2)	3 (5.7)	2 (0.7)
Abdominal abscess	2 (0.6)	0	6 (2.0)
Amylase increased	2 (0.6)	3 (5.7)	1 (0.3)
Abdominal pain	1 (0.3)	2 (3.8)	3 (1.0)
Ileus	1 (0.3)	2 (3.8)	0

TEAEs occurred overall more often in the eravacycline treated subjects, with events beginning between 2 and 7 days after the start of study medication.

The most commonly reported events in both treatment groups were nausea, vomiting and diarrhoea, with nausea and vomiting at higher rates in the eravacycline group compared to the active comparator. Also notable are a higher frequency of headache, infusion site phlebitis and an increase of lipase and amylase in eravacycline treated subjects with, however, overall low absolute and relative incidences.

Overall observation in the total safety population:

The TEAE rate was slightly higher in the eravacycline group compared to the meropenem group in both the newly submitted study and the integrated safety pool and confirmed the results seen in the safety pool 1. The rate of severe TEAEs and SAEs as well as SAEs leading to discontinuation of the drug was similar in both treatment groups and comparable to the rates seen in study pool 1. 4 SAEs in the eravacycline arm and one SAE in the meropenem arm led to death in the submitted study. However, none of the SAEs has been evaluated as related to study drug by the investigator, which is endorsed by CHMP. Narratives to the cases of death in the newly submitted study have been investigated by the CHMP. No one of the cases was associated to eravacycline.

Table S-Add1: Overall summary of TEAEs in the safety population of TP-434-025

Table 37: Overall Summary of TEAEs, Safety Population

Type of AE	Eravacycline 1.0 mg/kg q12h (N = 250) n (%)	Meropenem 1 g q8h (N = 249) n (%)
Number of subjects who experienced at least 1 AE	94 (37.6)	78 (31.3)
TEAE	93 (37.2)	77 (30.9)
TEAE related to study drug	28 (11.2)	13 (5.2)
Severe TEAE	12 (4.8)	13 (5.2)
TEAE leading to premature discontinuation of study drug	4 (1.6)	5 (2.0)
SAE	15 (6.0)	16 (6.4)
SAE related to study drug	0	0
SAE leading to premature discontinuation of study drug	2 (0.8)	1 (0.4)
SAE leading to death	4 (1.6)	1 (0.4)

Abbreviations: AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects in the Safety population; n=number of subjects in the specific category; q8h=every 8 hours; q12h=every 12 hours; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Notes: AE terms were coded using MedDRA Version 20.0. Percentages were calculated as 100 × (n/N). Related to study drug is defined as possibly, probably or definitely related to study drug. Events with missing relationship to study drug are considered related to study drug. Events with missing severity are considered severe.

Furthermore, similar results compared to safety pool 1 were obtained when investigating the SOCs with the highest TEAE incidences in the eravacycline and meropenem arm: While the order of SOC type with the greatest number of TEAEs were comparable in both study arms (Gastrointestinal disorders, general conditions including administration site conditions, infections), the TEAE incidences in the respective SOC group were in several cases higher in the eravacycline arm compared to the meropenem group, i.e. for Gastrointestinal disorders; General disorders and administration site conditions; Infections and infestations; Injury, poisoning and procedural complications and skin and subcutaneous tissue disorders. These results are comparable with safety pool 1.

Table S-Add2: Incidence of TEAEs by MedDRA SOC - report TP-434-025

Table 38: Incidence of TEAEs by MedDRA SOC, Safety Population

MedDRA SOC	Eravacycline 1.0 mg/kg q12h (N = 250) n (%)	Meropenem 1 g q8h (N = 249) n (%)
Subjects with at least 1 TEAE	**93 (37.2)**	**77 (30.9)**
Blood and lymphatic system disorders	5 (2.0)	8 (3.2)
Cardiac disorders	12 (4.8)	13 (5.2)

Table 38: Incidence of TEAEs by MedDRA SOC, Safety Population

MedDRA SOC	Eravacycline 1.0 mg/kg q12h (N = 250) n (%)	Meropenem 1 g q8h (N = 249) n (%)
Ear and labyrinth disorders	1 (0.4)	0
Eye disorders	0	1 (0.4)
Gastrointestinal disorders	32 (12.8)	20 (8.0)
General disorders and administration site conditions	22 (8.8)	11 (4.4)
Hepatobiliary disorders	2 (0.8)	2 (0.8)
Infections and infestations	21 (8.4)	18 (7.2)
Injury, poisoning, and procedural complications	10 (4.0)	4 (1.6)
Investigations	14 (5.6)	16 (6.4)
Metabolism and nutrition disorders	7 (2.8)	10 (4.0)
Musculoskeletal and connective tissue disorders	1 (0.4)	2 (0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.6)	1 (0.4)
Nervous system disorders	3 (1.2)	3 (1.2)
Psychiatric disorders	4 (1.6)	3 (1.2)
Renal and urinary disorders	3 (1.2)	4 (1.6)
Reproductive system and breast disorders	1 (0.4)	2 (0.8)
Respiratory, thoracic, and mediastinal disorders	8 (3.2)	8 (3.2)
Skin and subcutaneous tissue disorders	3 (1.2)	0
Vascular disorders	9 (3.6)	9 (3.6)

Abbreviations: AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects in the Safety population; n=number of subjects in the specific category; q8h=every 8 hours; q12h=every 12 hours; SOC=system organ class; TEAE=treatment-emergent adverse event.

Notes: AE terms were coded using MedDRA Version 20.0. Percentages were calculated as 100 × (n/N). Subjects reporting an AE SOC more than once are counted only once for that SOC.

Adverse events of special interest:

Adverse events of interest were defined as AEs that have previously been associated with the administration of tetracyclines.

- Acute pancreatitis (MedDRA narrow)
- Acute renal failure (MedDRA narrow)
- Hypersensitivity (MedDRA narrow)
- Anaphylactic reaction (MedDRA narrow)

- Hepatic disorders (Drug-related MedDRA broad)
- Pseudomembranous colitis (MedDRA narrow)
- Infusion-site complication (CMQ)
- Thrombophlebitis (CMQ)
- Nausea and vomiting (CMQ)
- Pseudotumor cerebri / Elevated intracranial pressure (CMQ)
- Photosensitivity (CMQ)

Earlier observations:

For the many of the entities listed above no significant safety concerns arose (i.e. pseudomembranous colitis (one case in the comparator arm), pseudotumor cerebri (no cases), photosensitivity (no cases), acute renal failure (3 cases in the comparator arm)).

Overall observation in the total safety population:

No new safety signal is detected for the mentioned three diagnosis after submission of the new study.

To mention are specifically:

Hypersensitivity and anaphylactic reaction (based on data from the integrated phase 2/3 safety pool):

Allergic/hypersensitivity reactions were rarely (twice, "rash") observed in the eravacycline arm and evaluated as mild in the submitted study. This observation is in agreement with observations made in safety pool 1. There, hypersensitivity reactions occurred as well in low frequency and were evaluated as mild to moderate. No case of anaphylactic reaction was observed

As shown in Table S - Add 3 the rate of allergic reactions is overall comparable and low between eravacycline and comparator as shown in the integrated analysis pool.

Thus, it was requested to include rash as uncommon AEs (frequency 1/1000 to 1/100) in the Xerava SmPC, section 4.8. The categorization of AEs according to frequencies should be in this context in general performed based on the frequency observed in the all cIAI only pool. The applicant has implemented both aspects in the SmPC. Furthermore, based on data showing that 9/1176 individuals have been categorized as hypersensitive in the integrated phase 2/3 pool, the applicant has listed hypersensitivity as uncommon (<1%) AE in the SmPC, section 4.8 based on the frequency of hypersensitivity seen in the new cIAI only pool, which is endorsed.

Table S – Add 3 Significant Treatment-Emergent Adverse Events by Standardized Medical Query, Preferred Term, and Severity Integrated Phase 2 and Phase 3 pool

	All Eravacycline (N=1176)			All Comparators (N=1045)		
Preferred Term	**mild**	**moderate**	**severe**	**mild**	**moderate**	**severe**
Hypersensitivity	**4 (0.3)**	**5 (0.4)**	**0**	**3 (0.3)**	**4 (0.4)**	**1 (0.1)**
Application site hypersensitivity	0	0	0	0	0	1 (0.1)
Dermatitis allergic	1 (0.1)	0	0	0	0	0
Dermatitis contact	0	1 (0.1)	0	0	0	0
Hypersensitivity	0	2 (0.2)	0	1 (0.1)	1 (0.1)	0
Infusion site urticaria	0	0	0	0	1 (0.1)	0
Rash	3 (0.3)	1 (0.1)	0	1(0.1)	0	0

Rash erythematous	0	0	0	1 (0.1)	0	0
Scrotal oedema	0	1(0.1)	0	0	0	0
Toxic skin eruption	0	0	0	0	1 (0.1)	0
Urticaria	0	0	0	0	1 (0.1)	0

Hepatic disorders

Earlier observations:

Hepatic disorders were equally distributed in cases and controls with a frequency of 1.0% (eravacycline) and 1.1% (comparator). The majority of TEAEs were reported in single subjects in the eravacycline group (exception: prothrombin time prolonged in ≥1 subject in the eravacycline group (0.2%) versus no subjects in the comparator group). None of the events were serious or severe or led to treatment discontinuation.

Two eravacycline-treated subjects and one comparator-treated subject satisfied the criteria for potential drug-induced liver injury as defined by Hy's Law. One of the eravacycline subjects already met the criteria at baseline, prior to eravacycline treatment start.

Overall observation in the total safety population:

No changes in the distribution of liver disorders are detected in the latest submitted study and the integrated phase 2/3 pool.
Liver enzymes were in the majority of cases within the normal range in both the eravacycline and the meropenem arm. Shifts in 2 toxicity degrees are again observed for ASAT and ALAT under Xerava in the recently submitted study, however in a comparable frequency compared to meropenem and in comparable frequency as observed in safety pool 1. A toxicity grade > 2 is very rarely observed for ASAT, ALAT and bilirubin in both study arms. Of note, bilirubin elevations occurred again more often in Xerava treated subjects compared to subjects treated with meropenem. These were mostly mild to moderate in degree. These results confirm the observations made in safety pool 1.
Two subjects in the eravacycline treatment arm and 1 subject in the meropenem arm met the criteria of drug induced liver injury. One subject in the eravacycline arm met DILI criteria already at screening. Overall 5 subjects under eravacycline and 2 subjects treated with comparator developed potential DILI according to Hy's law in the integrated phase 2/3 pool. An evaluation of the narratives of patients with laboratory signs of DILI treated with eravacycline allows, however, only in one case to evaluate the association between eravacycline and signs of DILI as possible. Thus, no clear safety signal is detected here at this stage.

Acute pancreatitis (SMQ)

Earlier obervations

a) All Phase 2 and 3 pool

Three subjects in the ervacycline group and 1 subject in the comparator group were diagnosed with pancreatitis in the All Phase 2 and 3 pool.

Of the three acute pancreatitis TEAEs among eravacycline-treated subjects, one resolved during eravacycline treatment, and a second one began 13 days after the completion of eravacycline treatment in a subject who also had evidence of acute pancreatitis at screening. Both were attributable to the underlying disease or a complication of surgery. The applicant considers that neither case is likely to have been caused by eravacycline treatment. In the third case, symptoms and laboratory abnormalities developed near the end of the planned course of eravacycline treatment in a

subject who received both i.v. and p.o. eravacycline; treatment was completed and the event resolved. In view of these results the company concludes that there is no clear association between eravacycline treatment and pancreatitis.

b) All phase 1 pool

No cases of acute pancreatitis were seen in the All Phase 1 pool.

Updated observation and evaluation based on the total safety population:

As seen in safety pool 1, elevations of lipase and amylase were observed under treatment with eravacycline in the newly submitted study, which were in their frequency comparable to meropenem and similar to the frequencies seen in study pool 1. The aspect of lipase elevations is also well reflected in the pooled analyses taking all phase 2 and 3 studies into account, showing that 19% of the individuals reached mild lipase elevations up to 2x and 13% of individuals showed lipase elevation >2 under the study period (rates are comparable to comparator treatment). Pancreas enzyme elevations resulted in the reporting of 5 TEAEs in the newly submitted study (4 eravacycline, 1 meropenem), which all resolved. One TEAE of lipase elevation was evaluated as severe in the eravacycline arm. While rates of lipase and amylase elevations are comparable between eravacycline and comparators in the integrated phase 2/3 pool, the number of observed pancreatitis cases is higher under eravacycline (n=7) compared to comparator treatment (n=3) as shown in the integrated safety pool. Of note, 2 TEAEs of pancreatitis were observed under treatment with eravacycline in the current study (none in the meropenem arm), which in one case was evaluated as SAE. Based on the narrative evaluation to pancreatitis cases under eravacycline submitted by the applicant, the association of pancreatitis with eravacycline is not likely (n=2)/not clearly evaluable (n=1) in three cases, was possible in one case and likely in an additional case. For two subjects presenting elevated pancreatic enzymes together with nausea/vomitus which have been evaluated as pancreatitis, narratives have not been submitted. A warning of pancreatitis as a class effect of tetracyclines is currently included in the Xerava SmPC section 4.4. Based on the observation that rare cases of pancreatitis have been observed under eravacycline treatment, which can be evaluated as at least possibly associated, and based on the known class effect for tetracyclines, CHMP requested to include pancreatitis into section 4.8 of the Xerava SmPC as uncommon occurring adverse event, which was subsequently implemented by the applicant.

Thrombophlebitis (CMQ)

Earlier observations:

Thrombophlebitis has been reported in patients treated with eravacycline.

a) All Phase 2 and 3 pool

TEAEs meeting the Thrombophlebitis CMQ occurred in 2.1% of subjects in the eravacycline group and in 0.3% of subjects belonging to the comparator group. The most frequently reported event by PT was phlebitis. Other reported events included thrombophlebitis and deep vein thrombosis. None of the events was assessed as severe or led to treatment discontinuation. Deep vein thrombosis was reported as serious in two subjects in the eravacycline group. Of note, pulmonary embolism was only observed in the comparator arm (2 cases).

The majority of the remaining events is captured by the Infusion-site complication CMQ, and reflects localized issues associated with the administration of i.v. eravacycline. There were two exceptions which included non-serious saphenous vein phlebitis (PT phlebitis) and non-serious right leg thrombophlebitis (PT thrombophlebitis superficial).

b) All Phase 1 pool

3.6% of subjects experienced TEAEs meeting the Thrombophlebitis CMQ criteria. All of the reported events (by PT) were phlebitis; the majority was moderate in severity, all were non-serious, and none led to study drug discontinuation.

Table S7. Summary of Thrombophlebitis CMQ in the All Phase 1 and All Phase 2/Phase 3 pools

MedDRA Preferred Term	All Phase 1 Pool	All Phase 2/Phase 3 Pool	
	All Eravacycline N = 358 n (%)	All Eravacycline N= 926 n (%)	All Comparator N = 796 n (%)
Thrombophlebitis CMQ	**13 (3.6)**	**19 (2.1)**	**2 (0.3)**
Deep vein thrombosis	0	4 (0.4)	0
Phlebitis	13 (3.6)	8 (0.9)	1 (0.1)
Thrombophlebitis	0	6 (0.6)	1 (0.1)
Thrombophlebitis superficial	0	2 (0.2)	0

Individuals receiving eravacycline i.v. experienced more often infusion complications such as phlebitis and thrombophlebitis than individuals treated with active comparator. Infusion site reactions are included in the Xerava SmPC sections 4.4 and 4.8.

Overall observation in the total safety population:

As observed in safety pool 1, reactions at the infusion site were more often observed in the eravacycline arm compared to the comparator arm. Of note, 6 cases of infusion site thrombosis were observed in the current study. Thus, the number of infusion site thrombosis is summed up to 10 cases under eravacycline and 1 case under comparator in the integrated phase 2/3 safety pool. Phlebitis, thrombophlebitis and infusion site reactions are already included in the Xerava SmPC 4.8 as possible site effect.

Nausea and vomiting (CMQ):

Earlier observations:

a) Phase 2 and 3 pool

TEAEs meeting the nausea and vomiting CMQ criteria occurred in 15.6% (13.6% / 6.6%) of eravacycline subjects and in 3.6% (2.5% / 1.9%) of the comparator pool. These events were typically observed shortly after treatment initiation, all were non-serious, and the majority was mild to moderate in intensity. 1.1% of the eravacycline group and 0.4% of the comparator group discontinued study drug treatment due to these side effects. Rates of nausea and vomiting observed in eravacycline treatment groups in the cIAI population who received only i.v. eravacycline were lower than in the Phase 2/Phase 3 pool (both i.v. and p.o. treatment with eravacycline).

b) All Phase 1 pool

27.9% of subjects experienced nausea, vomiting and retching. All of the events were non-serious. A single event of nausea was assessed as severe; all other events were mild or moderate in severity. TEAEs in 2.5% of subjects led to study drug discontinuation. The majority of subjects in the All Phase 1 pool who discontinued due to TEAEs received multiple doses of oral eravacycline, including subjects who received doses above the therapeutic dose.

TEAEs meeting the nausea and vomiting occurred 3.5 times more often in eravacycline iv treated subjects compared to the comparator pool and had with 15.6% a high incidence rate.

Nausea and vomiting are adequately mentioned as often occurring side effects in the Xerava SmPC section 4.8.

Overall observation in the total safety population:

Nausea and vomiting were also in the newly submitted study and in the integrated safety pool an often occurring side effect. The frequencies remained similar.

Serious adverse event / deaths / other significant events

Earlier observations:

a) Deaths

Deaths were reported for 7 subjects (0.8%) who received eravacycline treatment and 6 subjects (0.8%) who received comparator treatment. The only TEAE which led to death that was reported in more than one subject was pulmonary embolism, experienced by two subjects in the comparator group.

b) Serious TEAEs

Table S8. Summary of Serious Treatment-Emergent Adverse Events (Including Deaths) – All Phase 2 / Phase 3 Pool (> 1 individual)

System Organ Class Preferred Term	All Eravacycline n (%)	All Comparator n (%)
Total Exposed (n)	**926**	**796**
Any SAE n(%)	**33 (3.6)**	**24 (3.0)**
Pneumonia	2 (0.2)	2 (0.3)
Abdominal abscess	1 (0.1)	2 (0.3)
Liver abscess	1 (0.1)	1 (0.1)
Duodenal ulcer haemorrhage	2 (0.2)	1 (0.1)
Ileus	2 (0.2)	0
Wound dehiscence	2 (0.2)	1 (0.1)
Pulmonary embolism	0	2 (0.3)
Deep vein thrombosis	2 (0.2)	0
Atrial fibrillation	1 (0.1)	1 (0.1)

a) All Phase 2 and 3 pool

The overall incidence of serious TEAEs was similar for the treatment groups. A total of 33 subjects (3.6%) in the eravacycline group and 24 subjects (3.0%) subjects in the comparator group experienced serious TEAEs.

Individual SAEs reported in ≥1 subject in either treatment group included duodenal ulcer

haemorrhage, abdominal abscess, pneumonia and wound dehiscence (all in both eravacycline and comparator groups), deep vein thrombosis and ileus (in the eravacycline group only), and pulmonary embolism (in the comparator group only). No serious TEAEs were considered as related to eravacycline.

b) All Phase 1 pool

There were no serious TEAEs in the All Phase 1 pool.

Overall observation in the total safety population:

Five cases of death were noted under eravacycline (4) and meropenem (1) in the newly submitted study TP-434-025, for which an association to study drug treatment is not likely. Altogether 11 (eravacycline) and 7 (comparator) deaths have been noted in the integrated phase 2/3 pool. Thus the rate of mortality is similar and, as demonstrated in table S12, covering a wide range of different SOCs in both arms. No safety signal is detected here.
As observed in safety pool 1, SAEs occurred equally often in both study arms of the newly submitted study, covering a wide range of different SOCs and PTs. SAEs were in the majority of cases only seen once within each PT. SAEs within the SOC pulmonary diseases occurred slightly more often in the eravacycline arm (4x, 1,6%) compared to the meropenem arm (2x, 0.8%), covering, however, different PTs in both study arms. Overall, no new safety signal is detected here.

Laboratory findings

a **Overall observation in the total safety population:**
No safety concerns arose for electrolytes, blood cell count or parameters related to renal function.

- **Analytes related to liver function and evaluation of drug induced liver injury**

Earlier observations:

a) Phase 2 and 3 pool

Baseline mean values for ALT, AST, bilirubin, direct bilirubin, and indirect bilirubin for eravacycline-treated subjects and comparator-treated subjects were within the normal range.

Table S9. AST, ALT and bilirubin elevations in the all phase 2/3 pool

	All phase2/3		cIAI			cUTI	
Parameter	All Eravac N= 926 n (%)	All Comp N = 796 n (%)	Eravac. 1mg/kg q24h N=326	Eravac. 1.5 mg/kg q24h N=53	ERT 1.0 g q24h N=298	Eravac. 1.5 mg/kg q24h +po N=547	Levofloxacin 750 mg po q24h N=498
ALT or AST ≥ 3xULN	31 (3.3)	28 (3.5)	18 (5.5)	3 (5.7)	22 (7.4)	10 (1.8)	6 (1.2)
ALT or AST ≥ 5xULN	8 (0.9)	7 (0.9)	6 (1.8)	2 (3.8)	5 (1.7)	0	2 (0.4)
ALT or AST ≥ 10xULN	2 (0.2)	2 (0.3)	1 (0.3)	1 (1.9)	2 (0.7)	0	0
Total bilirubin ≥ 1.5xULN	42 (4.5)	12 (1.5)	25 (7.7)	10 (18.9)	10 (3.4)	7 (1.3)	2 (0.4)
Total bilirubin ≥ 2xULN	16 (1.7)	7 (0.9)	10 (3.1)	5 (9.4)	6 (2.0)	1 (0.2)	1 (0.2)
Hy's criteria met	2 (0.2)	1 (0.1)	1 (0.3)	0	1 (0.3)	1 (0.2)	0

In the eravacycline group ALT or AST elevations >3, >5 and 10 times > ULN, respectively, were comparable to the comparator group. Furthermore, 42 subjects (4.5%) and 16 subjects (1.7%) showed elevations in direct bilirubin >1.5 times and > 2 times of the ULN, respectively, with lower frequencies in the comparator group (1.5% and 0.9%).
In the cIAI pool post-baseline elevations in direct bilirubin >1.5 times the ULN were observed for 25 subjects (7.7%) in the eravacycline 1.0 mg/kg q12h group, 10 subjects (18.9%) in the eravacycline 1.5 mg/kg q24h group, and 10 subjects (3.4%) in the ertapenem group. Post-baseline elevations in direct bilirubin >2 times the ULN were observed for 10 subjects (3.1%) in the eravacycline 1.0 mg/kg q12h group, five subjects (9.4%) in the eravacycline 1.5 mg/kg q24h group, and six subjects (2.0%) in the ertapenem group.

b) All Phase 1 pool

No clinically significant shifts of liver values were detected in the all phase 1 pool.

Overall, AST and ALT elevations are noted for eravacycline, which are mostly in the range 3x to 5x > ULN and occurred in about the same frequency as observed for the active comparator. Specifically in the cIAI group, higher relative incidences of strong ALT and AST elevations 5x and 10x > ULN are seen for the dosage 1.5 mg/kg q24h compared to active comparator, which are, however, observed in a low absolute number of individuals.
Bilirubin values were clearly higher in the eravacycline arm in the all phase 2 and 3 pool (>1.5 and >2 ULN: 6.2% eravacycline/ 2.4% active comparator) as well as in the cIAI eravacycline arm compared to active comparator. Also here and of note stronger elevations are especially seen in the eravacycline 1.5 mg/kg q24h arm within the cIAI group.
Two eravacycline treated subjects (one of them already at baseline) and one subject in the comparator arm fulfilled the criteria for drug induced liver injury (DILI). Thus, a higher frequency of DILI is not induced by eravacycline. CHMP requested to include elevations of AST, ALT and bilirubin as common events in section 4.8 of the Xerava SmPC, which has been subsequently implemented by the applicant.

Overall and updated observation in the total safety population:

Liver enzymes were in the majority of cases within the normal range in both the eravacycline and the meropenem arm in the newly submitted study TP-434-025. Shifts in 2 toxicity degrees are again observed for ASAT and ALAT under eravacycline in the recently submitted study, however in a comparable frequency compared to meropenem and in comparable frequency as observed in safety pool 1. A toxicity grade > 2 is very rarely observed for ASAT, ALAT and bilirubin in both study arms. Of note, bilirubin elevations occurred again more often in eravacycline-treated subjects compared to subjects treated with meropenem. These were mostly mild to moderate in degree. These results confirm the observations made in safety pool 1.
The applicant has discussed whether AST, ALT and bilirubin should be listed as side effect in section 4.8 of the SmPC. The view of the applicant is endorsed that both liver enzyme and bilirubin/aPTT elevations were in the majority of cases of mild nature and not associated with any AEs. Of the patients meeting Hy's law criteria only one patient could be evaluated as possibly related to eravacycline. Although in most cases of rather mild nature, AST, ALT and bilirubin elevations are relatively often observed under eravacycline. The applicant has subsequently listed AST, ALT and bilirubin elevations as uncommon events in the Xerava SmPC, which was endorsed by CHMP based on the frequencies of all TEAEs observed in the cIAI only pool.

- **Analytes related to pancreatic injury**

Earlier observations:

a) All phase 2 and 3 pool

Baseline mean values for amylase, triacylglycerol lipase, GGT, LDH, and ALP in eravacycline-treated subjects and comparator-treated subjects were within the normal range. For most of the analytes, there were no changes from baseline at any time point that resulted in mean values outside the normal range.

The relative amount of worst lipase elevations (Grade 3 and 4) was similar between eravacycline and the active comparator group. Subjects in the eravacycline group displayed clinically notable abnormalities of lipase and amylase (defined as a ≥2-grade increase from baseline) more frequently.

Table S10. Summary of lipase elevations: All Phase 2 and Phase 3 Pool

Worst lipase elevation	All Eravacycline N=926		All Comparator N=796	
<1.1 x ULN	642	70.2%	566	71.9%
1.1 - 1.5 x ULN	105	11.5%	99	12.6%
1.6 - 2.0 x ULN	54	5.9%	35	4.4%
2.1 -5.0 x ULN	87	9.5%	64	8.1%
>5.1 x ULN	26	2.8%	23	2.9%
TOTAL	**914**		**787**	

Table S11. Summary of amylase and lipase elevations: All Phase 2/Phase 3 Pool

Measurement	All Eravacycline N=926		All Comparator N=796	
	Subjects with 2-Grade Increase n (%)	TEAEs possibly consistent with pancreatitis (number of subjects)	2-Grade Increase n (%)	TEAEs possibly consistent with pancreatitis (number of subjects)
Amylase only	10 (1.1)	Amylase increased (2), Nausea (2), Vomiting (2)	8 (1.0)	
Lipase only	103 (11.1)	Amylase increased (1), Lipase increased (2), Nausea (13), Vomiting (6), Abdominal pain (1), Abdominal pain upper (1), Pancreatic necrosis (1)	69 (8.7)	Vomiting (2)
Amylase and lipase	39 (4.2)	Amylase increased (4), Lipase increased (6), Nausea (4), Abdominal pain upper (1), Pancreatitis acute (1)	34 (4.3)	Amylase increased (1), Lipase increased (2), Nausea (3), Vomiting (1), Pancreatitis acute (1)
Total	**152 (16.4%)**		**111 (13.9%)**	

a) <u>All phase 1 pool</u>

Baseline mean values for amylase, lipase, ALP, lactate dehydrogenase (LDH), and gamma-glutamyltransferase (GGT) in subjects were within the normal range. Six subjects in the All Phase 1 Pool had at least a 2-grade worsening or Grade 4 abnormality in lipase; one of these subjects also had at least a 2-grade worsening or Grade 4 abnormality in amylase. One subject in the Phase 1 QTc study (Study TP-434-004) had 3-grade worsening in lipase during the moxifloxacin dosing period (comparator).

<u>Overall observation in the total safety population:</u>

As mentioned above in the section "pancreatitis" lipase and amylase elevations are confirmed in the newly submitted study and the integrated safety pool (similar frequency as observed in safety pool 1). In view of the additional observations of pancreatitis cases under eravacycline an update of the Xerava SmPC section 4.8 has been requested by CHMP (pancreatitis as uncommon AE), which has been subsequently implemented by the applicant.

Table S-Add 4 Distribution of worst Lipase elevations: Integrated Phase 2 and Phase 3 pool

Worst lipase elevation	Statistic	All Eravacycline (N=1176)	All Comparator (N=1045)
< 1.1xULN	N (%)	787 (66.9)	706 (67.6)
>= 1.1xULN to <= 1.5x ULN	N (%)	152 (12.9)	144 (13.8)
>=1.5xULN to <= 2.0ULN	N (%)	69 (5.9)	58 (5.6)
>2xULN to <5.0x ULN	N (%)	114 (9.7)	91 (8.7)
> 5x ULN	N (%)	42 (3.6)	34 (3.3)
Total	N (%)	**1164 (99.0)**	**1033 (98.9)**

Table S-Add 5 Significant TEAEs by SMQ and PT in the integrated phase 2 /3 pool

Significant Treatment-Emergent Adverse Events by Standardized Medical Query and Preferred Term
Phase 2 and Phase 3

Standardized Medical Query Preferred Term	Statistic	Integrated Phase 2 & 3 Studies All ERV (N=1176)	 All Comparators (N=1045)
Any Significant Treatment-Emergent Adverse Event	n (%)	258 (21.9)	93 (8.9)
Acute pancreatitis	n (%)	7 (0.6)	3 (0.3)
Pancreatic necrosis	n (%)	1 (0.1)	0
Pancreatitis acute	n (%)	3 (0.3)	1 (0.1)
Pancreatitis necrotising	n (%)	1 (0.1)	0
Amylase increased + Nausea	n (%)	0	1 (0.1)
Lipase increased + Nausea	n (%)	2 (0.2)	2 (0.2)
Lipase increased + Vomiting	n (%)	1 (0.1)	0

- **Coagulation:**

<u>Earlier observations:</u>

a) All Phase 2 and 3 Pool

Activated partial thromboplastin time (aPTT) and prothrombin international normalized ratio (INR) were evaluated.

Table S12. Summary of abnormal post-baseline aPTT and INR parameters – All Phase 2 and 3 Pool

Parameter	All Eravacycline (N=830 (aPTT) and 832 (INR))		All Comparator (N=725)	
	Actual value	Change from baseline	Actual value	Change from baseline
Worst aPTT (sec (mean (SD))	31.6 (9.49)	2.6 (10.35)	28.3 (7.64)	-0.1 (10.06)
INR	1.31 (0.584)	0.09 (0.601)	1.14 (0.342)	-0.04 (0.36)

Mean baseline aPTT in subjects treated with eravacycline or comparator were in normal range. In eravacycline-treated patients subsequently measured aPTT values were slightly above the normal range (30.2 to 33.1 sec, normal range (24.3 to 30.4 sec)). Mean INR in eravacycline subjects where slightly above the normal range at baseline and remained slightly above the normal range except for the Test of Cure visit (INR 1.16± 0.316, normal range (0.8-1.2)) and Follow-up visit (INR 1.12± 0.280). In the comparator group, INR values were in general within the normal range. Of note, aPTT changes were pronounced in the 1.5mg/kg/24h dosage group (38.7 (±16.32) sec), change from baseline 7.0 sec) compared to the 1.0mg/kg/12h dosage group (33.3 (±11.03), change from baseline 3.6 sec) in the cIAI pool.

b) All Phase 1 pool

Values for aPTT and INR were normal at baseline and changes from baseline at each study visit were generally small and not clinically significant.

In summary, mild elevations of aPTT are noted with eravacycline in phase 2 and 3 studies, with more pronounced aPTT elevations seen in the 1.5 mg/kg/24 dosage group.

Overall observation in the total safety population:

aPTT values behaved similar in the newly submitted study and the integrated phase 2/3 pool. No new safety concern arose here.

- **Vital signs**

Earlier observations:

a) All Phase 2/Phase 3 Pool

Mean ± SD values for SBP and DBP at baseline were in the normal range and comparable in verum and active comparator group. At later time points there were small changes in either mean ± SD for

SBP (-0.6 ±15.2 mmHg to 7.4 ±19.8 mmHg) or DBP (-1.3 ± 13.4 mmHg to 1.0 ± 13.7 mmHg) in those subjects treated with eravacycline or with comparator (SBP (-5.1 ± 14.5 mmHg to 2.2 ± 15.1 mmHg) or DBP (-4.6 ± 11.8 mmHg to 0.4 ± 11.7 mmHg))
A similar pattern was observed for HR. For subjects treated with eravacycline the mean ± SD HR value was 82.6 ± 14.0 bpm (range 47 to 130 bpm) with variances from -1.9 ± 8.0 bpm to -17.3 ± 16.3 bpm later on. For comparator treated subjects mean ± SD HR value was 81.9 ± 13.6 bpm (range 50 to 130 bpm) with a range from -1.3 ± 7.6 bpm to -17.2 ± 17.9 bpm at later time points.

Table S13. Summary of Abnormal Post-Baseline Vital Signs – All Phase 2 and 3 Pool

Abormality	All Eravacycline N = 926; n (%)	All Comparator N = 796; n (%)
Diastolic Blood Pressure >20 mmHg increase from baseline	64 (6.9)	67 (8.4)
Systolic Blood Pressure ≥140 mmHg	384 (41.5)	306 (38.4)
Heart Rate <60 bpm	93 (10.0)	55 (6.9)
Heart Rate >120 bpm	8 (0.9)	8 (1.0)

Table S14. Summary of Abnormal Post-Baseline Vital Signs – cIAI Only Phase 2/Phase 3 Pool

Abnormality	Eravac. 1.0 mg/kg q12h 2.0 N = 326	Eravac. 1.5 mg/kg q24h N=53	Ertapenem 1.0 g q2h N = 298 n (%)
Diastolic Blood Pressure >20 mmHg increase from baseline	34 (10.4)	5 (9.4)	44 (14.8)
Systolic Blood Pressure ≥140 mmHg	158 (48.5)	17 (32.1)	146 (49.0)
Heart Rate <60 bpm	21 (6.4)	7 (13.2)	17 (5.7)
Heart Rate >120 bpm	5 (1.5)	1 (1.9)	5 (1.7)

b) All Phase 1 Pool

The relative frequency for SBP and HR abnormalities in the verum and placebo group was comparable. 11 subjects (3.1%) had a post-baseline DBP measurement of >20 mmHg increase from baseline compared to 1 subject (0.9%) in the placebo group.

No systematic clinically significant changes in BP were observed compared to baseline in phase 1, 2 and 3 studies. The rates of systolic and diastolic BP elevations were comparable in the eravacycline and in the comparator group.

Of note, the rate of “bradycardic episodes” was twice as high in the eravacycline arm (1.5 mg/kg q24) compared to eravacycline 1.0 mg/kgq12h and active comparator (Table S16). Furthermore, the rate of bradycardic episodes was in general higher in subjects treated with eravacycline compared to active comparator. Bradycardic episodes are currently not included in the Xerava SmPC. At CHMP request, the applicant has further investigated the issue of bradycardic episodes in relation to the compound

and has shown that no higher risk for chronotropic effects of Xerava could be detected, which was endorsed by CHMP.

Overall observation in the total safety population:

While patients with bradycardic episodes were more abundant in the eravacycline arm (6.4%) compared to the meropenem arm (2.8%) of the newly submitted study, the rate of individuals exceeding the thresholds for vital signs (systolic and diastolic blood pressure, heart rate) are roughly comparable between study arms in the integrated phase 2/3 pool and especially in the updated cIAI only pool. Overall the majority of individuals were in the normal range in both the eravacycline and comparator arm. The view of the applicant (answer to the question "bradycardic episodes") that no safety signal is detected here was endorsed by CHMP.

Table S – Add 6 – Summary of Abnormal Post-Baseline vital signs; integrated safety pool

Abnormality	All Eravacycline N=1176 n (%)	All Comparators[a] N=1045 n (%)
Diastolic Blood Pressure >20 mmHg increase from baseline	98 (8.3)	94 (9.0)
Systolic Blood Pressure ≥140 mmHg	501 (42.6)	407 (38.9)
Heart Rate <60 bpm	109 (9.3)	62 (5.9)
Heart Rate >120 bpm	10 (0.9)	10 (1.0)

bpm=beats per minute

a. Comparators include ertapenem, meropenem and levofloxacin

Table S – Add 7 - Summary of abnormal post-baseline vital signs; cIAI only Phase 2/phase 3 pool

Abnormality	Eravacycline 1.0 mg/kg q12h i.v. N=576 n (%)	Eravacycline 1.5 mg/kg q24h i.v. N=53 n (%)	Comparators[a] N=547 n (%)
Diastolic Blood Pressure >20 mmHg increase from baseline	68 (11.8)	5 (9.4)	71 (13.0)
Systolic Blood Pressure ≥140 mmHg	275 (47.7)	17 (32.1)	247 (45.2)
Heart Rate <60 bpm	37 (6.4)	7 (13.2)	24 (4.4)
Heart Rate >120 bpm	7 (1.2)	1 (1.9)	7 (1.3)

bpm=beats per minute

a) Comparator includes ertapenem and meropenem

QT interval investigations

Earlier observations:

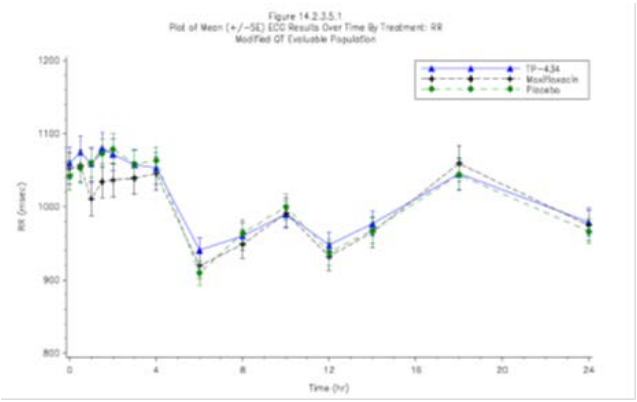
QT Interval Study TP-434-004: A Randomized, Placebo- and Positive-Controlled, Three-Way, Crossover Study to Evaluate the Effects of an Intravenous Infusion of Eravacycline (TP-434) on Cardiac Repolarization in Healthy Male and Female Subjects: A Thorough QT/QTc Study

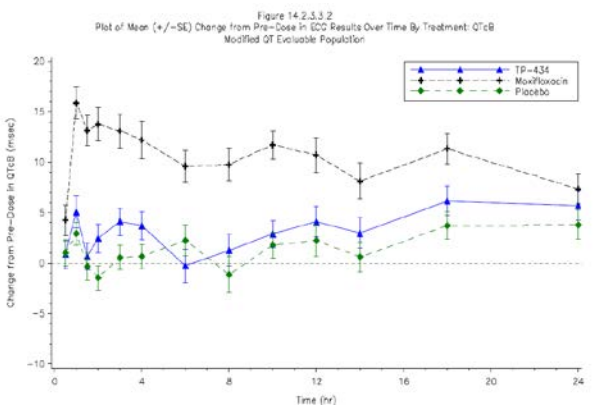
No clinically significant prolongation of the QT interval corrected by individual formula (QTcI) was detected in healthy volunteers under i.v. eravacycline (study TP-434-004). After a single i.v. dose of eravacycline (1.5 mg/kg), the maximum placebo- adjusted mean change in QTcI interval at each post-dose time point was <10 msec (upper bound of the 1-sided 95% confidence interval [CI]).

- There was no evidence of clinically significant prolongation of the QT interval corrected by Fridericia's formula (QTcF) or the QT interval corrected by Bazett's formula (QTcB) demonstrated.

Time-matched placebo-adjusted mean changes from pre-dose in RR, PR, and QRS intervals following a single dose of eravacycline 1.5 mg/kg i.v. were generally small and similar to placebo.

- No subject had a QTcI interval >480 msec or a QTcI change from pre-dose >30 msec at any post-dose timepoint following a single dose of eravacycline 1.5 mg/kg i.v.
- No subject had a QTcF or QTcB interval >480 msec or change from pre-dose >60 msec following eravacycline.





Electrocardiograms – All Phase 2/Phase 3 Pool

Of the 926 subjects in the eravacycline group, 20 subjects (2.2%) had an abnormal ECG finding at any study visit (including screening and baseline) and of the 796 subjects in the comparator group, 19 subjects (2.4%) had an abnormal ECG finding at any study visit.

No remarkable difference in ventricular rate or QRS duration between the eravacycline group and the comparator group at comparable visits were observed.

- PR interval mean change from baseline was 1.3 (±26.7) msec in the eravacycline group and 0.5 (±28.1) msec in the comparator group.
- QT interval mean change from baseline was 10.1 (±42.3) msec in the eravacycline group and 6.2 (±39.8) msec in the comparator group.
- QTcF interval mean change from baseline was 2.7 (±28.1) msec in the eravacycline group and -1.3 (±24.0) msec in the comparator group.

Electrocardiograms - cIAI Only Phase 2/Phase 3 Pool

- PR interval mean change from baseline was 0.5 (±25.95) msec in the eravacycline 1.0 mg/kg q12h group, -1.1 (±29.15) in the eravacycline 1.5 mg/kg q24h group and -1.0 (±21.1) msec in the ertapenem group.
- QT interval mean changes from baseline were 16.7 (±43.8), 23.5 (±51.2) and 12.5 (±41.3) msec, respectively.
- QTcF interval mean changes from baseline were 3.0 (±25.9), 4.2 (±8.9) and 2.9 (±22.3) msec respectively.

In view of these results no significant changes in QRS complexes, PR or QT intervals were observed in association with eravacycline.

Overall observation in the total safety population:

No new safety signal could be detected with regard to PQ, QT and QRS interval.

Post-baseline and change from baseline QTcB value distributions were similar between the eravacycline and meropenem groups in the newly submitted study TP-434-025. There were more

subjects in the eravacycline group with a >60 msec increase in QTcB (15/224 [6.7%] and 10/222 [4.5%] subjects for the eravacycline and meropenem groups, respectively); however, there were more subjects in the meropenem group with a QTcB at the EOT Visit >500 msec (3/228 [1.3%] and 6/227 [2.6%] subjects for the eravacycline and meropenem groups, respectively). These results reflect the results detected in the integrated safety pool 2/3 (of note, QTcF is calculated here). Here, at EOT 4 (480-500msec) and 2 (>500msec) subjects were detected in the eravacycline compared to 2 (480-500msec) and 2 (>500msec) subjects in the comparator arm, showing relevant elevated Qtc values when scrutinizing QTc changes at every treatment day. The number of subjects with QTc values > 480ms was overall very low and was comparable between the eravacycline and the comparator arm. No safety signal was detected.

Safety in special populations

a **Earlier observations:**

No significant differences in the safety profile arose in association with gender, BMI, age or APACHE score. Furthermore Xerava appeared to be safe in patients with renal or hepatic impairment.

Table S15. Overview of Treatment-Emergent Adverse Events for the All Phase 2/Phase 3 Pool – Influence of renal function

TEAE Category	Moderate/Severe: CrCl 15 to <60 mL/min		Normal/Mild: CrCl ≥60 mL/min		Augmented: CrCl ≥130 mL/min	
	All Eravac. (N = 122) n (%)	All Comp. (N = 78) n (%)	All Eravac. (N = 793) n (%)	All Comp. (N = 702) n (%)	All Eravac. (N = 190) n (%)	All Comp. (N = 147) n (%)
≥ 1 TEAE	65 (53.3)	26 (33.3)	292 (36.8)	160 (22.8)	80 (42.1)	26 (17.7)
≥ 1 Severe TEAE	5 (4.1)	4 (5.1)	34 (4.3)	17 (2.4)	6 (3.2)	4 (2.7)
≥ 1 Treatment-Related TEAE	35 (28.7)	7 (9.0)	161 (20.3)	55 (7.8)	37 (19.5)	8 (5.4)
≥ 1 TEAE Leading to Study Drug Discontinuatio	5 (4.1)	0	20 (2.5)	18 (2.6)	4 (2.1)	1 (0.7)
≥ 1 Serious TEAE	7 (5.7)	8 (10.3)	26 (3.3)	13 (1.9)	3 (1.6)	5 (3.4)
≥ 1 Serious TEAE Related to Study Drug	0	1 (1.3)	0	0	0	0
≥ 1 TEAE Leading to	3 (2.5)	3 (3.8)	4 (0.5)	2 (0.3)	0	1 (0.7)

Of note, patients with CrCl < 50 ml/min have been excluded from the clinical phase 2/3 studies. As a result, the subgroup of patients with moderate/severe renal function actually mostly includes those with a mild renal impairment.

Table S16. Overview of Treatment-Emergent Adverse Events for the All Phase 2/Phase 3 Pool – Hepatic Function

TEAE Category	Child-Pugh Class A		Child-Pugh Class B		AST and/or ALT >2xULN		AST and/or ALT ≤2xULN	
	All Eravac. (N = 772) n (%)	All Comp. (N = 675) n (%)	All Eravac. (N = 88) n (%)	All Comp. (N = 76) n (%)	All Eravac. (N = 36) n (%)	All Comp. (N = 34) n (%)	All Eravac. (N = 817) n (%)	All Comp. (N = 704) n (%)
≥ 1 TEAE	296 (38.3)	151 (22.4)	46 (52.3)	30 (39.5)	14 (38.9)	8 (23.5)	317 (38.8)	167 (23.7)
≥ 1 Severe TEAE	27 (3.5)	15 (2.2)	8 (9.1)	4 (5.3)	2 (5.6)	2 (5.9)	32 (3.9)	17 (2.4)
≥ 1 Treatment-Related TEAE	178 (23.1)	57 (8.4)	14 (15.9)	3 (3.9)	5 (13.9)	1 (2.9)	178 (21.8)	56 (8.0)
≥ 1 TEAE Leading to Study Drug Discontinuation	19 (2.5)	14 (2.1)	4 (4.5)	2 (2.6)	2 (5.6)	1 (2.9)	18 (2.2)	16 (2.3)
≥ 1 Serious TEAE	21 (2.7)	13 (1.9)	7 (8.0)	8 (10.5)	1 (2.8)	1 (2.9)	25 (3.1)	20 (2.8)
≥ 1 Serious TEAE Related to Study Drug	0	1 (0.1)	0	0	0	0	0	1 (0.1)
≥ 1 TEAE Leading to Death	2 (0.3)	3 (0.4)	4 (4.5)	3 (3.9)	1 (2.8)	1 (2.9)	5 (0.6)	4 (0.6)

Furthermore, most patients with severe hepatic impairment, (Child-Pugh Class C) have not been included in the safety pool, thus not allowing conclusions on the safety profile in patients with markedly decreased liver function.

For all races (Caucasian, Black/African, Asian and others) the most commonly reported TEAE related SOCs were Gastrointestinal Disorders. Of note, the applicant mentioned that the most commonly reported TEAEs were “increased lipase” in Asians in both the compound and comparator group (17.5%, 16.7%). In contrast to this, TEAEs most commonly reported in Caucasians included nausea, vomiting, diarrhoea and palpitations and nausea and abdominal abscess in low frequency in the Black/African American group.

The majority of the patients who received eravacycline in the **All Phase 2/3 pool** were Caucasian (93%; 861/926) and exposure in non-Caucasian patients has therefore been limited. Accordingly, meaningful comparisons between patients of different races/ethnicities are not possible, as the other groups comprised only few patients each (in the eravacycline group in the All Phase 2/3 pool: black/African/American 16 patients vs. 17 in the comparator group, Asian: 40 vs. 12 and Hispanic/Latino: 25 vs. 27).

Pregnancy and lactation has not been systematically scrutinized with regard to the safety profile of Xerava. Two pregnancies were reported among eravacycline-treated subjects in subjects with cUTI. One pregnancy was electively terminated and the other pregnancy resulted in a healthy child.

Updated observations based on the integrated phase 2/3 safety pool:

A trend towards a higher frequency of AEs is seen in association with higher BMI, which is however in agreement with a higher morbidity risk of this population. For sex and age no clear relationship to AE frequency is observed in the integrated phase 2/3 pool.
The safety evaluation according to ethnicity is difficult to perform due to the still small subject number in the majority of subgroups. Overall TEAE frequencies and SOC representation after the mentioned stratifications reflect the results earlier obtained in safety pool 1.
Subjects with APACHE II scores ≥10 treated with eravacycline 1.0 mg/kg q12h or comparator experienced more TEAEs than subjects with scores <10 treated at the same dose, consistent with a higher expected morbidity in these subjects. The same trend is observed for the comparator group.
The rate of treatment discontinuation is low and comparable in the eravacycline arm and comparator arm. The rate of serious TEAEs is comparable in the low and high APACHE group treated with eravacycline.
While the rate of TEAEs is higher in renal impaired individuals under eravacycline and stronger rising compared to the comparator arm, the rate of serious TEAEs and TEAEs leading to treatment discontinuation remained comparable and low after stratifying according to renal function.
In both study arms worse hepatic function is associated with a higher rate of TEAEs, which is slightly more pronounced in the eravacycline treated group regarding SAEs/deaths and study drug discontinuation. These observations are in agreement with the observations made in safety pool 1.
Overall, no new safety signal was detected.

Safety related to drug-drug interactions and other interactions

CYP3A Induction

In the clinical study TP-434-020, concomitant administration of the strong CYP 3A4/3A5 inducer rifampin (600 mg p.o. q24h for 10 days) induced eravacycline metabolism, leading to a decreased exposure following a single i.v. dose by approximately 25% and increased clearance (CL) by approximately 54%. However, the exposure following i.v. administration of eravacycline + rifampin overlaps with the exposure following eravacycline alone.

In this study, safety assessments included AEs, clinical laboratory safety tests (haematology, serum chemistry, electrolytes, coagulation, urinalysis, and lipid profile), vital signs, physical examinations, and 12-lead ECGs. Three of the 12 subjects (25%) reported a single TEAE during the i.v. eravacycline portion of the study (nausea, polyuria and infusion site pain were each reported once). Only one of the 12 subjects reported a TEAE (headache) during the co- administration of eravacycline and rifampin. All TEAEs were mild in severity and two (nausea and infusion site pain during the i.v. eravacycline portion) were assessed as related to study drug. There were no SAEs or TEAEs leading to discontinuation.

CYP3A Inhibition

In study TP-434-016, concomitant administration of the strong CYP3A inhibitor itraconazole 200 mg p.o. q12 for 2 doses then q24h for 2 additional doses) had little impact on the PK of eravacycline (1.0 mg/kg i.v. administered as two single doses 10 days apart) by reducing its conversion to its metabolites. This inhibition produced increases in Cmax and exposure to eravacycline of approximately 5%. CL was decreased by approximately 23%.

In this study, safety assessments included AEs, clinical laboratory safety tests (haematology, serum chemistry, electrolytes, coagulation, urinalysis, and lipid profile), vital signs, physical examinations, and 12-lead ECGs. Overall, four of 12 (33.3%) subjects in Part A (single i.v. dose of eravacycline) and four of 12 (33.3%) subjects in Part B (single oral dose of eravacycline) of the study experienced a

TEAE. All TEAEs were considered mild or moderate in severity and those experienced during treatment periods that included eravacycline were consistent with the known safety profile of eravacycline. No deaths or SAEs occurred during the study. There were no clinically meaningful changes or significant abnormalities in clinical laboratory, vital signs, ECGs or physical examination results.

Other mechanisms of interaction

Eravacycline is not a substrate for the major human uptake or efflux transporters *in vitro. Thus,* co-administration with inhibitors of these transporters is unlikely to affect plasma concentrations of eravacycline. Furthermore, eravacycline and its metabolites do not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4 *in vitro*, nor do they induce CYP1A2, 2B6 or 3A4 making interactions with medicinal products that are substrates for these enzymes unlikely.

Discontinuation due to adverse events

The overall rate of discontinuation in the eravacycline group remains low in the integrated phase 2/3 safety pool.

2.6.1. Discussion on clinical safety

Safety data obtained in the newly submitted study (IGNITE-4) overall confirmed the safety profile observed for eravacycline in former studies. Only a small part of individuals discontinued the study due to adverse drug reactions in both study arms. The rate of SAEs in both study arms was comparable.

The most commonly reported adverse events for eravacycline belonged to the SOCs Gastrointestinal Disorders and General reactions including infusion site reactions, which confirms the AE profile observed for the drug in the former safety pool 1 (earlier phase 2/3 pool). As observed earlier, eravacycline appears to induce more frequently infusion site reactions than does the comparator, as reflected in a higher rate of local infusion site thrombosis/thrombophlebitis. This effect was also observed earlier in safety pool 1 and is included in the Xerava SmPC, section 4.8.

As observed earlier in study pool 1, about 13% of subjects showed moderate lipase elevations. As also seen in safety pool 1, the rate was comparable to the rate observed under treatment with the comparator. In five cases (4 eravacycline, 1 meropenem) lipase increases resulted in AE reporting in the current study. Analysis of the integrated safety pool including the results of all studies demonstrates a numerically higher rate of pancreatitis cases compared to comparator treatment (7 cases verses 3 cases). The study of narratives allowed the conclusion that one case in the eravacycline arm can be evaluated as possibly associated and one case as probably associated with study drug. A warning was introduced in the Xerava SmPC section 4.4, mentioning that medicines belonging to the class of tetracyclines may have the potential to induce pancreatitis. Furthermore, based on the knowledge about an existing class effect of tetracyclines and pancreatitis and the fact the cases are observed with eravacycline, an inclusion of pancreatitis in section 4.8. of the Xerava SmPC was requested and was subsequently implemented by the applicant.

Liver function tests were in the majority of cases in the normal range under eravacycline or meropenem in the newly submitted study. Increases of ASAT and ALAT were observed under both eravacycline and comparator which, however, were in the majority of cases of mild nature and equally distributed in frequency between eravacycline and comparator arm in both the recently submitted study and the integrated safety pool. Of note, the frequency of bilirubin increase was clearly higher with eravacycline as compared to meropenem. However, elevations of bilirubin were overall mild.

Thus, elevations of ASAT, ALAT and bilirubin were included as uncommon events in the Xerava SmPC section 4.8.

Of note, altogether 5 (eravacycline) and 2 (comparator) potential DILI cases based on Hy's law criteria were identified in the integrated phase 2/3 safety pool. The study of the narratives of the five potential DILI cases treated with eravacycline showed that only one of these cases can be evaluated as possibly related to eravacycline treatment. Thus, no safety signal was detected.

As seen already earlier, a slight increase in aPTT values was again observed under eravacycline in the newly submitted study, which was, however, of mild nature and not associated with a higher rate of bleeding events in the study. In conclusion, no safety signal was detected here either.

Overall, a low rate of hypersensitivity reactions and development of rash is observed with eravacycline according to the updated analysis based on the integrated phase 2/3 safety pool. Although low in frequency and comparable in the study arms, CHMP requested to include hypersensitivity and rash in the Xerava SmPC, section 4.8. as uncommon AEs. The applicant has implemented the CHMP request.

The number of subjects that developed a deep vein thrombosis under eravacycline or comparator has not changed in the integrated safety pool (4 cases under eravacycline, 0 cases under treatment with comparator) as no new cases have been observed in the newly submitted study IGNITE-4. As requested, the applicant has analysed clinical cases that developed DVT under treatment with Xerava regarding cardiovascular risk factors, provided information on the distribution of cardiovascular risk factors in compound and control arms and evaluated the knowledge about any class specific effects on the coagulation system. Cardiovascular risk factors between compound and control arm appear to be equally distributed. Based on the results obtained regarding the impact of eravacycline on coagulative parameters it can be concluded that Xerava does not enfold pro-thrombotic effects. Other tetracyclines have been shown to have no or slightly anti-coagulant effects. Patients who developed DVT under eravacycline presented several cardiovascular risk factors that predispose for thrombotic events and have in the majority of cases not received pharmacological DVT prophylaxis. The frequency of DVT observed under eravacycline is comparable to background incidences observed in hospitalized patients. Based on these observations it can be concluded that Xerava do not enfold pro-thrombotic effects. Thus, CHMP agreed that the view of the MAH not to include DVT in section 4.8 of the SmPC can be endorsed.

In conclusion, taking the safety outcome of all phase 2 and 3 studies as analysed in the integrated phase 2/3 safety study pool together, the safety profile of eravacycline was considered acceptable by CHMP.

From the safety database the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety profile of Xerava is appropriately characterised and is considered acceptable by CHMP.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Permanent teeth discolouration and a delay in ossification processes (foetal exposure in pregnancy during the 2nd and 3rd trimester, exposure to the breast-fed infant, and exposure in children under 8 years of age) Pseudomembranous colitis Emergence of resistance
Missing information	None

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Five-year observational study to monitor resistance of pathogens to eravacycline in Europe, USA and Asia/Pacific regions Ongoing	To evaluate the emergence of resistance of pathogens to eravacycline in hospitals in Europe, USA and Asia/Pacific regions	Emergence of resistance	Annual reports	Annual reports will be provided in Q2/Q3 every year for 5 years
			Final report	5 years post-approval

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Permanent teeth discolouration and a delay in ossification processes (foetal exposure in pregnancy during the 2nd and 3rd trimester, exposure to the breast-fed	Routine risk minimisation measures: SmPC section 4.1 where the indication for use in adult patients is presented SmPC section 4.2 where advice is given on use in children and adolescents SmPC section 4.2 where advice is given not to use in children under 8 years because of teeth	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Tooth discolouration follow-up form Additional pharmacovigilance activities:

Safety concern	***Risk minimisation measures***	***Pharmacovigilance activities***
infant, and exposure in children under 8 years of age)	discolouration SmPC section 4.4 where the risk of permanent teeth discolouration during the 2nd and 3rd trimester of pregnancy and in children under 8 years is highlighted SmPC section 4.6 where advice is given on risks associated with use during pregnancy and considerations for use SmPC section 4.6 where advice is given on risks associated with use during breast-feeding and considerations for use SmPC section 5.3 where information on non-clinical findings are provided PL section 1 where information is given on what Xerava is used for in adult patients PL section 2 where advice is given on use in children and the permanent effects on teeth caused by tetracycline class antibiotics PL section 2 where advice is given on risks associated with use during pregnancy including permanent staining of teeth and a delay in natural bone formation PL section 2 where advice is given on risks associated with use during breast-feeding including permanent staining of teeth Legal status (prescription only medicine) Additional risk minimisation measures: None	None
Pseudomembranous colitis	Routine risk minimisation measures: SmPC section 4.4 where advice is given on the recommended action in case of pseudomembranous colitis Listed as a class adverse reaction of antibiotics in SmPC section 4.8 PL section 2 where advice is given on the recommended action if symptoms occur Diarrhoea is listed as a side effect in PL section 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Quantification in ongoing Phase 3 cUTI Study TP-434-021 Additional pharmacovigilance activities: None

Safety concern	*Risk minimisation measures*	*Pharmacovigilance activities*
	Legal status (prescription only medicine) Additional risk minimisation measures: None	
Emergence of resistance	Routine risk minimisation measures: SmPC section 5.1 where guidance is provided on the mechanism of resistance Legal status (prescription only medicine) Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Five-year observational study to monitor resistance of pathogens to eravacycline in Europe, USA and Asia/Pacific regions

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of eravacycline with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers eravacycline to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Xerava (eravacycline) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication is *treatment of complicated intra-abdominal infections (cIAI) in adults*. Intra-abdominal infections include a wide spectrum of pathological conditions. In uncomplicated IAIs the infectious process only involves a single organ and does not proceed to the peritoneum. Complicated intra-abdominal infection extends beyond the hollow viscus of origin into the peritoneal space and is associated with either abscess formation or peritonitis. The peritoneal contamination may result from spontaneous perforation (e.g. appendicitis, perforated ulcer or diverticulitis), surgical intervention, or trauma.

3.1.2. Available therapies and unmet medical need

The management of cIAIs usually involves surgical and/or percutaneous drainage, removal of diseased tissue and adequate source control in conjunction with the use of broad-spectrum antibiotics or antibiotic combinations.

3.1.3. Main clinical studies

The main pivotal studies (TP-434-008 [IGNITE 1] and TP-434-025 [IGNITE 4]) were randomised, double-blind, double-dummy, multicentre studies to evaluate the non-inferiority of eravacycline to ertapenem (TP-434-008) or meropenem (TP-434-025) in patients with cIAI. The studies included adult patients hospitalised with cIAI, including intra-abdominal abscess or peritonitis in need for acute surgical or percutaneous intervention and at least one symptom of systemic inflammatory response. Subjects with most severe infections, including those with septic shock, were excluded from the studies. Patients with renal failure, significant hepatic disease or immunocompromised patients were also excluded.

3.2. Favourable effects

Clinical cure rates in the MITT population were 87.0% in the eravacycline group and 88.8% in the ertapenem group in study TP-434-008. The corresponding numbers in the CE population (co-primary analysis population) were 92.9% and 94.5%, respectively. The lower limits of the 99% CI were -9.2% and -7.9%, respectively. The lower limits of the 99% CI were above the predefined NI-margin of -12.5%. In study TP-434-025 clinical cure was approximately 92 % and 96-97% in both arms in the MITT population and CE populations, respectively. The difference in clinical cure rates between the eravacycline and meropenem groups in the MITT population at the TOC visit was 0.8 (95% CI: -4.1; 5.8).

The results of the sensitivity analyses were supportive of the primary analyses results.

In sub-population analyses (including age, gender, race, geographic region, site of infection, abscess/no abscess, APACHE II score, renal function, and prior antibacterial treatment) no major clinically meaningful differences between treatment groups were detected. The response rates were similar for test and comparator regimens, but somewhat lower in treatment groups of patients with renal impairment.

Favourable per-subject microbiological response at the TOC visit for the micro-ITT population was in the same range as the favourable clinical response in the MITT population for eravacycline and comparator groups. Favourable per pathogen microbiological response ranged from 85% to 100% in both treatment groups for the majority of pathogens. Favourable response rates below 85% in the pooled eravacycline groups were noted for *E. cloacae* (81.0%), *E. faecalis* (83.3%), *E. faecium* (84.4%), *B. caccae* (76.5%) and *B. ovatus* (74.4%).

3.3. Uncertainties and limitations about favourable effects

As previously noted, critical findings were noted during the inspection of one investigator site. The findings were considered to be site specific and were mainly due to lack of experience and GCP knowledge. Another aspect was the poor performance of the monitor responsible for this particular site. In the opinion of the GCP inspectors, elimination of the data from this site was sufficient and CHMP agreed that the issues from this site do not indicate the need of further inspections.

In the assessment of new antibacterial agents, PK-PD analyses play a central role for dose-finding before embarking into clinical studies, but also to support the results from the pivotal studies that the dose is sufficient to cover for the wild-type population of organisms against which the agent is expected to be clinically active. Moreover, the same data are important for the determination of MIC breakpoints. PTA simulations based on preclinical PK/PD targets and human PK data did not provide support for the proposed dose regimen of eravacycline to cover for pathogens belonging to the wild-type populations. Moreover, no relationships between MIC and outcome in the clinical programme were detected. Such relationships would have been valuable for the assessment of the adequacy of the dose, because of the lack of support from PK-PD analyses.

The polymicrobial features of cIAI, the role of surgery in this infection as well as the lack of solid PK/PD support causes some uncertainties for which pathogens against which it would be considered acceptable to claim that eravacycline has been demonstrated to exert clinical activity.

The study population in the pivotal study included a relatively limited number of “high-risk” patients such as elderly (aged ≥ 75 years), patients with renal impairment, and patients with high APACHE II

score. Considering the serious nature of cIAI, the reported mortality rate was low. Taken together, this implies that the majority of patients had infections of rather mild to moderate severity. Due to the limited number of patients with APACHE II score for ≥10 and in particular, ≥15, uncertainties remain with respect to an overall generalization of the study results to patients with more severe cIAI. The limitations of the study population have been included in section 4.4 of the Xerava SmPC.

Results from the EOT and FU visits for the MITT and CE populations indicate that the clinical cure rate for the eravacycline arm in study TP-434-008 was lower than for the comparator and for both treatment arms in study TP-434-025. As compared to the TOC visit, clinical cure rates were also in general lower, in particular for the eravacycline arm in study TP-434-008. The difference between the treatment arms is influenced by the larger numbers of patients that were lost to follow-up in the eravacycline arm.

3.4. Unfavourable effects

Overall, 1284 subjects have been exposed to eravacycline in completed studies, thereof 926, who obtained at least 1.5 mg/kg q24 in a multiple i.v. dose setup. Taking the second submitted pivotal study into consideration with 250 additional individuals exposed to eravacycline, the novel integrated phase 2/3 safety pool is composed of 1176 individuals treated with at least 1.5 mg/kg q 24h eravacycline and 1045 individuals treated with comparator. The mean duration of exposure was consistent and approximately 7 days across the phase 2/3 studies included in the integrated safety pool.

AEs of major importance to mention are side effects at the gastrointestinal tract (nausea, vomiting) and side effects at the injection site (such as phlebitis).

Isolated cases of pancreatitis have been observed during eravacycline treatment which can be evaluated as at least possibly related to eravacycline. Further, other medicines of the class have been associated with such effects. Therefore a causal relation is a reasonable possibility. As a result, pancreatitis has been included in section 4.8 of the Xerava SmPC.

Mild elevations of bilirubin are occurring with a higher frequency in the eravacycline arm compared to the comparator arm in the integrated phase 2/3 safety pool. As a result, elevations of bilirubin, AST and ALT have been included in the Xerava SmPC, section 4.8.

As with other tetracyclines, use of Xerava in children under 8 years of age may cause permanent discolouration of the teeth-this has been included in section 4.4. of the SmPC. Similarly, pseudomembranous colitis (which is associated with administration of many antibacterials) has been included in sections 4.4 and 4.8 of the Xerava SmPC.

3.5. Uncertainties and limitations about unfavourable effects

The exact frequency of drug induced pancreatitis is not entirely clear.

3.6. Effects Table

Table 2. Effects table for Xerava for the treatment of cIAI in adults

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Clinical cure in patients with cIAI	Proportion of patients with a favourable clinical response at TOC in MITT and CE populations (Study TP-434-008)	% (n/N)	MITT 87.0 (235/270) CE 92.9 (222/239)	MITT 88.8 (238/268) CE 94.5 (225/238)	Strength of evidence Non-inferiority to ertapenem using a 12.5% margin. No relevant differences between treatments in relevant sub-populations. Microbiological response rates generally similar to clinical response rates for pathogens isolated.	
	Proportion of patients with a favourable clinical response at TOC in MITT and CE populations (Study TP-434-025)	% (n/N)	MITT 92.4 (231/250) CE 96.9 (218/225)	MITT 91.6 (228/249) CE 96.1 (222/231)	Non-inferiority to meropenem using a 12.5% margin. No relevant differences between treatments in relevant sub-populations. Microbiological response rates generally similar to clinical response rates for pathogens isolated. Uncertainties (both studies) Lack of support for the dose regimen from PTA simulations to cover for pathogens belonging to the wild-type population. Efficacy in severe cIAI uncertain.	
Unfavourable Effects						
Nausea and vomiting	Outcome in the all phase 2/3 pool (safety pool 1)	N (%)	126 (13.6) 61 (6.6)	20 (2.5) 15 (1.9)	Higher rate in eravacycline treated patients compared to active comparator	
Injection site reactions	Outcome in the all phase 2/3 pool (safety pool 1)	N (%)	39 (3.4)	5 (0.4)	Higher rate in eravacycline treated patients compared to active comparator	
Cases of pancreatitis	Outcome in the updated integrated phase 2/3 pool	N (%)	7(0.6)	3 (0.3)	2 of 7 pancreatitis cases are evaluated as possible and likely associated with eravacycline	

- Abbreviations: cIAI, complicated intra-abdominal infection; TOC, test of cure; MITT, modified intent to treat; CE, clinically evaluable

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The similar clinical cure rates achieved with eravacycline and its comparators for the co-primary endpoint indicate that eravacycline is effective in the treatment of complicated intra-abdominal infections.

Determining which pathogens should be considered treatable with eravacycline is complicated by a high proportion of poly-microbial infections, the unclear impact of surgery on clinical outcome, and discrepancy between PK/PD predictions and clinical outcomes.

CHMP considered that clinical efficacy has been established in cIAI for *Escherichia coli*, viridans *Streptococcus spp.*, *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus aureus* and *Klebsiella pneumoniae*.

High success rates may not be reproducible in subjects with more severe infections for which the antimicrobial chemotherapy most likely would be of higher importance relative to source control measures. Although the clinical cure rate was similar in patients with more severe cIAI in the phase 3 study reflected by higher APACHE II scores, the number of patients with higher scores was low, which adds to this uncertainty. With regard to the sought indication, complicated intra-abdominal infections, the Xerava SmPC section 4.4 have been updated to accurately reflect limitations of the included study population.

The safety profile of Xerava appears overall acceptable, with a low rate of SAEs, gastrointestinal and infusion site side effects as major AEs to mention.

3.7.2. Balance of benefits and risks

A similar clinical and microbiological cure rate in the treatment of cIAI has been shown for eravacycline and its comparators in two pivotal studies and the safety profile appears overall acceptable.

CHMP agrees that the benefit-risk balance of eravacycline is considered positive.

3.8. Conclusions

The overall benefit-risk balance of Xerava is positive by CHMP.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Xerava is favourable in the following indication:

- treatment of complicated intra-abdominal infections (cIAI) in adults

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that eravacycline is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.