13 November 2025
EMADOC-1700519818-2559306
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xerava

International non-proprietary name: Eravacycline

Procedure No. EMA/VR/0000265697

Note

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

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BID	twice a day
BMI	body mass index
bpm	beats per minute
CI	confidence interval
cIAI	complicated intra-abdominal infection
CL	clearance
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CrCl	creatinine clearance
CRP	C-reactive protein
CT	computerised tomography
cUTI	complicated urinary tract infection
CYP	cytochrome P450
DILI	drug-induced liver injury
ECG	electrocardiogram
EOT	end of treatment
FU	follow-up
g	gram(s)
GGT	gammaglutamyl transferase
i.v.	intravenous
kg	kilogram(s)
L	litre(s)
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
min	minute(s)
µg	microgram(s)
µM	micromolar

mL	millilitre(s)
MRSA	methicillin-resistant *Staphylococcus aureus*
ND	not determined
PD	pharmacodynamics
PK	pharmacokinetics
p.o.	oral
PT	preferred term
q12h	every 12 hours
q24h	every 24 hours
QD	once a day
SAE	serious adverse event
SD	standard deviation
SMQ	Standardised MedDRA query
SOC	system organ class
TEAE	treatmentemergent adverse event
TOC	Test of Cure
TP-434	eravacycline
ULN	upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Paion Pharma GmbH submitted to the European Medicines Agency on 10 April 2025 an application for a variation.

The following variation was requested:

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of complicated intra-abdominal infections (cIAI) from the age of 8 years and older for XERAVA, based on final results from study TP-434-028; this is a phase 1, open-label, multicenter study to determine the pharmacokinetics and safety of intravenous eravacycline in children with suspected or confirmed bacterial infection. As a

consequence, sections 4.1, 4.2, 5.1, 5.2, and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0397/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0397/2023 was completed.

The PDCO issued an opinion on compliance for the PIP P/0397/2023.

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 MAH 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.

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: N/A

Timetable	Actual dates
Submission date	10 April 2025
Start of procedure:	26 April 2025
CHMP Rapporteur's preliminary assessment report circulated on:	19 June 2025
CHMP Rapporteur's updated assessment report circulated on:	17 July 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 July 2025
MAH's responses submitted to the CHMP on:	10 September 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	20 October 2025
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on:	9 November 2025
CHMP opinion:	13 November 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

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 (CAIAIs) 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).

Claimed therapeutic indication

The indication applied for was:

Xerava is indicated **in adults and in children from the age of 8 years** for the treatment of complicated intra-abdominal infections (cIAI) ~~in adults~~ (see sections 4.4 and 5.1).

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

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).

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 microbiota, 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).

Clinical presentation and 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.

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. Few broad-spectrum antibacterial agents are formally approved for use in paediatric patients.

2.1.2. 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 paediatric posology was as follows:

The recommended dose regimen for adolescents (12 - 17 years) is 1.5 mg/kg and that for children (8 - 11 years) is 2.0 mg/kg eravacycline every 12 hours for 4 to 14 days. ~~The safety and efficacy of Xerava in children and adolescents less than 18 years of age have not been established. No data are available.~~ Xerava should not be used in children aged under 8 years because of teeth discolouration.

Method of administration

Intravenous use.

Xerava is administered only by intravenous infusion over approximately 1 hour.

2.1.3. The development programme/compliance with CHMP guidance

The studies underlying the application were performed in accordance with the agreed paediatric investigation plan. No separate scientific advice for the extension was sought.

2.1.4. General comments on compliance with GCP

The application included a statement confirming that all the clinical trials carried out outside the European Union (USA) meet the ethical requirements of Directive 2001/20/EC.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable. Xerava is indicated for the treatment of complicated intra-abdominal infections (cIAI) in adults and the aim is to extend to 8 years and older patients. The active substance in Xerava, eravacycline, is a fluorocycline and belongs to the tetracycline class of antibiotics.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH provided an eravacycline ERA document (dated 24 Apr 2025; see Discussion below).

2.2.2. Discussion on non-clinical aspects

Assessment of paediatric data on non-clinical aspects

No new non-clinical data has been provided for this procedure, which is acceptable as there are no safety concerns identified for the new age-range that would require a more in-depth discussion.

Environmental risk assessment.

The MAH committed to submit an updated ERA in the future that takes into account the 2024 CHMP ERA GL requirements (if possible, within 2 years). As such, no conclusion can be made on the ERA status at this point.

2.2.3. Conclusion on the non-clinical aspects

There are no novel non-clinical issues identified that are of relevance to approval decision.

2.3. Clinical aspects

2.3.1. Introduction

This application was intended to support the broadening of the currently approved indication for eravacycline to include the paediatric patient population aged ≥8 years of age based on Study TP-434-028.

GCP

The Clinical trial was performed in accordance with GCP as claimed by the MAH.

This application is supported by a clinical study (Study TP-434-028). The studied population included children with suspected or confirmed bacterial infection. The study included 9 patients 12 to <18 years of age (singe 1.5 mg/kg dose) and 10 patients 8 to <12 years of age (single 1.75 mg/kg dose).

2.3.2. Pharmacokinetics

This application is intended to broaden the currently approved indication for eravacycline to include the paediatric patient population aged ≥8 years based on Study TP-434-028.

Study TP-434-028 is a Phase 1, open-label multicenter study to determine the pharmacokinetics and safety of intravenous eravacycline in children with suspected or confirmed bacterial infection.

The primary endpoints were based on PK and included the PK parameters Cmax and AUC.

The already approved formulation of eravacycline (powder for concentrate for solution for infusion) is intended to be used in paediatric patients.

Methods

Bioanalytical methods

The samples from study TP-434-028 were analysed using a validated LC-MS/MS method. The bioanalytical method performed adequately in accordance with the validation performed.

Target population

The PK in the target population was described using non-compartmental analysis and PopPK analysis with data from Study TP-434-028. PK data were available in 19 patients in Study TP-434-028 and included 9 patients 12 to <18 years of age receiving a single 1.5 mg/kg dose and 10 patients 8 to <12 years receiving a single 1.75 mg/kg dose. Patients received a single 60-minute infusion.

Blood samples for the determination of eravacycline were collected at multiple time-points following the single dose administration and included the following time-points: 5-10 minutes from the end of infusion, 0.5-1h, 2.5-3.5h, 4-5h and at 24 h after infusion.

Non-compartmental analysis

Subject demographic and baseline characteristics of the paediatric patients in Study TP-434-028 are summarized in Table 1.

Table 1 Summary of Demographic and Baseline Characteristics (Safety Population)

	Cohort 1 (N=9)	**Cohort 2 (N=10)**	**Total (N=19)**
Age (years)			
n	9	10	19
Mean (SD)	14.3 (1.73)	10.4 (0.84)	12.3 (2.40)
Median	15.0	11.0	11.0
Min, Max			
Sex, n (%)			
Male	6 (66.7%)	8 (80.0%)	14 (73.7%)
Female	3 (33.3%)	2 (20.0%)	5 (26.3%)
Weight (kg)			
n	9	10	19
Mean (SD)	60.26 (12.589)	39.00 (10.759)	49.07 (15.723)
Median	60.60	36.50	43.00
Min, Max			
Body Mass Index (kg/m^2)			
n	9	9	18
Mean (SD)	22.13 (3.847)	20.91 (5.023)	21.52 (4.385)
Median	21.60	21.60	21.60
Min, Max			
Creatinine Clearance (mL/min per 1.73 m^2) [b]			
n	9	9	18
Mean (SD)	111.47 (19.788)	124.29 (49.697)	117.88 (37.283)
Median	100.50	112.00	106.90
Min, Max	90.2, 138.8	69.0, 233.3	69.0, 233.3
Type of Infection, n (%)			
Intra-Abdominal Infection	0	0	0
Urinary Tract Infection	0	1 (10.0%)	1 (5.3%)
Pneumonia (CAP, HAP, VAP)	1 (11.1%)	1 (10.0%)	2 (10.5%)
Skin	2 (22.2%)	1 (10.0%)	3 (15.8%)
Other	6 (66.7%)	7 (70.0%)	13 (68.4%)

Following the single IV infusion of eravacycline, plasma concentrations of eravacycline were detectable in all subjects at the initial plasma sampling time point 5 to 10 minutes after the end of the 60-minute infusion period. The observed plasma concentrations of eravacycline declined in a multi-phasic manner thereafter and were approximately half of initial peak concentration within an hour (Figure 1). Most of eravacycline was eliminated from plasma within 4 to 5 hours after the end of infusion. The shape of the concentration versus time curve was similar between both treatment groups. The corresponding PK vs time figure for adult cIAI patients is included in Figure 2 (from the CSR of Study TP-434-008 in procedure EMEA/H/C/004237/0000).

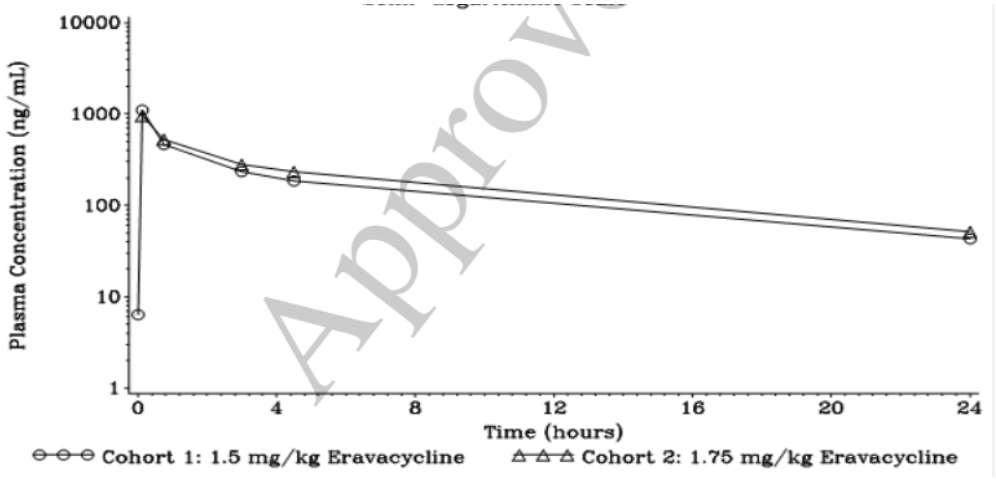


Figure 1 Mean Plasma Concentrations of Eravacycline Versus Time (Pharmacokinetic Population in paediatric patients in Study TP-434-028)

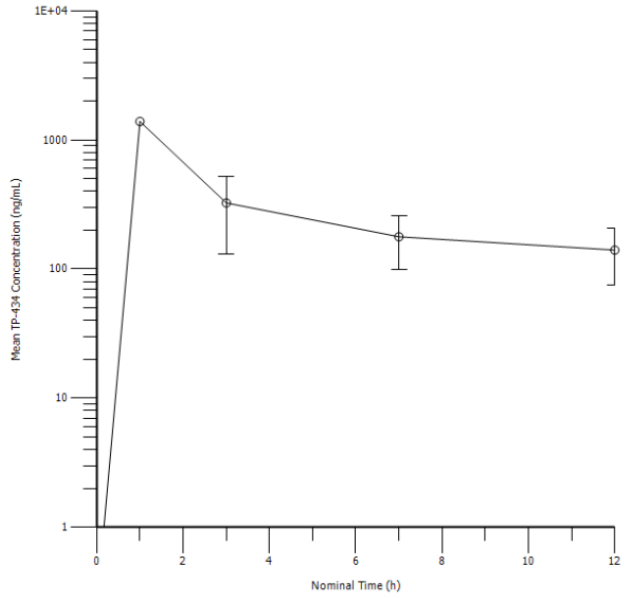


Figure 2 Mean Plasma Concentrations of Eravacycline Versus Time in adult cIAI patients in Study Study TP-434-008.

Cmax, AUC(0-t), and AUC(0-inf) of observed eravacycline (Table 2) were similar for both treatment groups. Tmax values ranged from 1.05 – 1.57 hours for both treatment groups. The mean (%CV) AUC0-inf was 5320 ng*h/mL (48.8%) in adult cIAI patients (from the CSR of Study TP-434-008 in procedure EMEA/H/C/004237/0000).

Table 2 Mean (CV) Plasma Pharmacokinetic Parameters of Eravacycline in paediatric patients in Study TP-434-028

Parameter (unit)	12 to <18 years; 1.5 mg/kg Eravacycline (N=9)	8 to <12 years; 1.75 mg/kg Eravacycline (N=10)
C_{max} (ng/mL)	1100 (69.8)	953 (68.6)
$AUC_{(0-t)}$ (ng•h/mL)	4020 (39.3)	4440 (23.5)
$AUC_{(0-inf)}$ (ng•h/mL)	4570 (38.2)	5080 (23.2)
$AUC_{(0-24)}$ (ng•h/mL)	3980 (39.6)	4430 (23.3)
T_{max} (h)(a)	1.20 (1.05, 1.30)	1.38 (1.20, 1.57)
$t_{1/2}$ (h)	8.76 (15.5)	8.28 (17.8)
CL (L/h)	22.3 (42.8)	14.0 (30.7)
V_d (L)	222 (38.1)	143 (29.3)

Abbreviations: CV, coefficient of variation; h, hours.
Note: (a) For Tmax, the median (minimum, maximum) values are presented

PK data from the metabolites TP-498 and TP-6208 were also quantified (data not shown).

Population pharmacokinetic analysis

An adult population PK model was updated by including paediatric PK data from Study TP-434-028.

Objectives

The objectives were to

- Re-evaluate the previously developed population PK model of IV eravacycline
- Provide adjusted dosing predictions for children 8-12 years and 13-17 years old.

Methods

Model development

The PK analysis population consisted of all adult and paediatric subjects who received at least one dose of IV eravacycline and who had at least one measurement of eravacycline plasma concentration, whether the subject completed all treatments or not. For more details on the adult PopPK model see initial submission (EMEA/H/C/004237/0000).

The previous model that best described eravacycline was a 3-compartment model with linear elimination. Theoretical allometric functions on clearances and on volumes of distribution (i.e., exponents of 0.75 and 1, respectively) were considered along with relevant covariate effects.

A bias in goodness-of-fit (GOF) plots for the paediatric population (Study TP-434-028) was observed and was associated to high observed eravacycline concentrations. The above-described final model appeared to underpredict peak eravacycline concentrations in the paediatric population at the population levels. This bias identified in the observed concentrations versus the population predicted concentrations at high concentrations indicates a mischaracterization of V1 in the paediatric population. The model was refined to optimize the GOF plots.

The PK-covariate relationships already included in the optimized model were kept in the model. The remaining PK-covariate trends were screened using visual inspection.

The population PK analysis was performed using the non-linear mixed effect model (NLME) in NONMEM (Version 7.3).

Simulations

Virtual paediatric patients with age-weight matched information were simulated based on published Center for Disease Control and Prevention (CDC) growth charts.

Monte Carlo simulations were performed using the updated population PK model of IV eravacycline. A total of 500 virtual subjects (250 males and 250 females) were allocated in each simulation scenario and age group. For adults, cIAI patient characteristics were resampled from the 610 patients included in the PK population. The following simulation scenario of IV eravacycline were evaluated:

Children [8 to <12 years]

- 1.75 mg/kg once daily (QD)
- 1.15 mg/kg twice daily (BID)
- 1.5 mg/kg BID
- 2 mg/kg BID

Adolescents [12 to <18 years]

- 1.5 mg/kg QD
- mg/kg BID
- 1.25 mg/kg BID
- 1.5 mg/kg BID

For the adults, the reference dosing regimen was 1 mg/kg BID.

The population of interest was the patients with cIAI with normal hepatic function without cytochrome P450 3A (CYP3A) inhibitor or inducer. Therefore, the effects of cUTI, other bacterial infection and presence of strong CYP3A inducers or inhibitors were not considered in the simulations.

Descriptive statistics of NCA parameters were computed by age group and dosing regimen in virtual children and adolescents and compared with the descriptive statistics in adults.

Results

Model development

The model was improved by estimating the allometric exponents of body weight on clearance and volume parameters and re-assessing the infection effect on central volume of distribution. A third category of infection was added in the model (i.e., cIAI, cUTI and other bacterial infection). This third category was needed since paediatric patients enrolled in Study TP-0434-028 had various types of bacterial infection. Finally, the effect of cIAI on CL was removed since it appeared not significant.

The appropriateness of the updated population PK model for paediatric population was evaluated using VPC on plasma concentration-time profiles of eravacycline. A total of 1000 replicates of the original observed subjects were simulated with the population PK model. Results of the VPC by study in TP-434-028 are presented in Figure 3.

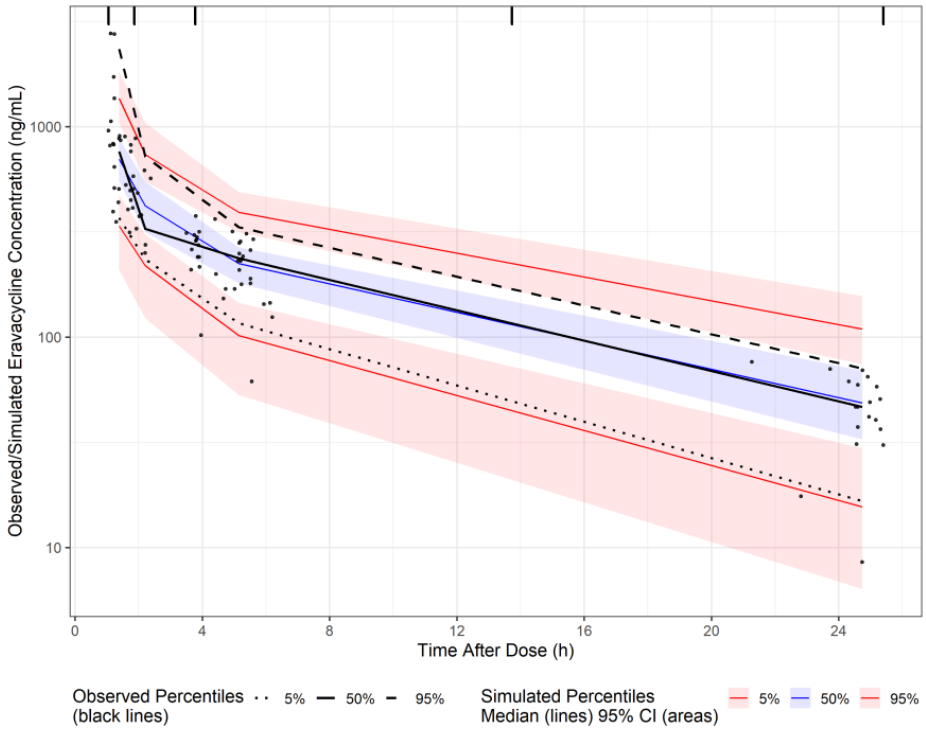


Figure 3 Visual Predictive Check - Model-Predicted and Observed Concentrations of Eravacycline – Study TP-434-028

Typical population PK parameters of eravacycline after IV administration derived with dataset with PK data in adults, children and adolescents are presented in Table 3.

Table 3 Typical Population PK Parameters of Eravacycline Following Eravacycline IV Administration – Adults, Children and Adolescents

Parameter	**Estimate (RSE)**	**BSV (Shrinkage)**
CL (L/h)	**11.8 (2.1%)** × $(Weight/70)^{0.679}$ × $(Age/45)^{-0.287}$ × 0.674 if Severe HEP × 0.654 if Strong CYP3A inhibitor (TP-434-016) × 1.72 if Strong CYP3A inducer (TP-434-020)	**43.6%** (11.2%)

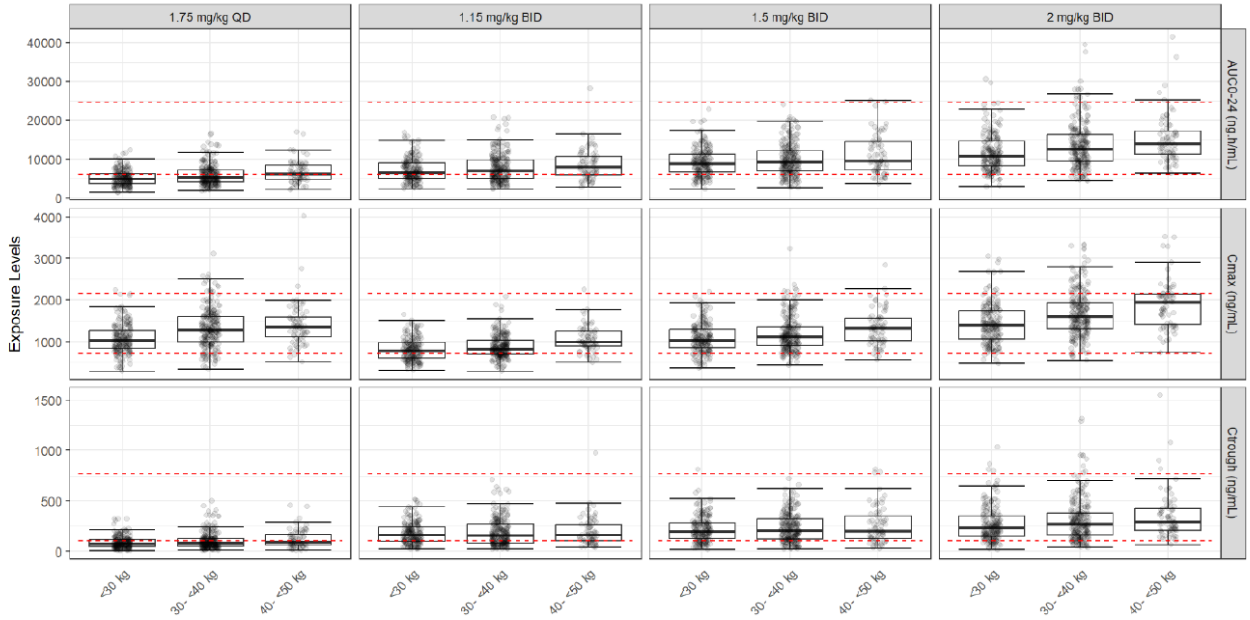
V1 (L)	**22.5 (11.2%)** × (Weight/70)$^{0.421}$ × 2.14 if cIAI × 1.67 if cUTI × 3.39 if other bacterial infection	**71.3%** (15.7%)
Q2 (L/h)	**32.1 (3.3%)** × (Weight/70)$^{0.679}$ × exp(-0.305 × (Dose/Weight - 1.0))	**51.8%** (24.6%)
V2 (L)	**109 (2.5%)** × (Weight/70)$^{0.421}$	**36.0%** (31.5%)
Q3 (L/h)	**5.25 (3.4%)** × (Weight/70)$^{0.679}$ × exp(-0.285× (Dose/Weight - 1.0))	
V3 (L)	**175 (1.7%)** × (Weight/70)$^{0.421}$	
Proportional Error	**19.3%**	
Additive Error (ng/mL)	**1.54**	

BSV, between-subject variability; cIAI, complicated intra-abdominal infection; CL, clearance; cUTI, complicated urinary tract infection; CYP3A, cytochrome P450 3A; HEP, hepatic impairment; IV, intravenous; PK, pharmacokinetic; Q2 and Q3, intercompartment clearances; RSE, relative standard error; V1, central volume of distribution; V2 and V3, peripheral volumes of distribution. Note: Correction factors of 1.79 and 1.76 on residual errors were applied for the different assays used in Studies TP-434-013 and TP-434-014, respectively. These correction factors were applied as IPRED/THETA)

Simulations

The population PK model summarized in Table 3 was used to generate the simulations. Steady state exposure levels of eravacycline predicted in children and adolescent populations are summarized by dosing regimens and weight groups and compare to adult exposure levels following 1 mg/kg BID in Figure 4.

a) Children



b) Adolescents

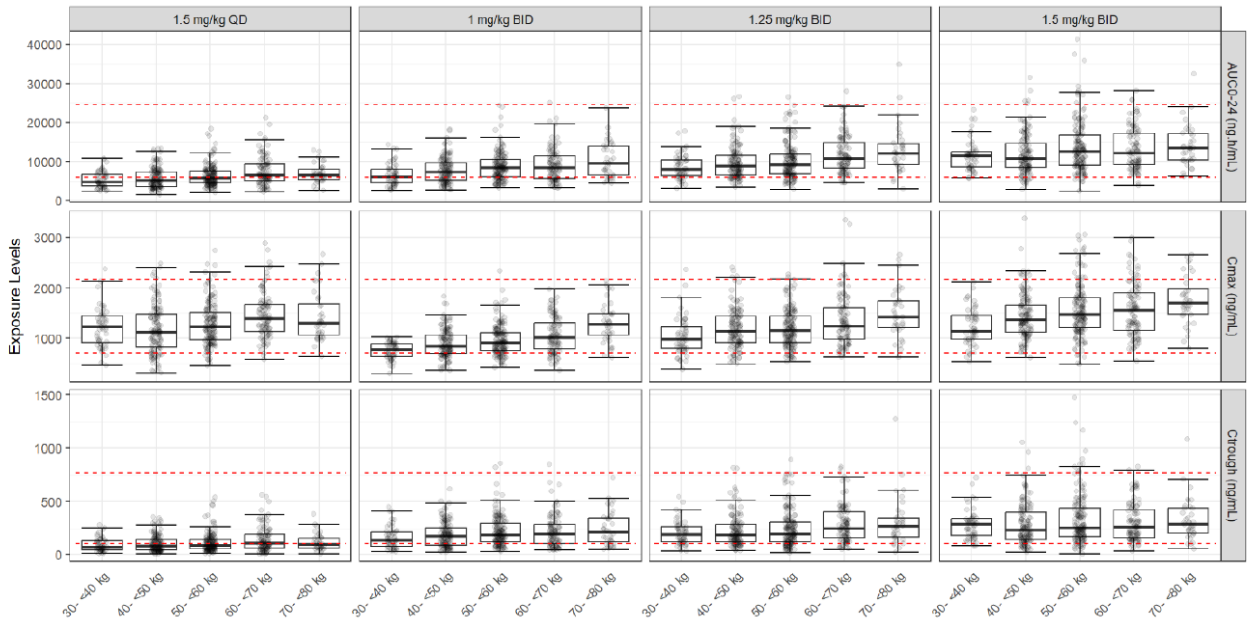


Figure 4 Comparison of Steady-State Exposures in Children, Adolescents and Adults with Complicated Intra-Abdominal Infection After IV Administration of Eravacycline – By Weight Group. AUC0-24, area under the curve from time 0 to 24 hours; BID, twice daily; Cmax, maximum concentration; Ctrough, minimum concentration; IV, intravenous; QD, once daily. Note: Only weight groups with N>20 are displayed; Red dashed lines represent the 5th and 95th percentiles of exposure in adults at 1 mg/kg BID.

The steady-state exposures in children (8 to < 12 years of age) at a dose of 2 mg/kg BID and in adolescents (12 years to < 18 years of age) at a dose of 1.5 mg/kg BID are generally contained within the exposures in adults with cIAI (i.e., geometric means within 20% of the geometric means in adults for AUC0-24, Cmax, Ctrough).

2.3.3. Pharmacodynamics

The activity of eravacycline has been well characterized in a comprehensive series of *in vivo* and *in vitro* microbiology studies provided in the original marketing application. No new *in vivo* or *in vitro* studies were performed in support of this paediatric submission.

2.3.4. PK/PD modelling

No probability of target attainment (PTA) analyses were provided.

2.3.5. Discussion on clinical pharmacology

The MAH submitted PK data from Study TP-434-028 in paediatric patients where PK was listed as the primary objective. The benefit-risk in patients 8-<12 years may be extrapolated from the adult population via PK bridging extrapolation of efficacy/safety from adults by means of exposure matching. However, the PK analyses have major limitations which means the initially proposed doses of 2 mg/kg and 1.5 mg/kg in paediatric patients aged 8-12 and 12-18 years, respectively were considered unacceptable. It was, however, possible to support an adult posology (1 mg/kg) in a subset of paediatric patients weighing at least 50 kg without any updated PK analyses. The MAH updated the SmPC accordingly to (1) restrict the claimed indication in SmPC Section 4.1 to (adults and) adolescents weighing at least 50 kg and (2) recommend 1 mg/kg to both adults and adolescents weighing at least 50 kg in SmPC Section 4.2.

A 50 kg weight cut-off should be implemented based on the observed body weight distribution in the evaracycline arm in the adult pivotal efficacy and safety Study TP-434-008 (IGNITE-1). The body weight ranged from 47 to 123 kg. The adult eravacycline dosing regimen is body-weight based and this has been shown to be adequate in the body weight range from 50 kg and above.

For extrapolation of efficacy, AUC is considered the most relevant exposure metric for the exposure matching since AUC/MIC was identified as the PK/PD index in the initial submission (EMEA/H/C/004237/0000). For extrapolation of safety, both AUC and Cmax are considered relevant.

The PK data was analysed using non-compartmental analysis and PopPK modelling.

PK sampling was included with measurement of eravacycline. The PK sampling included collection of several samples following a single dose which allowed calculation of PK parameters using non-compartmental analysis including Cmax and AUC.

The mean (%CV) AUC0-inf were 4570 (38.2%) and 5080 (23.2%) ng*h/mL in patients 12 to <18 years of age (1.5 mg/kg) and 8 to <12 years of age (1.75 mg/kg), respectively. This is overall comparable to the observed mean AUC0-inf in adult cIAI patients (5320 ng*h/mL [48.8%CV] following 1 mg/kg). However, for the 8-12 year age group, a higher-than-observed dose of 2 mg/kg was initially proposed which has not been sufficiently justified by updated PopPK analyses. Based on this comparison it is unclear why a higher-than-studied dose of 2 mg/kg is proposed in patients 8-12 years since (a) the exposures were overall comparable between paediatric patients and adults and (b) the exposure is higher following the studied dose in patients 8-12 years than in patients 12-18 years.

For the 12-18 year age group, the recommended dose is 50% higher than the recommended dose in adults. This higher dose cannot be accepted without updated fit-for-purpose PopPK models due to the following limitations of Study TP-434-028:

• A limited number of adolescents were studied (n=9)

• Only a single dose was studied (whereas the recommended dose regimen is BID)

• A sparse PK sampling schedule was applied

• None or very few paediatric patients were included with cIAI. The data indicates that the PK differed between adult cIAI patients and the paediatric patients in Study TP-434-028 (after accounting for differences in the mg/kg dose). However, it is highly unclear if this reflects an underlying PK difference between adults and paediatric patients, or if this difference exists due to the paediatric patients having a different type of infection.

The non-compartmental analysis was based on the observed PK data from Study TP-434-028 in patients ≥9 years and ≥28.5 kg. The proposed indication includes patients aged ≥8 years where patients aged 8 years are expected to weigh approximately 20 kg and above. Thus, the observed PK data from Study TP-434-028 is not covering the entire target population. Since this non-compartmental analysis cannot be used to extrapolate the PK below the studied age- and weight range, updated PopPK analyses (including simulations) would be needed to support the initially proposed posology.

The final paediatric PopPK model was a jointly estimated (adult+paediatric) model including data from all patients in Study TP-434-028. The number of paediatric patients in low in comparison to the number of adult patients included in the PopPK dataset. The Applicant observed model misspecifications when re-estimating the adult PopPK model on a dataset including paediatric data. This resulted in an updated paediatric PopPK model.

The PopPK model used to describe PK in the target population was a 3-compartment model with linear elimination from the central compartment. The most relevant parameter-covariate relationships for this procedure (paediatric indication) included age on CL, weight on all clearance + volume terms with estimated coefficients and ”other bacterial infection” on central volume of distribution. The goodness-of-fit plots, including a VPC of the paediatric data, did not indicate any major signs of model mis-specification as such. The final paediatric model was used to perform simulations to support the proposed posology. However, there are several concerns with the presented model which need to be resolved by an updated PopPK model before the proposed posology can be accepted. The detailed concerns with the PopPK model are outlined below.

The current implementation of the parameter-covariate relationship between CL and age is not acceptable; The CL-age relationship was found significant when developing the adult PopPK model and it is unreasonable to assume that the CL-age relationship can be extrapolated in paediatric patients. Firstly, paediatric eravacycline PK will differ from adults due to the lower body weight and it is unreasonable to assume that age would be a covariate on CL in patients ≥8 years after accounting for body weight. The CL-age relationship is likely driven by the rather large amount of adult PK data in relation to the rather limited amount of paediatric PK data. Furthermore, it is inappropriate to estimate coefficients for age and weight simultaneously since age and weight are highly correlated in paediatric patients.

The body weight-PK relationship with estimated allometric coefficients of clearance- and volume terms is not acceptable. The body weight-PK relationship was fixed to literature values when developing the adult PopPK model. The body weight-PK relationship is likely driven by the rather large amount of adult PK data in relation to the rather limited amount of paediatric PK data. Furthermore, it is inappropriate to estimate coefficients for age and weight simultaneously since age and weight are highly correlated in paediatric patients. Thus, it is questionable whether the body weight-PK relationship in paediatric patients is identifiable under these circumstances and

allometric exponents fixed to literature values (0.75 for clearance terms and 1 for volume terms) would have been more appropriate.

The paediatric PK model included ”other bacterial infection” on volume of distribution which needs to be explored further, before the clinical relevance of this covariate can be assessed. ”Other bacterial infection” was introduced in the paediatric PopPK model (not included as a covariate in the adult PopPK model). Importantly, all paediatric patients except one had ”other bacterial infection”. Thus, it is not possible to identify if the different volume associated with ”other bacterial infection” is due to the type of infection, or if paediatric patients as a group have different volume than adults. An updated PopPK model (where age and body weight should be implemented differently) would be required in order to potentially support the initially proposed doses.

The final paediatric model included dose-dependent inter-compartmental clearance to the peripheral compartments. This seems overall reasonable considering that this is similar to the adult PopPK model.

The parameter precision (RSEs) were not reported for the parameter-covariate relationships. This information is considered important and would be needed in order to support the initially proposed posology.

The current paediatric PK simulations are not considered acceptable for supporting the initially proposed posology. The Applicant used the paediatric PopPK model to perform PK simulations including AUC and Cmax. Although these are relevant PK metrics to include, the paediatric PopPK model is unacceptable, and thus, updated PopPK simulations would be needed to support the initially proposed doses.

Regarding PKPD, the Applicant did not perform any PTA analyses which would be needed to support the initially proposed paediatric doses.

Regarding dose justification, the initially proposed doses are not sufficiently justified. The need for a higher-than-studied dose in patients 8-12 years of age (2 mg/kg) is highly unclear since the observed PK data indicated comparable observed exposures compared to adults and the exposure in 8-12 years of age had higher observed exposure than patients 12-18 years. The initially proposed target population included patients ≥8 years whereas the observed PK data were limited to patients ≥9 years. An 8 year-old patient may weigh ~20 kg and above whereas the observed PK data were limited to patients and ≥28.5 kg.

Since the initially proposed paediatric doses would have to be based on extrapolation of efficacy and safety from adults, any potential dose recommendations diverging from the adult dose should be based on exposure matching (should be based on AUC for efficacy since AUC/MIC was concluded as the PK/PD index in the original submission).

Since the adult posology (1 mg/kg) is considered a reasonable dose for a subset of adolescents (above 50 kg), all the issues related to the initially proposed doses are not pursed further.

Regarding SmPC Section 5.2, no descriptive PK information from Study TP-434-028 was included given the limitations described above. However, a statement was added that a population pharmacokinetic (PopPK) study was conducted, but that no conclusion on dose recommendation could be drawn in paediatric patients <50 kg.

2.3.6. Conclusions on clinical pharmacology

PK-data were presented from 19 paediatric patients in Study TP-434-028. The PK data were analysed using non-compartmental analysis and using PopPK modelling. There are major

limitations with Study TP-434-028, and the study cannot be used to support a paediatric posology higher than the adult posology.

Despite these limitations, a peadiatric posology was achieved in adolescents weighing at least 50 kg. The new claimed indication in SmPC Section 4.1 was restricted to (adults and) adolescents weighing at least 50 kg. In SmPC Section 4.2, the adult posology (1 mg/kg) is recommended for adolescents weighing at least 50 kg.

2.4. Clinical efficacy

2.4.1. Main study

A Phase 1, Open-label, Multicenter Study to Determine the Pharmacokinetics and Safety of Intravenous Eravacycline in Children with Suspected or Confirmed Bacterial Infection - Study (TP-434-028)

TP-434-028 was a Phase 1, open-label, single-dose study to evaluate PK, safety, and tolerability of i.v. eravacycline in children with suspected or confirmed bacterial infection who were receiving systemic antibiotic therapy, other than eravacycline. The study aimed to evaluate the PK and safety of i.v. eravacycline in a paediatric population at exposures predicted to be comparable to the exposures previously studied in adults. Efficacy was not an objective of this study and no efficacy endpoints were studied.

Methods

The treatment duration was 1 day in a hospital setting following i.v. administration of eravacycline. All on-site PK and safety assessments were completed within 24 hours (±60 minutes) following completion of study drug infusion. A safety follow-up visit or telephone call occurred on Day 7 (+2 days). Subjects and/or their legal representatives were asked to provide information about AEs and concomitant medications and procedures. If the subject remained in hospital at the time of the scheduled follow-up visit, the visit may have been conducted as a face-to-face interview instead of a telephone call.

Safety and tolerability were assessed by monitoring and recording adverse events (AEs), clinical laboratory test results, vital sign measurements, and physical examination findings.

Study participants

Two cohorts defined by age group were enrolled simultaneously:

- Cohort 1: 12 to <18 years of age (adolescents)
- Cohort 2: 8 to <12 years of age (children)

All potential study participants underwent a screening evaluation.

The study planned to enroll a total of 20 subjects in 2 cohorts (12 to <18 years of age and 8 to <12 years of age). A total of 19 subjects were enrolled and completed the study.

Male or female subjects were eligible if they were 8 to <18 years of age and hospitalized, in stable condition, and receiving or planned to receive within 24 hours systemic antibiotic therapy, other than eravacycline, for a suspected or confirmed bacterial infection and were likely to have survived the current illness.

Treatments

Eravacycline was administered intravenously as a single 1.50 mg/kg dose (Cohort 1: 12 to <18 years) or 1.75 mg/kg dose (Cohort 2: 8 to <12 years). Subjects received their assigned dose as a 60-minute infusion on Day 1 of the study.

Objectives

The primary objective of this study was to evaluate the PK of i.v. eravacycline in children 8 to <18 years of age. The secondary objective was to evaluate the safety and tolerability of i.v. eravacycline in children 8 to <18 years of age with suspected or confirmed bacterial infection.

Efficacy was not an objective of this study.

Outcomes/endpoints

See under **Error! Reference source not found. Error! Reference source not found.** and **Error! Reference source not found. Error! Reference source not found.**, for PK and safety endpoints, respectively.

No efficacy endpoints were studied.

Sample size

The Cohort 1 population included 9 adolescents with a median age of 15 years and body weight of 60.6 kg. The proportions of female and male adolescents were 33.3% and 66.7%, respectively. The Cohort 2 population included 10 children with a median age of 11 years and body weight of 36.5 kg. The proportions of female and male children were20.0% and 80.0%, respectively.

Randomisation

No randomisation was done in the study.

Blinding (masking)

The study was open label, no blinding was done.

Results

Participant flow

Figure 5 Study Design for IV Eravazycline PK Study in Pediatric Subjects

Recruitment

Overall, 19 subjects were enrolled in the study; 9 subjects were enrolled in Cohort 1 and 10 subjects were enrolled in Cohort 2. All 19 subjects completed treatment and completed the study.

All 19 subjects were included in the Safety Population and the PK Population.

Conduct of the study

Baseline data

Table 4 Summary of Demographic and Baseline Characteristics (Safety Population)

	Cohort 1 (N=9)	Cohort 2 (N=10)	Total (N=19)
Age (years)			
n	9	10	19
Mean (SD)	14.3 (1.73)	10.4 (0.84)	12.3 (2.40)
Median	15.0	11.0	11.0
Min, Max			
Sex, n (%)			
Male	6 (66.7%)	8 (80.0%)	14 (73.7%)
Female	3 (33.3%)	2 (20.0%)	5 (26.3%)
Reproductive Status [a], n (%)			
Pre-Menarche	0	2 (100%)	2 (40.0%)

	Cohort 1 (N=9)	Cohort 2 (N=10)	Total (N=19)
Sterile	0	0	0
Post-Menopausal	0	0	0
Potentially Able to Bear Children	3 (100%)	0	3 (60.0%)
Race, n (%)			
Black or African American	1 (11.1%)	2 (20.0%)	3 (15.8%)
White	6 (66.7%)	6 (60.0%)	12 (63.2%)
Other	2 (22.2%)	2 (20.0%)	4 (21.1%)
Ethnicity, n (%)			
Hispanic or Latino	1 (11.1%)	1 (10.0%)	2 (10.5%)
Not Hispanic or Latino	8 (88.9%)	9 (90.0%)	17 (89.5%)
Height (cm)			
n	9	9	18
Mean (SD)	164.40 (9.290)	136.63 (17.212)	150.52 (19.599)
Median	165.10	131.00	156.45
Min, Max			
Weight (kg)			
n	9	10	19
Mean (SD)	60.26 (12.589)	39.00 (10.759)	49.07 (15.723)
Median	60.60	36.50	43.00
Min, Max			
Body Mass Index (kg/m 2)			
n	9	9	18
Mean (SD)	22.13 (3.847)	20.91 (5.023)	21.52 (4.385)
Median	21.60	21.60	21.60
Min, Max			
Creatinine Clearance (mL/min per 1.73 m 2) [b]			
n	9	9	18
Mean (SD)	111.47 (19.788)	124.29 (49.697)	117.88 (37.283)
Median	100.50	112.00	106.90
Min, Max	90.2, 138.8	69.0, 233.3	69.0, 233.3

	Cohort 1 (N=9)	Cohort 2 (N=10)	Total (N=19)
Type of Infection, n (%)			
Intra-Abdominal Infection	0	0	0
Urinary Tract Infection	0	1 (10.0%)	1 (5.3%)
Pneumonia (CAP, HAP, VAP)	1 (11.1%)	1 (10.0%)	2 (10.5%)
Skin	2 (22.2%)	1 (10.0%)	3 (15.8%)
Other	6 (66.7%)	7 (70.0%)	13 (68.4%)

Abbreviations: CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; Min, minimum; Max, maximum; VAP, ventilator-associated pneumonia.

Note: Percentages were based on the number of subjects in the safety population in each treatment sequence and overall.

(a) Reproductive status was collected for female subjects only. Percentages were based on total number of female subjects per cohort and Total.

(b) Creatinine clearance was collected at screening and calculated using serum creatinine (mg/dL) and height (cm) via the revised Schwartz equation: Creatinine clearance = 0.413 * height / (serum creatinine).

Cohort 1: 12 to <18 years of age (adolescents); 1.5 mg eravacycline per kg.

Cohort 2: 8 to <12 years of age (younger children); 1.75 mg eravacycline per kg.

2.4.2. Conclusions on the clinical efficacy

No clinical efficacy data were collected during the study. The application relies on extrapolation of efficacy and safety in the sought indication from adults, making the popPK modelling pivotal.

2.5. Clinical safety

Introduction

The safety of eravacycline has been evaluated in 20 clinical studies involving a total of 1 534 subjects. The majority of subjects successfully completed the studies. Of subjects in the cIAI Only Phase 2/Phase 3 pool, 576 subjects were treated with eravacycline 1.0 mg/kg q12h, the intended commercial dose, and the majority of those subjects successfully completed the studies.

Of the 358 healthy subjects participating in phase 1 trials, 51.7% reported at least one TEAE; 0.6% experienced severe TEAEs, 39.9% experienced TEAEs judged by the investigator to be related to study drug, and 4.7% experienced TEAEs that led to discontinuation from study drug. There were no SAEs or deaths in the Phase 1 subjects. Three additional Phase 1 studies with eravacycline have recently completed. Safety data from these studies are similar to the collective data in the pooled analyses.

Of the 1176 subjects who received eravacycline during Phase 2/Phase 3 trials, 38.0% reported at least one TEAE while 25.4% who received a comparator reported at least one TEAE. Events judged by the investigator to be related to study treatment were more frequent in the eravacycline group

(19.0%) than in the comparator group (7.3%). Rates of TEAEs leading to discontinuation from study drug, serious TEAEs, and deaths were low and similar in both groups.

Most side effects were found in the gastrointestinal tract (nausea, vomiting) and 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, 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.

Patient exposure

Safety and tolerability were assessed by monitoring and recording adverse events (AEs), clinical laboratory test results, vital sign measurements, and physical examination findings.

The Cohort 1 population included 9 adolescents with a median age of 15 years and body weight of 60.6 kg. The proportions of female and male adolescents were 33.3% and 66.7%, respectively. The Cohort 2 population included 10 children with a median age of 11 years and body weight of 36.5 kg. The proportions of female and male children were 20.0% and 80.0%, respectively.

Adverse events

All (TE)AEs were summarized overall and by cohort, relationship to study drug, and severity. An overall summary of AEs is presented in table 5. A summary of TEAEs by SOC and PT is presented in table 6.

Overall, 1 or more TEAEs were reported in 12 of 19 subjects (63%). A total of 19 TEAEs were reported in 7 subjects (78%) in Cohort 1, and 6 TEAEs were reported in 5 subjects (50%) in Cohort 2. The most frequently reported TEAEs were nausea (5 subjects, 26%), headache and vomiting (3 subjects each, 16%), and hyperhidrosis (2 subjects, 11%). All other TEAEs were reported by 1 subject each (5%).

Overall, 16 treatment-related TEAEs were reported in 9 subjects (47%) during the study; 12 treatment-related TEAEs were reported in 5 subjects (56%) from Cohort 1 and 4 treatment-related TEAEs were reported in 4 subjects (40%) from Cohort 2. Treatment-related TEAEs that occurred during the study were nausea (26.3%); vomiting (15.8%), hyperhidrosis (10.5%) and headache (15.8%); and tongue ulceration, rash, infusion site pain, decreased appetite, and pleural effusion (1 subject each, 5%)

Table 5 Overall summary of adverse events (Safety population)

	Cohort 1 (N=9) **n (%)**	**Cohort 2 (N=10)** **n (%)**	**Total (N=19)** **n (%)**
Any AE	8 (89%)	5 (50%)	13 (68%)
Any TEAE	7 (78%)	5 (50%)	12 (63%)

	Cohort 1 (N=9) **n (%)**	**Cohort 2 (N=10)** **n (%)**	**Total (N=19)** **n (%)**
Any Treatment-related TEAE	5 (56%)	4 (40%)	9 (47%)
Any moderate TEAE	3 (33%)	1 (10%)	4 (21%)
Any Treatment-related moderate TEAE	3 (33%)	1 (10%	4 (21%)
Any severe TEAE	2 (22%)	0 (0%)	2 (11%)
Any Treatment-related severe TEAE	1 (11%)	0 (0%)	1 (5%)
Any SAE	2 (22%)	0 (0%)	2 (11%)
Any Treatment-related SAE	1 (11%)	0 (0%)	1 (5%)
Any TEAE leading to early discontinuation	0 (0%)	0 (0%)	0 (0%)
Any fatal AE	0 (0%)	0 (0%)	0 (0%)

Abbreviations: AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Note: A TEAE was defined as any AE that occurred after administration of eravacycline or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator. A treatment-related AE was defined as an AE that was considered to be possibly, probably, or definitely related to study drug. If the relationship information was missing, the AE was considered Related. n was the number of subjects with at least 1 AE in each category. Percentages were based on the number of subjects in the safety population per cohort and Total.

Cohort 1: 12 to <18 years of age (adolescents); 1.5 mg eravacycline per kg.

Cohort 2: 8 to <12 years of age (children); 1.75 mg eravacycline per kg.

Table 6 Summary of Treatment-Emergent Adverse Events (Safety population)

	Cohort 1 (N=9) **n (%)**	**Cohort 2 (N=10)** **n (%)**	**Total (N=19)** **n (%)**
Total Number of TEAEs	19	6	25
Number of Subjects with at least one TEAE	7 (78%)	5 (50%)	12 (63%)
Gastrointestinal disorders	5 (56%)	1 (10%	6 (32%)
Nausea	5 (56%)	0 (0%)	5 (26%)

	Cohort 1 (N=9) **n (%)**	**Cohort 2 (N=10)** **n (%)**	**Total (N=19)** **n (%)**
Vomiting	2 (22%)	1 (10%)	3 (16%)
Constipation	1 (11%)	0 (0%)	1 (5%)
Tongue ulceration	1 (11%)	0 (0%)	1 (5%)
Skin and subcutaneous tissue disorders	3 (33%)	2 (20%)	5 (26%)
Hyperhidrosis	1 (11%)	1 (10%)	2 (11%)
Dermatitis contact	1 (11%)	0 (0%)	1 (5%)
Pruritis	0 (0%)	1 (10%)	1 (5%)
Rash	1 (11%)	0 (0%)	1 (5%)
Nervous system disorders	2 (22%)	1 (10%)	3 (16%)
Headache	2 (22%)	1 (10%)	3 (16%)
Psychiatric disorders	1 (11%)	1 (10%)	2 (11%)
Adjustment disorder with anxiety	0 (0%)	1 (10%)	1 (5%)
Insomnia	1 (11%)	0 (0%)	1 (5%)
Respiratory, thoracic, and mediastinal disorders	2 (22%	0 (0%)	2 (11%)
Nasal congestion	1 (11%)	0 (0%)	1 (5%)
Pleural effusion	1 (11%)	0 (0%)	1 (5%)
General disorders and administration site conditions	1 (11%)	0 (0%)	1 (5%)
Infusion site pain	1 (11%)	0 (0%)	1 (5%)
Immune system disorders	1 (11%)	0 (0%)	1 (5%)
Anaphylactic reaction	1 (11%)	0 (0%)	1 (5%)
Metabolism and nutrition disorders	0 (0%)	1 (10%)	1 (5%)
Decreased appetite	0 (0%)	1 (10%)	1 (5%)

Abbreviations: AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Note: A TEAE was defined as any AE that occurred after administration of eravacycline or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator. At each level of subject summarization, a subject was counted once if 1 or more events were reported for that subject. Percentages were based on the number of subjects in the safety population per cohort and Total. Adverse events were coded using MedDRA Version 24.0. n was the number of subjects with at least 1 AE in each category. Percentages were based on the number of subjects in the safety population per cohort and Total.

Cohort 1: 12 to <18 years of age (adolescents); 1.5 mg eravacycline per kg.

Cohort 2: 8 to <12 years of age (children); 1.75 mg eravacycline per kg.

A total of 2 severe TEAEs (anaphylactic reaction and pleural effusion) were reported in 2 subjects (11%), 6 moderate TEAEs were reported in 3 subjects (16%), and 17 mild TEAEs were reported in 7 subjects (37%). In Cohort 1, severe TEAEs were reported in 2 subjects (22%). Moderate TEAEs were reported in 3 subjects (33%) from Cohort 1 and 1 subject (10%) from Cohort 2. Mild TEAEs were reported in 3 subjects (33%) from Cohort 1 and 4 subjects (40%) from Cohort 2.

Serious adverse event/deaths/other significant events

There were no deaths or discontinuations due to TEAEs during the study.

Two SAEs were reported in 2 subjects during the study: pleural effusion in one subject and gastroenteritis salmonella in another subject.

Laboratory findings

In Cohorts 1 and 2 and overall, mean haematology and serum chemistry results were within the normal ranges at the time points assessed, and the mean values and changes from baseline were similar at each time point assessed after dosing for each cohort. There were no shifts in haematology or serum chemistry values from no toxicity at baseline to Grade 2 or higher on Day 2 during the study.

Mean vital sign measurements observed after dosing in each cohort were similar to those observed at baseline. Mean values and changes from baseline were similar at all time points.

2.5.1. Discussion on clinical safety

The study included a total of 19 subjects in two age-differentiated cohorts, 12 to <18 years of age (adolescents, cohort 1) and 8 to <12 years of age (children, cohort 2). Participants received a single dose of 1.50 mg/kg (Cohort 1) or 1.75 mg/kg (Cohort 2). Treatment-emergent adverse events and treatment-related adverse events were numerically more common in cohort 1. Most common adverse reactions were nausea, vomiting, headache and hyperhidrosis. Laboratory investigations did not reveal any abnormalities or major shifts from baseline.

Two events were reported as serious: pleural effusion and gastroenteritis salmonella. The case of pleural effusion was considered possibly related to study treatment and was resolved on day 33. From the presented information, it is not clear why the investigator and MAH consider the event as possibly related to the study drug other than the temporal association. The case is confounded by a severe heart defect and two prior instances of pleural effusion, one of them just days prior to administration of eravacycline, and several concomitant medications. Therefore, it is considered

that this case is unlikely to be related to eravacycline and more likely caused by underlying medical conditions. The case of gastroenteritis was not related to the study drug. There were no deaths due to TEAEs.

Two treatment emergent events were reported as severe: pleural effusion and anaphylactic reaction. Pleural effusion is discussed above. The case of anaphylactic reaction occurring the same day as eravacycline was administered to a patient with underlying conditions suggesting an activated immune system. The time to onset supports the conclusion that the anaphylactic reaction was more likely caused by cefazolin, although the reaction to eravacycline may have contributed to the reaction.

The MAH did not provide an updated RMP, proposing that an updated RMP will be provided after the final indication is agreed. The MAH is reminded of their commitment to provide the RMP as soon as possible after the end of this procedure or at the next regulatory opportunity.

2.5.2. Conclusions on clinical safety

Data from the study add information on safety of eravacycline from 19 paediatric patients. Data is very limited given the small number of subjects and single-dose regimen and clinical safety must, to some extent, be extrapolated from adults via establishing that there is a comparable PK profile. No new safety concerns have been identified based on the submitted data.

2.5.3. PSUR cycle

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.

2.6. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are being updated to include the updated indication, posology in paediatric patients, to update information regarding pharmacodynamics and pharmacokinetics, and to update instructions for preparation to include paediatric dosages. The Package Leaflet (PL) is updated accordingly.

The wording of the updated indication approved with this procedure is as follows:

Xerava is indicated in adolescents from the age of 12 years weighing at least 50 kg, and in adults, for the treatment of complicated intra-abdominal infections (cIAI) (see sections 4.4 and 5.1).

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed by QRD and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for several local representatives.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.6.1. User consultation

A justification for not performing a user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are in line with previous information and do not require user consultation with target patient groups. The justification for not performing a user consultation with target patient groups on the package leaflet has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This application concerned an application to extend the indications for Xerava to include treatment of paediatric patients (8 years to less than 18 years of age) for the treatment of complicated intra-abdominal infections (cIAI).

cIAI in children is a serious and life-threatening disorder characterised by extension of the infection from its original locus into a normally sterile location of the abdominal cavity. It is usually associated with peritonitis with or without abscess formation and may lead to sepsis. The most common cause of cIAI in children is appendicitis but it can also be caused by e.g. trauma. The infection is often polymicrobial, especially when it is associated with faecal contamination.

3.1.2. Available therapies and unmet medical need

cIAI is treated by drainage, surgical removal of damaged tissue and control of the source of infection. Pharmacological therapy consists of broad-spectrum antibiotic treatment with e.g. beta-lactam antibiotics combined with other antibiotics. 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. Few broad-spectrum antibacterial agents are formally approved for use in paediatric patients.

3.1.3. Main clinical studies

This application is based on the results from the Study TP-434-028 which is a clinical Phase 1 study in patients aged 8-12 years. The primary objective was to evaluate PK and safety of eravacycline. This small, single-arm study did not include efficacy endpoints.

The benefit-risk is determined by extrapolation of efficacy and safety from the adult patient population by means of PK exposure matching. Thus, the PK data collected in Study TP-434-028 is considered pivotal for determining the benefit-risk balance of eravacycline in paediatric patients.

Study TP-434-028 included 19 paediatric patients in two cohorts. Cohort 1 included 9 patients treated with a single 1.5 mg/kg dose where age ranged from 11 to 17 years. Cohort 2 included 10 patients treated with a single 1.75 mg/kg dose where age ranged from 9 to 11 years.

Study TP-434-028 included paediatric patients with suspected or confirmed bacterial infection whereas no paediatric patient with cIAI were included in Study TP-434-028.

3.2. Favourable effects

The PK analyses included data from all 19 patients in Study TP-434-028 which included several PK samples following a single eravacycline dose.

The PK-data were analysed using non-compartmental analyses separately for Cohort 1 and 2. Comparisons with corresponding adult PK exposures showed that the PK exposures in terms of AUC following the studied posology appeared comparable between adults and children aged 8-18 years.

The PK-data were also analysed using PopPK modelling which included PK simulations for the proposed posology indicating comparable exposures compared to adults.

3.3. Uncertainties and limitations about favourable effects

No efficacy data have been generated in paediatric patients. Efficacy and safety assumptions in the paediatric population may be extrapolated from the adult population via PK bridging.

However, the PK analyses have major limitations which means the initially proposed doses of 2 mg/kg and 1.5 mg/kg in paediatric patients aged 8-12 and 12-18 years, respectively is unacceptable.

For the 8-12 years age group, a higher-than-observed dose of 2 mg/kg is proposed which has not been sufficiently justified by updated PopPK analyses. The need for a higher-than-studied dose in patients 8-12 years of age (2 mg/kg) is highly unclear since the observed PK data indicated comparable observed exposures compared to adults and the exposure in 8-12 years of age had higher observed exposure than patients 12-18 years.

For the 12-18 years age group, the recommended dose is 50% higher than the recommended dose in adults. This higher dose cannot be accepted without updated fit-for-purpose PopPK models due to the following limitations of Study TP-434-028:

• A limited number of adolescents were studied (n=9)

• Only a single dose was studied (whereas the recommended dose regimen is BID)

• A sparse PK sampling schedule was applied

• None or very few paediatric patients were included with cIAI. The data indicates that the PK differed between adult cIAI patients and the paediatric patients in Study TP-434-028 (after accounting for differences in the mg/kg dose). However, it is highly unclear if this reflects and underlying PK difference between adults and paediatric patients, or if this difference exists due to the paediatric patients having a different type of infection.

On the other hand, the adult posology (1 mg/kg) is considered a reasonable dose in a subset of paediatric patients weighing at least 50 kg and can be supported without updated PopPK analyses. Thus, the MAH agreed to update SmPC Section 4.1 by restricting the population of the claimed extended indication to (adults and) adolescents weighing at least 50 kg and to update SmPC Section 4.2 by recommending 1 mg/kg to adolescents weighing at least 50 kg and adults.

3.4. Unfavourable effects

Data is very limited given the small number of subjects and single-dose regimen and clinical safety must, to some extent, be extrapolated from adults via establishing that there is a comparable PK profile. Comparisons with corresponding adult PK exposures showed that the PK exposures in terms of Cmax following the studied posology appeared comparable between adults and children aged 8-18 years.

Most common adverse reactions were nausea, vomiting, headache and hyperhidrosis, which is consistent with the currently known safety profile. Laboratory investigations did not reveal any

abnormalities or major shifts from baseline. No subjects died, and since the study was single dose, no subject discontinued treatment.

3.5. Uncertainties and limitations about unfavourable effects

This is a very limited study consisting of 19 paediatric subjects, who received one single dose of eravacycline and were followed up for safety events at days 2 and 7. None of the subjects had a cIAI, which is the sought indication. No new safety information was identified in the data; however no safety conclusion can be drawn for a normal treatment duration or repeated dosing.

Comparisons of the observed Cmax indicated comparable exposures between paediatric patients and adults. However, the observed PK data were limited to patients ≥9 years and ≥28.5kg whereas the target population includes patients from ≥8 years which is expected to weigh approximately ≥20 kg.

3.6. Effects Table

Table 7 Effects Table for the Xerava paediatric indication extension

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Unfavourable Effects						
Known ADR: nausea		N (%)	5/19 (26%)	SmPC: Common		Study TP-434-028
Known ADR: vomiting		N (%)	3/19 (16%)	SmPC: Common		Study TP-434-028
Known ADR: headache		N (%)	3/19 (16%)	SmPC: Uncommon		Study TP-434-028
Known ADR: hyperhidrosis		N (%)	2/19 (11%)	SmPC: Uncommon		Study TP-434-028
SAE: Pleural effusion		N (%)	1/19 (5%)	SmPC: Not listed	Reported as SAE, considered possibly related by investigator	Study TP-434-028
TEAE: Anaphylactic reaction		N (%)	1/19 (5%)	SmPC: Not listed	Reported as a severe TEAE, not considered related by the investigator	Study TP-434-028

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

This extension of indication application to include the paediatric population (from 8 to 18 years) for the treatment of cIAI did not include efficacy data in children. Efficacy and safety assumptions in

the paediatric population may be extrapolated from the adult population via PK bridging (i.e. exposure matching) which could be supported by EMA guidance (EMEA/CHMP/EWP/147013/2004) and precedence.

However, the PK analyses have major limitations which means that the initially proposed doses of 2 mg/kg and 1.5 mg/kg in paediatric patients aged 8-12 and 12-18 years, respectively were unacceptable.

On the other hand, the adult posology (1 mg/kg) is considered a reasonable dose in a subset of paediatric patients weighing at least 50 kg and can be supported without updated PopPK analyses. Thus, the MAH agreed to update SmPC Section 4.1 by restricting the population of the claimed extended indication to (adults and) adolescents weighing at least 50 kg and to update SmPC Section 4.2 by recommending 1 mg/kg to adolescents weighing at least 50 kg and adults.

Of note, the initially proposed age limit of 8 years is due to a risk of permanent tooth discolouration in younger children.

In the safety analysis, the most common adverse events of nausea, vomiting, headache, and hyperhidrosis are already known and described in the SmPC. Two previously not listed events of pleural effusion and anaphylactic reaction were reported in the study; pleural effusion was considered related by the investigator, whereas anaphylactic reaction was considered not related. No new safety concerns have been identified based on the submitted data.

3.7.2. Balance of benefits and risks

The balance of benefit risk for the extension of indication of treatment of cIAI to include patients aged 12 years and older and weighing at least 50 kg is positive.

Of note, the balance of benefits and risk for the initially proposed extension of indication of treatment of cIAI to include patients aged 8 years and older was considered negative in the light of the supporting evidence provided.

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The overall B/R of Xerava for paediatric subjects 12 years and older and weighing at least 50 kg is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of complicated intra-abdominal infections (cIAI) from the age of 12 years weighing at least 50 kg for XERAVA, based on final results from study TP-434-028; this is a phase 1, open-label, multicenter study to determine the pharmacokinetics and safety of intravenous eravacycline in children with suspected or confirmed bacterial infection. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2, and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB are recommended.

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.

In addition, 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.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0397/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Xerava-H-C-004237-VR/0000265697'

Attachments

1. Product information (changes highlighted) as adopted by the CHMP on 13 November 2025

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by **27 November 2025**. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by **27 November 2025**. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.