17 August 2023
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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Vyepti

eptinezumab

Procedure no: EMEA/H/C/005287/P46/005

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	24 Apr 2023	24 Apr 2023	☐
☐	CHMP Rapporteur Assessment Report	30 May 2023	06 Jun 2023	☐
☐	CHMP members comments	12 Jun 2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	15 Jun 2023	n/a	☐
☐	CHMP adoption of conclusions:	22 Jun 2023	22 Jun 2023	☐
☐	Re-start of procedure	19 July 2023	19 July 2023	☐
☐	CHMP Rapporteur Assessment Report	02 Aug 2023	01 Aug 2023	☐
☐	CHMP members comments	07 Aug 2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	10 Aug 2023	n/a	☐
☒	CHMP adoption of conclusions:	17 Aug 2023	17 Aug 2023	☐

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1. Introduction

On 29 March 2023, the MAH submitted a paediatric study for Vyepti in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH states that **trial 18922A** is conducted as part of a global development programme for eptinezumab in paediatric patients with migraine as per the *Paediatric Investigation Plan* agreed with the EMA, UK MHRA, and the initial *Paediatric Study Plan* agreed with the US FDA, as well as to fulfil US FDA PMR 3796-2. The paediatric eptinezumab migraine programme agreed with the EMA/PDCO includes the following trials:

- 1 PK trial in children (6 to 11 years) and adolescents (12 to 17 years) (Trial 18922A; where the Main Study Period is completed and the Extension Period is ongoing)
- 2 efficacy and safety trials:

  - 19356A: trial in adolescents with chronic migraine (ongoing)

  - 19357A: trial in children and adolescents with episodic migraine (planned)
- All participants who complete the 2 efficacy and safety trials are offered participation in a long-term extension trial (Trial 19379A; ongoing)

2.2. Information on the pharmaceutical formulation used in the study

The strength, formulation, and mode of administration of eptinezumab used in Trial 18922A are presented in Panel 1

Panel 1 Pharmaceutical Formulation

IMP	Strengths	Formulation	Mode of Administration
Eptinezumab	100 mg/mL (1 mL/vial)	Concentrate for solution for infusion	IV

For participants assigned to eptinezumab 300 mg (the content of 3 vials), a 100 mL bag of sodium chloride 9 mg/mL (0.9%) solution for injection was used to prepare the solution for infusion.

For participants assigned to eptinezumab 150 mg (the content of 1.5 vials), a 100 mL bag of sodium chloride 9 mg/mL (0.9%) solution for injection was used to prepare the solution for infusion.

No participants weighed less than 20 kg and thus no participants received eptinezumab 100 mg.

The pharmaceutical formulation of eptinezumab is an IV solution for infusion. The formulation is the same as that approved for use in adults.

3. Clinical Pharmacology

3.1. Pharmacokinetics

3.1.1. Introduction

Within this Article 46 of Regulation (EC) No 1901/2006 submission, the MAH provided a population PK analysis (Population Pharmacokinetic Report, dated 31 January 2023) of eptinezumab in paediatrics aged 6 to < 18 years using data from Study 18922A (Part A). The objective of this population PK analysis was to (i) characterise the PK of eptinezumab in paediatrics aged 6 to < 18 years, (ii) investigate the impact of body weight and age, and (iii) compare the PK between paediatrics and adults. This study was listed in the respective PIP EMEA-002243-PIP01-17(-M02).

The paediatric dosing was aimed to match eptinezumab exposure levels achieved in adults receiving 300 mg eptinezumab intravenously (IV). In Study 18922A the following doses were administered in Part A:

≤ 20 kg: 100 mg IV

>20 kg to ≤ 40 kg: 150 mg IV

>40 kg: 200 mg IV

Note: one child was inadvertently infused with 200 mg instead of 150 mg. It was included in the PK analysis.

3.1.2. Methods

3.1.2.1. Pharmacokinetic data analysis

In study 18922A, PK samples were drawn at immediately after end of infusion (+ 5 min) and 2 h (+/- 5 min) after end of infusion on Day 1 and then at end of Weeks 4, 8, 12 and 20.

The PK eptinezumab was analysed by noncompartmental analysis (NCA) and population PK modelling.

PK analysis was conducted using the nonlinear mixed-effects approach with NONMEM software, Version 7.

A previously developed population PK model for adults (n=2123), where data from eight clinical studies were used, served as a basis for the paediatric population PK model. The starting point was a 2-compartment model with zero order infusion, linear elimination and exponential interindividual variability (IIV) on clearance (CL), volume of distribution of the central and peripheral compartment (Vc and Vp, respectively), and inter-compartmental clearance (Q). A combined (proportional and additive) residual error model was used. Some previously identified covariates from the adult population were retained in the model and fixed to their prior adult estimates, i.e., creatine clearance capped at 150 ml/min (CLcr_cap), disease (DS; healthy, chronic migraine [CM] or episodic migraine [EM] patients) and baseline monthly migraine days (MMD) on CL, and disease on Vc. The impact of body weight, age and sex were then re-investigated as covariates in the paediatric population.

Area under the concentration-time curve from zero to week 12 ($AUC_{0\text{-}w.12}$) and maximum plasma concentration (C_{max}) were calculated as secondary PK parameters from the individual estimates.

In order to compare the PK between paediatrics and adults, the paediatric population PK model was used to simulate different dosing scenarios. A virtual population of 13300 paediatrics was generated using the body weight distribution for boys and girls provided by Centers for Disease Control and

Prevention. The ratio between the geometric means for each paediatric subgroup and the adult population was calculated as an assessment of the similarity to the adult population. If these ratios were within 60 % and 140 % in each paediatric subgroup, similarity between adults and paediatrics was claimed.

3.1.2.2. Evaluation and Qualification of Models

Model selection was done based on objective function values (OFV), plausibility and precision of parameter estimates, and graphical evaluation of goodness-of-fit (GOF). The predictive performance was investigated using visual predictive checks (VPCs). A Bootstrap analysis was done using 400 dataset replicates.

3.1.3. Results

Among the 28 paediatric patients included in the population PK analysis, 12 (43 %) were aged 6 to < 12 years and 16 (57 %) aged 12 to < 18 years. Mean body weight was 51.1 kg (min = 20 kg, max = 80 kg), where 11 paediatrics (39 %) had a body weight between 20 and 40 kg and 17 (61 %) a body weight of more than 40 kg. Overall, 20 (71 %) patients were female and 8 were male (29 %). In total, 160 plasma concentrations were available for analysis. In total, 17 patients received 300 mg and 11 150 mg. None received 100 mg.

The final population PK model in paediatrics, is a 2-compartment model with zero order absorption and first-order elimination. IIV is implemented on CL, Q, Vc, and Vp. Body weight was set as covariate on CL and Q (exponent 0.75), as well as on Vc and Vp (exponent 1). A population typical body weight of 70 kg was used for allometric scaling. Parameter estimates of the final paediatric population PK model are listed in Table . GOF plots and a VPC are shown in Figure 1 and Figure 2, respectively. Creatine clearance capped at 150 ml/min (CLcr_cap), disease (healthy, CM or EM patients) and baseline monthly migraine days as covariates on CL and disease on Vc were retained from the adult model using their fixed values. These values are not listed in the final parameter estimates of the paediatric modelling approach.

The secondary PK parameters were calculated at: median half-life (t½) 28.4 days (SD=5.3 days), $AUC_{0\text{-}W12}$ = 6.6*10⁴ µg*h/mL (SD=2.1*10⁴), and C_{max} = 125 µg/mL (SD=38).

Table 1: Parameter estimates and bootstrap results of the final paediatric population PK model for eptinezumab, Study 18922A Part A data

Model Parameters	Parameter Estimate
Volume of distribution, central compartment (V_c)	
Estimate (L)	3.13
RSE (%)	4.2
IIV (%)	29.7
Clearance (CL)	
Estimate (L/h)	0.00469
RSE (%)	3.4
IIV (%)	29.1
Volume of distribution, peripheral compartment (V_p)	
Estimate (L)	1.99
RSE (%)	2.7
IIV (%)	35.8
Inter-compartmental clearance (Q)	
Estimate (L/h)	0.0420
RSE (%)	12.1
IIV (%)	72.8
Residual error	
Estimate	0.0234
Estimate[a] (%)	15.3
RSE (%)	5.3

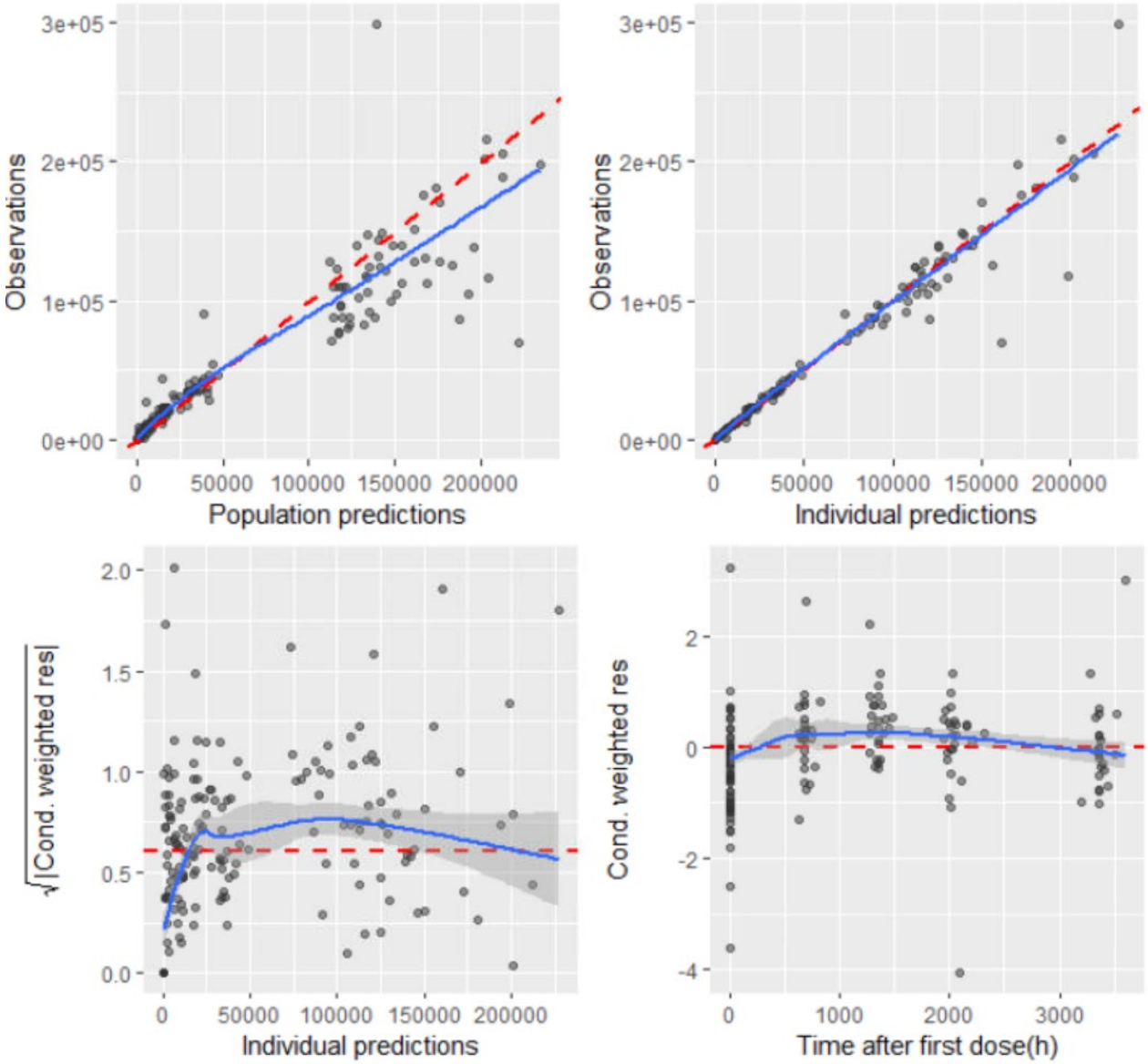
RSE (relative standard error) = standard error / estimate·100 from NONMEM® results
IIV = inter-individual variability

a Percentage standard deviation calculated as 100·sqrt(estimate)

Parameter	Final Model Value	Bootstrap Value [95% CI]	Difference[a] (%)
V_c [L]	3.13	3.11 [2.07,3.91]	-0.8
CL [L/h]	0.00469	0.00425 [0.00135,0.00479]	-9.5
V_P [L]	1.99	1.62 [0,2.01]	-18.5
Q [L/h]	0.042	0.0342 [0,0.0448]	-18.5
ϖ^2_{Vc}	0.0883	0.097 [0.0877,0.135]	9.9
ϖ^2_{CL}	0.0845	0.0953 [0.0839,0.143]	12.8
ϖ^2_{Vp}	0.128	0.141 [0.128,0.194]	9.8
ϖ^2_{Q}	0.728	0.802 [0.726,1.12]	10.2
σ^2	0.0234	0.0267 [0.00615; 0.0999]	14.1

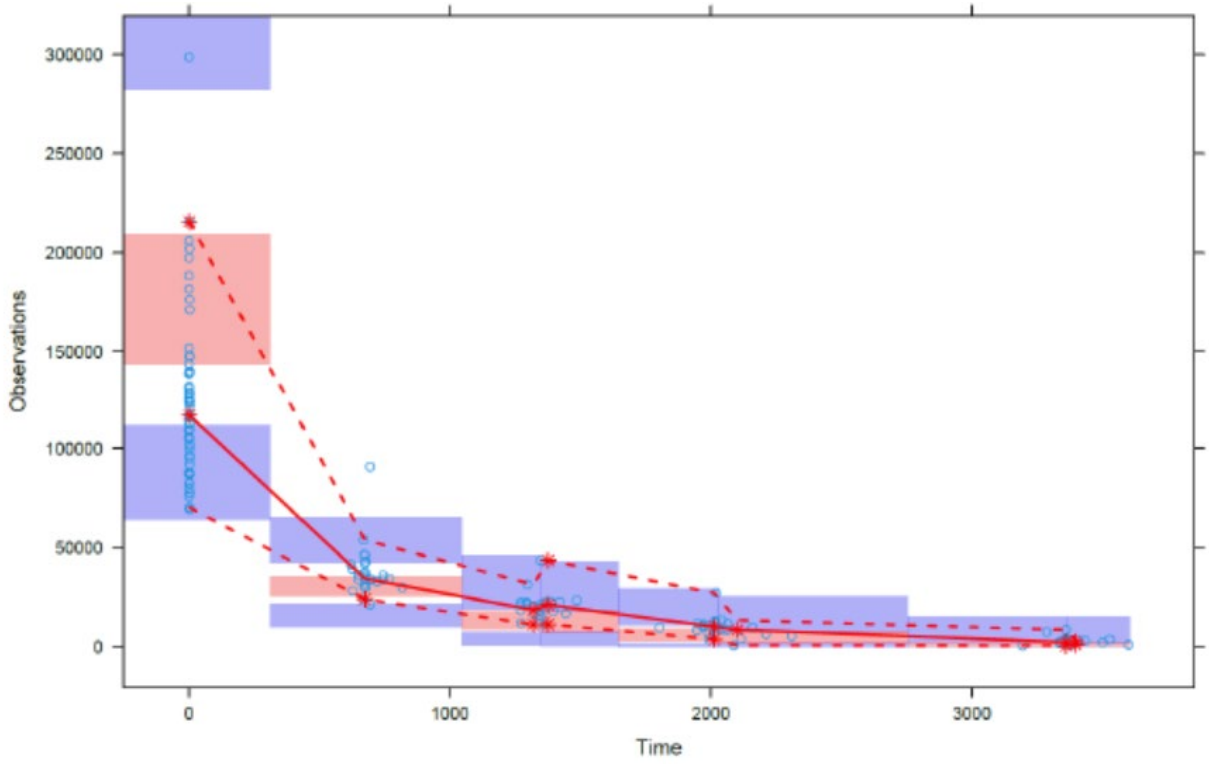
a Estimated as (bootstrap value – final model value) / final model value ·100

Figure 1: GOF plots of the final paediatric population PK model for eptinezumab, Study 18922A Part A data



Full blue line shows smoothed curves while dotted red lines are unity or zero lines.

Figure 2: VPC of the final paediatric population PK model for eptinezumab, Study 18922A Part A data



Full and dotted lines shows median and the 2.5th and 97.5th percentiles, respectivley, of observed data (blue circles) while the three shaded regions shows the 95% confidence intervals for the 97.5th percentile, median an 2.5th percentile for simulated data.

Simulations for different doses in paediatrics that intend to match eptinezumab exposure in adults after administration of 300 mg or 100 mg IV, were carried out. The following paediatric doses were simulated and results are presented as Boxplots in

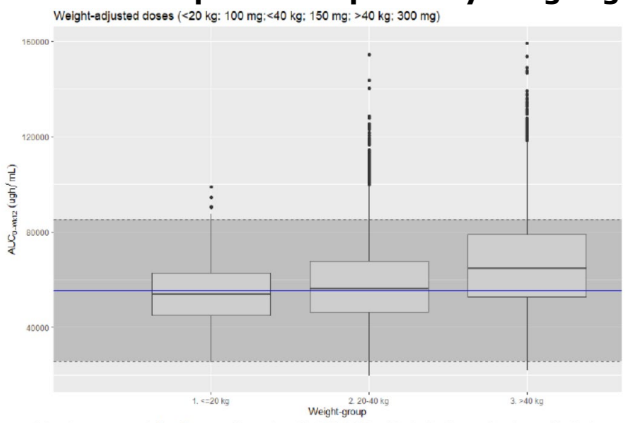
A comparison of simulated exposures between adults and paediatrics is listed in Table 2. In addition, PK parameters for adolescents and children are separated presented in Table 3.

Figure 3 and Figure 4.

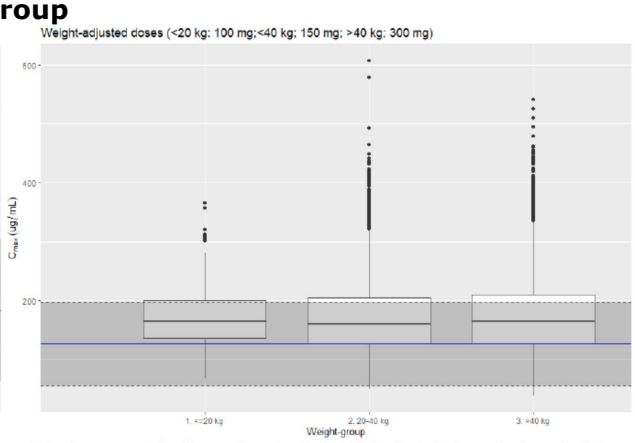
Adult dose:	300 mg IV	100 mg IV
Paediatric doses:		
≤ 20 kg:	100 mg IV	40 mg IV
>20 kg to ≤ 40 kg:	150 mg IV	50 mg IV
>40 kg:	300 mg IV	100 mg IV

A comparison of simulated exposures between adults and paediatrics is listed in Table 2. In addition, PK parameters for adolescents and children are separated presented in Table 3.

Figure 3: Simulated $AUC_{0\text{-}w12}$ (left) and C_{max} (right) in paediatrics following 300 mg adult dose equivalents per body weight group

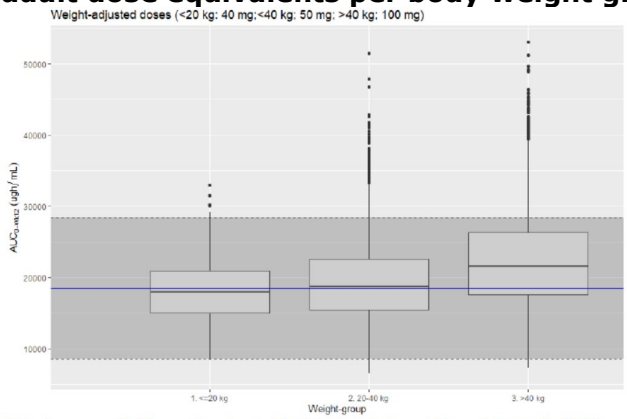


Adult reference range (5th-95th percentiles and median) highlighted in the background. The paediatric data (N = 13,300) are shown as boxes with median, 25th (Q1) and 75th (Q3) percentiles, whiskers defined as 1.5*interquartile range (Q3-Q1) and with outliers outside these ranges.

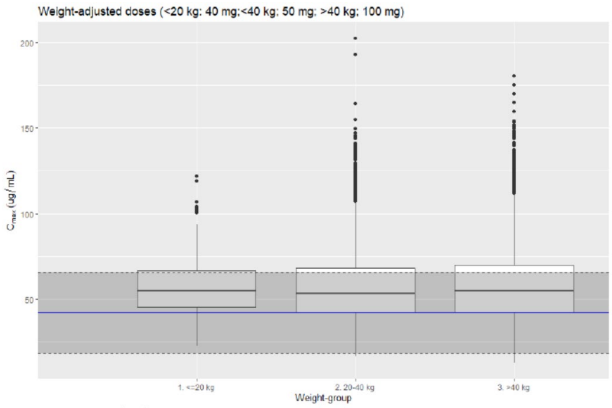


Adult reference range (5th-95th percentiles and median) highlighted in the background. The paediatric data (N = 13,300) are shown as boxes with median, 25th (Q1) and 75th (Q3) percentiles, whiskers defined as 1.5*interquartile range (Q3-Q1) and with outliers outside these ranges.

Figure 4: Simulated $AUC_{0\text{-}w12}$ (left) and C_{max} (right) in paediatrics following 100 mg adult dose equivalents per body weight group



Adult reference range (5th-95th percentiles and median) highlighted in the background. The paediatric data (N = 13,300) are shown as boxes with median, 25th (Q1) and 75th (Q3) percentiles, whiskers defined as 1.5*interquartile range (Q3-Q1) and with outliers outside these ranges.



Adult reference range (5th-95th percentiles and median) highlighted in the background. The paediatric data (N = 13,300) are shown as boxes with median, 25th (Q1) and 75th (Q3) percentiles, whiskers defined as 1.5*interquartile range (Q3-Q1) and with outliers outside these ranges.

Table 2: Ratios for geometric means in adults vs paediatric subgroups, simulated values

Parameter	Adults (n=2122)		Adolescents (n=16)		Children (n=12)	
	Geom. Mean	95%CI	Geom. Mean	Ratio (adol/adult)	Geom. Mean	Ratio (child/adult)
$AUC_{0\text{-}inf}$	59942	[59093;60804]	69738	1.16	66968	1.12
$AUC_{0\text{-}12w}$	52299	[51612;52996]	60792	1.16	60489	1.16
C_{max}	71	[70;73]	153	2.15	169	2.37

Table 3: Model-based PK parameters for adolescents and children

Subgroup	Parameter	mean	95% CI	(lower CI; upper CI)
Adolescents	CL (L/h)	0.004102	[0.003741,0.004499]	91;110
	V (L)	4.168697	[3.75586,4.626911]	90;111
	$AUC_{(0\text{-}inf)}$ (ug*h/mL)	73168.39	[66723.56,80235.72]	91;110
	$AUC_{(0\text{-}12w)}$ (ug*h/mL)	66634.84	[59872.4,74161.08]	90;111
	C_{max} (ug/mL)	125.2699	[108.8503,144.1662]	87;115
Children	CL (L/h)	0.002274	[0.00185,0.002796]	81;123
	V (L)	2.099162	[1.743604,2.527226]	83;120
	$AUC_{(0\text{-}inf)}$ (ug*h/mL)	69209.56	[56352.03,85000.73]	81;123
	$AUC_{(0\text{-}12w)}$ (ug*h/mL)	64991.51	[52659.1,80212.1]	81;123
	C_{max} (ug/mL)	128.4789	[105.6813,156.1943]	82;122

3.1.4. CHMP comment on PK modelling

Population PK model

No information regarding the quantification limit could be found in the population PK report. These should be provided along with the modelling exercises (LLOQ, BLQ).

A paediatric population PK model was developed based on prior knowledge in adults. By doing so, the MAH explained that previously identified covariates from the adult model were used for the paediatric model and fixed to their prior estimates (i.e., creatine clearance capped at 150 ml/min (CLcr_cap), disease (DS; healthy, chronic migraine [CM] or episodic migraine [EM] patients) and baseline monthly migraine days (MMD) on CL, and disease on Vc), except for allometric scaling exponents. These covariate parameters were not clearly listed and explained in the presented results for the paediatric model. Thus, their values and impact on the paediatric model are not clear. In addition, the use of fix covariates derived from the adult model is not deemed plausible. Firstly, what is the rationale of using creatine clearance capped at 150 ml/min in the paediatric model? Secondly, there were no healthy children in the dataset and it is not clear how many patients were EM or CM, or if these diseases differences can be reliably estimated considering that the data are very limited. In addition, these adult covariates may be correlated with weight related covariates on CL and V, that have been estimated for the adult population. However, in contrast 0.75 and 1 have been set for allometric scaling for the paediatric model, which is endorsed from the methodological point of use. And thirdly, is it plausible to assume the same MMD for the paediatric population? Overall, this strategy is currently questioned. Moreover, from the provided report it is not clear what exactly happened when age (and sex) was tested as covariate. So it is not entirely clear if or to which extent an age effect may be observed. Since the majority of the population (and the main target population) is female, an effect of sex may not be detected, even if existing. However, results could have been provided for that as well.

The MAH claims similarity of exposure if ratios between paediatrics and adults fulfil a 60 to 140 % criterion. This criterion appears arbitrarily chosen and deemed not acceptable given that the higher 300 mg adult fix dose is used for the exposure bridging approach (see below). In general, this range is considered too wide to use. Moreover, it should be considered that in adults the 100 mg dose, despite

slightly lower efficacy, was chosen as standard dose due to better safety (lower rate of hypersensitivity reactions). The bootstrap analysis included zero as lower boundary for the two parameters Q and Vp possibly indicating problems with these parameters. The GOF plots observed vs population predicted indicate in particular for the higher concentration a systemic overestimation. This could also be clearly observed by inspecting the VPC plot, showing a clear overprediction of C_{max}. In addition, an underprediction of exposure at later time points (from about 700 h post infusion) could be detected. The VPC was provided on linear scale only, limiting the possibility to comment on that. It should be provided on log scale as well.

The model-based simulations indicate a trend towards higher exposures for paediatrics compared to adults and it should be kept in mind, that no patient received 100 mg. Simulations for this dose in paediatrics are based on higher doses only. No confirmatory data are available for this case (see also below).

With regards to the boxplots (Figure 3 and Figure 4), there are deviations from the predicted exposure range for all paediatric weight ranges compared to the adult population. This deviation appears to increase with weight and is highest for the weight group >40 kg. Given that this body weight group is expected to be most similar to the adult population, this finding is counter-intuitive and questions the predictive power. A large proportion of outliers especially at the higher end of the predicted exposure range could be detected. This indicates that the model is not able to describe the observed paediatric data well, which is of concern.

Overall, it is doubted that the herein presented paediatric population PK model can be considered reliable and fit for the purpose of dose selection and dose confirmation to shape further clinical development for the paediatric population.

Study population, dose selection and confirmation for the paediatric population

Overall, 28 paediatric patients were included in the analysis. It is not clear how many of those were EM or CM patients, so the paediatric study population is considered not well described.
In addition, a participant received a dose of 150 mg instead of the foreseen 100 mg. Moreover, it seems that one patient received inadvertently 200 mg instead of 150 mg. No justification and comment could be found for this, respectively. It should be noted that no confirmatory data following 100 mg are available for the lowest paediatric weight cohort (<20 kg).

Besides the comments made regarding the model, the following comments regarding the selected doses are made. Firstly, it is not clear why exposure matching for the higher adult dose (300 mg IV) is primarily targeted in paediatrics, although the general recommended dose in adults is 100 mg. Considering that a flat exposure-response relationship was observed previously, it appears not plausible, why the exposure of the higher dose should be targeted. It should be avoided to expose patients to higher doses than actual needed.
Secondly, back-calculating the proposed paediatric doses of 100, 150, and 300 mg to body-weight doses, results in doses of about up to 7.5 mg/kg (body weight 15 to 40 kg). Compared to that, an adult weighing 70 kg receives 1.43 mg/kg (100 mg IV dose, generally recommended dose) and 4.29 mg/kg (300 mg IV dose), respectively. Considering the PK differences in paediatrics (e.g. clearance) and given that body weight affects clearance processes and volumes of distributions, the proposed higher per kg doses are not understood. In addition, a body weight effect was already observed in the adult population, resulting in higher exposure for lighter patients receiving the same dose as all other adults (i.e. 39 kg resulted in 50 % higher exposure, refer to SmPC).

All taken together, the provided paediatric population PK model is not considered acceptable for the indented context of use and thus should be revised and re-assessed. Paediatric dose selection should be further supported by consecutive exposure simulations targeting both authorized adult doses (100

mg and 300 mg IV). Simulation should be performed considering also other body weight limits (smaller increment), as well as more doses over a broad dose range (e.g. 10 different doses) to be overlaid with the observed adult exposure range. (OC)

3.1.5. Conclusion

The provided paediatric population PK model is not considered fit for the purpose of dose selection and dose confirmation in paediatrics. The model should be revised, and additional doses be simulated / investigated. One OC is asked that needs to be addressed by the MAH.

3.2. Clinical aspects

3.2.1. Introduction

The MAH submitted a study report for:

- Trial No. 18922A: An open-label, single-dose, pharmacokinetic study to evaluate IV eptinezumab in children and adolescents with migraine, followed by an optional, multiple-dose, open-label extension period (Main Study Period completed, Extension Period ongoing)

Trial 18922A was initiated in 2020. This first study of eptinezumab in paediatric patients (18922A) was conducted as part of a global development programme for eptinezumab in paediatric patients with migraine as per the paediatric investigation plan (PIP) agreed with the EMA and initial paediatric study plan (iPSP) agreed with the FDA. The results and outcome of the study will be reported in the Clinical Study Report (CSR) but no comparison with adults will be included. The present popPK report describes the population pharmacokinetic (PopPK) modelling and model-based simulations performed to support the eptinezumab dose recommendation for paediatric patients and also includes comparison with adults.

First patient first visit – 4 August 2020 (the date when the first *Informed Consent Form* was signed)

Data cut-off date – 20 October 2022 (the date of the last protocol-specified contact with any patient in the Main Study Period)

As of the date of the submitted study report, the Extension Period was ongoing.

3.2.2. Clinical study

Methods

Study participants

The trial included children and adolescents (6 to 17 years of age) with a diagnosis of migraine with or without aura according to ICHD-3 for ≥6 months prior to the Screening Visit and who had a frequency of migraine ≥4 MMDs for ≥3 months prior to the Screening Visit and who are requiring migraine prevention treatment.

Treatments

Each patient received a single open-label dose of eptinezumab IV based on the highest target adult exposure of eptinezumab (300 mg IV). The dose was adjusted for the patient's body weight according to the following guidelines (the paediatric dose adjustments are based on simulations using a

population PK (popPK) model to optimally match eptinezumab exposure following a 300 mg IV dose in adults):

– Patients weighing ≤20 kg received eptinezumab 100 mg IV

– Patients weighing >20 to ≤40 kg received eptinezumab 150 mg IV

– Patients weighing >40 kg received eptinezumab 300 mg IV

Treatment doses were adjusted accordingly if a patient changed weight bands during the study (Extension Period).

Objective(s) / Outcomes/endpoints

Objectives	Endpoints
Primary Objective • To characterize the pharmacokinetic (PK) profile of eptinezumab after a single intravenous (IV) administration in paediatric patients 6 to 17 years of age	**Single-Dose PK** • Primary endpoints (Main Study; Part A) – $AUC_{0\text{-}inf}$ and C_{max} • Secondary endpoints (Main Study; Part A) – $AUC_{0\text{-}t\ last}$ – C_{min} (C_{12wk}) – Time to maximum concentration (t_{max}) – Terminal elimination half-life ($t_{½}$) – Plasma clearance (CL) – Volume of distribution (Vz)
Secondary Objectives • To characterize the PK profile of eptinezumab after multiple IV administrations in paediatric patients 6 to 17 years of age (Extension Study; Part B)	**Multiple-Dose PK** • Secondary endpoints (Extension Study; Part B) – $AUC_{w44\text{-}w64}$ – C_{max} – C_{min} (C_{44wk}) – t_{max}
• To evaluate the immunogenicity of eptinezumab after single and multiple IV administrations in paediatric patients 6 to 17 years of age (Main and Extension Study; Parts A and B)	**Immunogenicity** • Secondary endpoints (both Parts A and B) – Development of anti-eptinezumab antibodies (ADAs) – Characterization of ADAs for neutralizing activity (NAbs)

Exploratory Objectives • To explore the efficacy of eptinezumab after single and multiple IV administrations in paediatric patients 6 to 17 years of age (Main and Extension Study; Parts A and B)	**Efficacy** • Exploratory endpoints – Change from Baseline in Pediatric Migraine Disability Assessment (PedMIDAS) score to all assessment weeks (both Parts A and B) – Change from Baseline in the number of monthly migraine days (MMDs) to the Week 1 to 12 monthly averages (Main Study, Part A) – Change from Baseline in the number of monthly headache days (MHDs) to the Week 1 to 12 monthly averages (Main Study, Part A)
Safety Objectives • To evaluate the safety and tolerability of eptinezumab after single and multiple IV administrations in paediatric patients 6 to 17 years of age (Main and Extension Study; Parts A and B)	**Safety Endpoints** • Adverse events • Absolute values and changes from Baseline in clinical safety laboratory test values, vital signs, weight, height, and electrocardiogram (ECG) parameter values • Potentially clinically significant (PCS) clinical safety laboratory test values, vital signs, weight changes, and ECG parameter values • Columbia-Suicide Severity Rating Scale (C-SSRS) score

Participants were followed-up for PK and safety tests until Day 169.

Analysis of the Exploratory Endpoints

Pediatric Migraine Disability Assessment Total Scores

The impact of migraines on children's day-to-day activities was assessed by patients and parents or caregivers, as applicable, who completed the PedMIDAS. The total score is a simple composite of the total of 6 questionnaire items. A score of 0 to 10 indicates little or no disability, 11 to 30 mild disability, 31 to 50 moderate disability, and more than 50 severe disability.

At Baseline, the median (min, max) PedMIDAS total score was slightly lower for children than for adolescents (39.0 [14, 132] *versus* 45.5 [0, 143]).

The absolute value and change from Baseline in the PedMIDAS disability score were descriptively summarized by visit and study period. Shifts from Baseline to each post-Baseline visit are presented for the PedMIDAS disability score categories (little to no disability, mild disability, moderate disability, and severe disability) by visit and study period.

Summaries and school status data are presented for the APTS_A and APTS_B for the Main Study Period and Extension Period, respectively.

Number of MMDs and MHDs

The treatment effect on the change from Baseline in number of MMDs and MHDs (Weeks 1 to 4, 5 to 8, 9 to 12, and 1 to 12) was calculated using 28-day intervals and summarized for the subset of patients with available eDiary data in the Main Study Period.

Sample size

A minimum of 32 patients were planned for enrolment: 16 children (aged 6 to 11 years) and 16 adolescents (aged 12 to 17 years).

However, due to recruitment difficulties, an interim population PK analysis was performed *ad hoc* based on data from 16 adolescents and 7 children. Based on that, the inclusion of 16 children as originally intended was deemed not necessary.

Following agreement with US FDA, EMA, and MHRA on a reduction of sample size of the children cohort, enrolment into the study was stopped when 16 adolescents and 12 children had been treated.

Results

Baseline data

The median age of the participants in this trial was 13.5 years (range 6 to 17 years), most participants were female (71%) and *White* or *Caucasian* (86%). At Baseline, 11 children had a weight >20 and ≤40 kg and 1 child had a weight >40 kg; all 16 adolescents had a weight >40 kg.

The median PedMIDAS total score at Baseline was slightly lower for children than for adolescents (39.0 *versus* 45.5).

Before the Screening Visit, 3 children (25%) and 8 adolescents (50%) had used preventive headache/migraine medication.

Baseline Weight and Age

Panel 2 Patient Characteristics (n = 28)

	N	Mean	SD	Minimum	Median	Maximum
Age (years)	28	12.6	3.3	6	13.5	17
Weight (kg)	28	51.1	18.8	20	52	80
				Counts (frequency)		
Weight group 20-40 kg				11 (39%)		
Weight group >40 kg				17 (61%)		
Boys				8 (29%)		
Girls				20 (71%)		
Children (6-11 yr)[b]				12 (43%)		
Adolescents (12-17 yr)[a]				16 (57%)		

[a] All 16 adolescents had a weight of > 40 kg; [b] 11 children weighed >20 to ≤40 kg and 1 child had a weight of >40 kg

PedMIDAS Total Score

Panel 16 PedMIDAS Total Score: Shift From Baseline to Week 12 in the Main Study Period (APTS_A)

Age Group (Years)	n at Visit 12	Post-Baseline	Baseline, n (%)			
			Little to No Disability	Mild Disability	Moderate Disability	Severe Disability
6 to 11	11	Little to no disability	0	3 (27.3)	1 (9.1)	2 (18.2)
		Mild disability	0	1 (9.1)	2 (18.2)	0
		Moderate disability	0	0	0	1 (9.1)
		Severe disability	0	0	0	1 (9.1)
12 to 17	15	Little to no disability	2 (13.3)	1 (6.7)	1 (6.7)	2 (13.3)
		Mild disability	0	2 (13.3)	1 (6.7)	1 (6.7)
		Moderate disability	0	0	0	0
		Severe disability	0	1 (6.7)	0	4 (26.7)
Overall	26	Little to no disability	2 (7.7)	4 (15.4)	2 (7.7)	4 (15.4)
		Mild disability	0	3 (11.5)	3 (11.5)	1 (3.8)
		Moderate disability	0	0	0	1 (3.8)
		Severe disability	0	1 (3.8)	0	5 (19.2)

Monthly Migraine Days and Monthly Headache Days (eDiary)

Only the 21 patients who enrolled under *Clinical Study Protocol* Edition 2.0 (Listing 16.2.1.1a) were asked to use the eDiary.

Parameter	Visit	Statistics	Age Group		
			6 to 11 Years (N=12)	12 to 17 Years (N=16)	Overall (N=28)
Baseline MMD	Baseline	n	5	5	10
		Mean (SD)	3.48 (2.835)	14.80 (9.668)	9.14 (8.984)
		Median	4.00	10.20	6.05
		Q1, Q3	1.30, 5.10	9.30, 25.00	4.00, 10.20
		Min, Max	0.0, 7.0	4.3, 25.2	0.0, 25.2

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Table 14.1.3.2.2a
Main Period: Migraine History
(APTS_A)

	Age Group		
	6 to 11 Years (N=12)	12 to 17 Years (N=16)	Overall (N=28)
Average Number of Headache Days per 28 day period 3 Months pre Screening			
n	12	16	28
Mean (SD)	7.8 (7.75)	9.5 (5.55)	8.8 (6.51)
Median	5.0	8.0	8.0
Min, Max	0, 28	0, 20	0, 28
Average Number of Migraine Days per 28 day period 3 Months pre Screening			
n	12	16	28
Mean (SD)	8.8 (5.24)	10.6 (3.46)	9.8 (4.33)
Median	7.0	11.0	10.0
Min, Max	4, 20	4, 16	4, 20
Average Number of Migraine Attacks Days per 28 day period 3 Months pre Screening			
n	12	16	28
Mean (SD)	8.6 (5.23)	9.9 (4.08)	9.3 (4.56)
Median	7.0	9.0	8.0
Min, Max	4, 20	4, 16	4, 20

Number analysed

Overall, 28 paediatric participants (12 children and 16 adolescents) with migraine were treated in the Main Study Period, of which 25 (11 children and 14 adolescents) have completed that period. Three participants withdrew from the trial - 1 child (*withdrawal of consent*) and 2 adolescents (*lost to follow-up* and "*other*" reason ["too busy with school and could not continue"]).

Based on baseline demographic data, both, patients with episodic and with chronic migraine, have been included. However, the respective numbers and distribution of patients with CM and EM across age groups does not become clear.

Safety results

	Age Group		
	6 to 11 Years (N=12) n (%) [Events]	12 to 17 Years (N=16) n (%) [Events]	Overall (N=28) n (%) [Events]
Patients with at least one			
Adverse event	7 (58.3) [16]	9 (56.3) [13]	16 (57.1) [29]
Treatment-emergent adverse event (TEAE)	7 (58.3) [16]	9 (56.3) [13]	16 (57.1) [29]
Serious TEAE	0	0	0
TEAE related to IMP	3 (25.0) [5]	6 (37.5) [7]	9 (32.1) [12]
Serious TEAE related to IMP	0	0	0
Severe TEAE	0	0	0
TEAE leading to IMP modification	0	0	0
TEAE leading to temporary interruption of IMP	0	0	0
TEAE leading to withdrawal of IMP	0	0	0
TEAE leading to withdrawal from the study	0	0	0
TEAE leading to death	0	0	0

The system organ classes with the highest incidences of TEAEs (>15% in either age group) were *infections and infestations* (4 children [33%]; 1 adolescent [6%]), *psychiatric disorders* (3 children [25%]; 1 adolescent [6%]), and *vascular disorders* (0 children; 3 adolescents [19%]). The only TEAE (preferred term) that was reported for more than 1 patient was orthostatic hypotension, which occurred in 3 adolescents (19%). All other TEAEs occurred as single events in single patients only. All events of orthostatic hypotension occurred in relation to infusion, resolved quickly/within the same day, were assessed as non-serious, *mild* or *moderate*, and *related* to IMP.

- Four (14%) patients had infusion-related reactions (migraine in 1 child; cough and rhinorrhoea in 1 child; and orthostatic hypotension in 2 adolescents).
- None of the patients had TEAEs leading to *death*, *serious* TEAEs, *severe* TEAEs, or TEAEs leading to IMP modification, temporary interruption of IMP, withdrawal of IMP, or withdrawal from the study.
- The mean changes from Baseline in clinical safety laboratory values, vital signs, and ECG parameters, and shifts in height and body mass index percentiles were generally small in both age groups, with no clinically relevant findings. In general, few patients had post-Baseline PCS values across the variables. With the exception of 1 adolescent with clinically significant post-Baseline vital signs values (low diastolic and systolic blood pressure) and an associated TEAE of orthostatic hypotension, the post-Baseline PCS values across the variables were considered not clinically relevant.

- Two patients had suicidal ideation as assessed using the C-SSRS (*wish to be dead* [C-SSRS score of 1] and *non-specific active suicidal thoughts* [C-SSRS score of 2] in a child and *wish to be dead* in an adolescent). These 2 patients reported associated TEAEs of depression and adjustment disorder with depressed mood, respectively.
- Two adolescents were positive for ADAs in a confirmatory assay: 1 at Week 20 and 1 at Weeks 12 and 20, but neither had NAbs. No child was positive for ADAs.

Pharmacokinetics

Pharmacokinetic (NCA) and Efficacy Results

After a single IV administration of eptinezumab to paediatric patients, eptinezumab Cmax and $AUC_{0\text{-}inf}$ were similar between dose level/weight group. The median terminal t½ for eptinezumab was similar between dose levels: 27.5 days (659.5 hours) and 29.2 days (699.9 hours) for the 150 mg and 300 mg dose levels, respectively. In the heavier patients who received 300 mg eptinezumab, the geometric mean CL was faster and Vz was larger by approximately 2-fold when compared to the lighter patients who received 150 mg. As only 1 patient was in a different category when results were summarized by age group, similar trends were observed when comparing by age group.

Plasma PK parameters of eptinezumab by dose level/weight group are summarized in Panel 15.

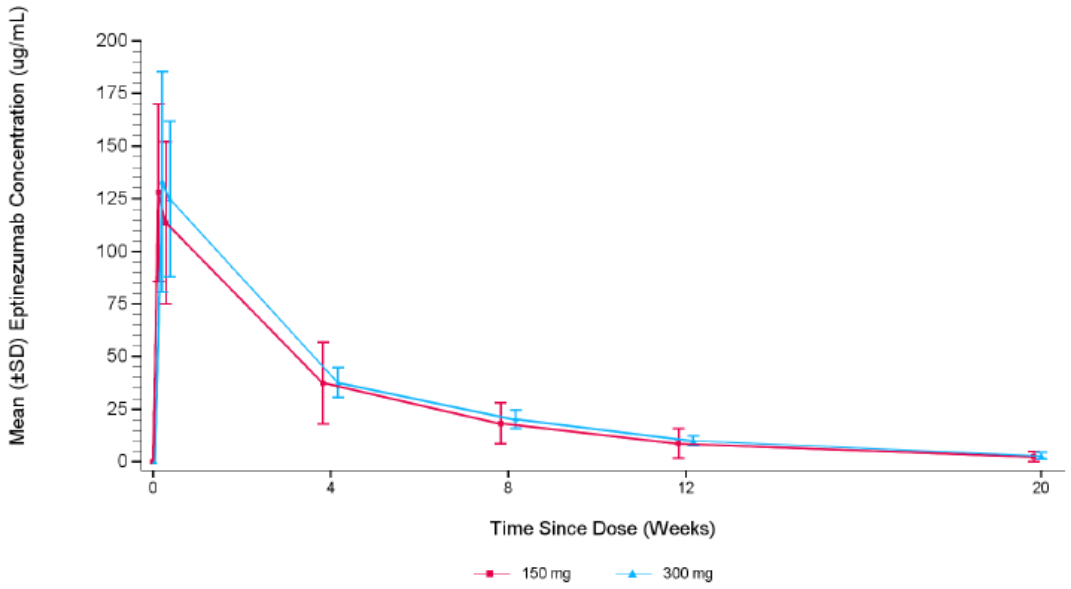
Panel 15 PK Parameters of Eptinezumab by Dose Level in the Main Study Period (PKS_A)

		Dose Level	
		150 mg	300 mg
		Weight Group	
Parameter (Unit)	Statistics	>20 kg to ≤40 kg	>40 kg
$AUC_{0\text{-}inf}$ (h·µg/mL)	n	10	16
	Missing (n)	1	1
	Geo mean (GeoCV%)	87780 (33.1)	94050 (18.3)
C_{max} (µg/mL)	n	11	17
	Missing (n)	0	0
	Geo mean (GeoCV%)	126.2 (31.9)	133.7 (33.9)
$AUC_{0\text{-}t\ last}$ (h·µg/mL)	n	11	17
	Missing (n)	0	0
	Geo mean (GeoCV%)	79260 (40.6)	88910 (18.8)
C_{12wk} (µg/mL)	n	10	16
	Missing (n)	1	1
	Geo mean (GeoCV%)	6.440 (117)	9.707 (28.9)
t_{max} (h)	n	11	17
	Median (Q1, Q3)	0.6830 (0.5830, 2.500)	2.483 (0.6330, 2.633)
$t_{½}$ (h)	n	10	16
	Missing (n)	1	1
	Median (Q1, Q3)	659.5 (584.5, 729.9)	699.9 (619.9, 758.0)
CL (L/h)	n	10	16
	Missing (n)	1	1
	Geo mean (GeoCV%)	0.001709 (33.1)	0.003190 (18.3)
Vz (L)	n	10	16
	Missing (n)	1	1
	Geo mean (GeoCV%)	1.591 (33.7)	3.233 (26.9)

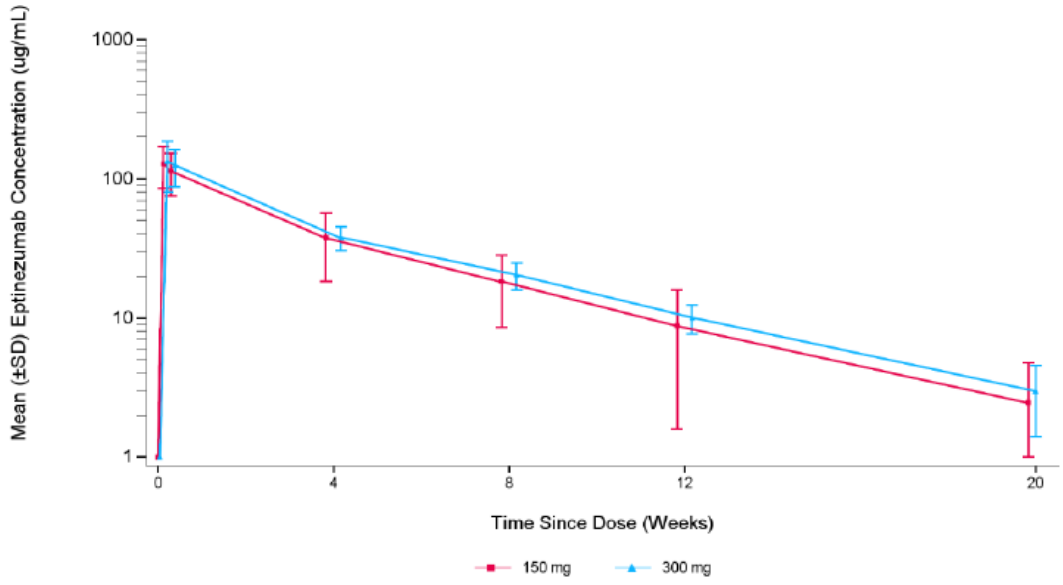
Abbreviations: Geo = geometric; Q1 = lower quartile; Q3 = upper quartile

Arithmetic mean (± SD) eptinezumab concentrations over the sampling period are presented by dose level on the linear and semi-logarithmic scales in Panel 13 and Panel 14, respectively.

Panel 13 Mean (± SD) Plasma Eptinezumab Concentration by Dose Level in the Main Study Period – Linear Scale (PKS_A)



Panel 14 Mean (± SD) Plasma Eptinezumab Concentration by Dose Level in the Main Study Period – Semi-log Scale (PKS_A)



A single IV administration of eptinezumab at 150 mg or 300 mg, depending on the body weight, resulted in overlapping mean plasma concentration-time curves in paediatric participants 6 to 17 years of age. Plasma exposure, in terms of C_{max} and $AUC0\text{-}_{inf}$, was similar between dose levels/weight groups/age groups. CL and Vz were different between dose levels/weight groups/age groups with heavier participants administered 300 mg eptinezumab displaying faster CL and a larger Vz by approximately 2-fold compared to lighter participants administered 150 mg. The plasma t1/2 of

eptinezumab was similar between dose levels with median of 27.5 days and 29.2 days for the 150 mg and 300 mg dose levels, respectively.

Overall, the PK profile of eptinezumab in paediatric participants 6 to 17 years of age was similar between dose levels/weight groups/age groups, except for CL and Vz.

Pediatric Migraine Disability Assessment Total Scores

An improvement in disability was seen in both age groups, with a median (min, max) score change from Baseline to Week 12 of -22.0 (-70, -6) in children and -17.0 (-117, 42) in adolescents.

The analysis of the shift in PedMIDAS disability score categories from Baseline to Week 12 showed improvements in disability in 9 children and 6 adolescents, no change in 2 children and 8 adolescents, and worsened disability in 1 adolescent (change from mild at Baseline to severe at Week 12). This, however, corresponds to 42% (18% children, and 60% adolescents) without benefit in PedMIDAS.

Monthly Migraine Days and Monthly Headache Days

Monthly Migraine Days

			Age Group		
Parameter	Visit	Statistics	6 to 11 Years (N=12)	12 to 17 Years (N=16)	Overall (N=28)
Baseline MMD	Baseline	n	5	5	10
		Mean (SD)	3.48 (2.835)	14.80 (9.668)	9.14 (8.984)
		Median	4.00	10.20	6.05
		Q1, Q3	1.30, 5.10	9.30, 25.00	4.00, 10.20
		Min, Max	0.0, 7.0	4.3, 25.2	0.0, 25.2
Weeks 1-4 MMD	Weeks 1-4	n	5	6	11
		Mean (SD)	5.26 (4.494)	12.88 (11.852)	9.42 (9.704)
		Median	3.40	13.25	5.90
		Q1, Q3	2.30, 5.90	0.00, 22.80	1.90, 17.90
		Min, Max	1.9, 12.8	0.0, 28.0	0.0, 28.0
	Change from Baseline to Weeks 1-4	n	3	5	8
		Mean (SD)	-0.60 (2.488)	-3.90 (6.914)	-2.66 (5.657)
		Median	-1.10	-7.10	-1.95
		Q1, Q3	-2.80, 2.10	-9.30, 2.80	-8.20, 2.45
		Min, Max	-2.8, 2.1	-10.2, 4.3	-10.2, 4.3

			Age Group		
Parameter	Visit	Statistics	6 to 11 Years (N=12)	12 to 17 Years (N=16)	Overall (N=28)
Weeks 5-8 MMD	Weeks 5-8	n	5	5	10
		Mean (SD)	4.58 (2.704)	11.46 (11.421)	8.02 (8.624)
		Median	4.20	13.40	5.60
		Q1, Q3	3.20, 7.00	1.30, 14.60	1.30, 13.40
		Min, Max	1.0, 7.5	0.0, 28.0	0.0, 28.0
	Change from Baseline to Weeks 5-8	n	4	5	9
		Mean (SD)	0.58 (1.715)	-3.34 (6.441)	-1.60 (5.109)
		Median	0.10	-3.00	-0.30
		Q1, Q3	-0.60, 1.75	-9.30, 2.80	-3.00, 2.80
		Min, Max	-0.9, 3.0	-10.4, 3.2	-10.4, 3.2
Weeks 9-12 MMD	Weeks 9-12	n	4	5	9
		Mean (SD)	4.03 (3.896)	7.04 (9.506)	5.70 (7.308)
		Median	3.40	4.00	4.00
		Q1, Q3	1.40, 6.65	0.00, 8.30	0.00, 8.30
		Min, Max	0.0, 9.3	0.0, 22.9	0.0, 22.9
	Change from Baseline to Weeks 9-12	n	3	5	8
		Mean (SD)	-0.43 (2.419)	-7.76 (6.590)	-5.01 (6.393)
		Median	-1.30	-9.30	-2.30
		Q1, Q3	-2.30, 2.30	-10.20, -2.30	-9.75, -0.80
		Min, Max	-2.3, 2.3	-16.7, -0.3	-16.7, 2.3

Parameter	Visit	Statistics	Age Group: 6 to 11 Years (N=12)	Age Group: 12 to 17 Years (N=16)	Overall (N=28)
Weeks 1-12 MMD	Weeks 1-12	n	6	6	12
		Mean (SD)	5.83 (4.178)	11.97 (10.758)	8.90 (8.414)
		Median	5.05	9.10	5.80
		Q1, Q3	3.00, 7.60	4.50, 22.80	3.05, 13.20
		Min, Max	1.5, 12.8	0.0, 26.3	0.0, 26.3
	Change from Baseline to Weeks 1-12	n	4	5	9
		Mean (SD)	0.45 (2.049)	-5.00 (5.596)	-2.58 (5.048)
		Median	0.40	-5.70	0.20
		Q1, Q3	-0.90, 1.80	-9.30, 0.30	-5.70, 0.60
		Min, Max	-2.0, 3.0	-11.4, 1.1	-11.4, 3.0

Monthly Headache Days

Parameter	Visit	Statistics	Age Group: 6 to 11 Years (N=12)	Age Group: 12 to 17 Years (N=16)	Overall (N=28)
Baseline MHD	Baseline	n	5	5	10
		Mean (SD)	6.56 (4.613)	17.66 (8.362)	12.11 (8.647)
		Median	7.00	14.00	10.55
		Q1, Q3	5.10, 8.00	11.40, 25.20	7.00, 14.00
		Min, Max	0.0, 12.7	9.7, 28.0	0.0, 28.0
Weeks 1-4 MHD	Weeks 1-4	n	5	6	11
		Mean (SD)	8.80 (9.063)	16.60 (12.371)	13.05 (11.224)
		Median	6.70	18.55	7.40
		Q1, Q3	3.50, 7.40	6.50, 28.00	3.50, 26.30
		Min, Max	1.9, 24.5	0.0, 28.0	0.0, 28.0
	Change from Baseline to Weeks 1-4	n	3	5	8
		Mean (SD)	-2.40 (3.274)	-3.00 (6.129)	-2.78 (4.962)
		Median	-1.60	0.00	-0.80
		Q1, Q3	-6.00, 0.40	-7.50, 1.10	-6.75, 0.75
		Min, Max	-6.0, 0.4	-11.4, 2.8	-11.4, 2.8

Parameter	Visit	Statistics	Age Group: 6 to 11 Years (N=12)	Age Group: 12 to 17 Years (N=16)	Overall (N=28)
Weeks 5-8 MHD	Weeks 5-8	n	5	5	10
		Mean (SD)	5.86 (4.127)	14.08 (12.915)	9.97 (10.024)
		Median	4.20	16.80	5.85
		Q1, Q3	3.20, 7.50	1.30, 24.30	2.10, 16.80
		Min, Max	2.1, 12.3	0.0, 28.0	0.0, 28.0
	Change from Baseline to Weeks 5-8	n	4	5	9
		Mean (SD)	-1.68 (6.343)	-3.58 (6.438)	-2.73 (6.068)
		Median	-0.20	-3.70	-0.90
		Q1, Q3	-5.75, 2.40	-8.40, 2.80	-8.40, 2.80
		Min, Max	-10.6, 4.3	-11.4, 2.8	-11.4, 4.3
Weeks 9-12 MHD	Weeks 9-12	n	4	5	9
		Mean (SD)	6.63 (3.783)	10.54 (9.115)	8.80 (7.153)
		Median	6.65	10.20	9.30
		Q1, Q3	3.40, 9.85	4.00, 15.60	4.00, 10.40
		Min, Max	2.8, 10.4	0.0, 22.9	0.0, 22.9
	Change from Baseline to Weeks 9-12	n	3	5	8
		Mean (SD)	-0.77 (2.656)	-7.12 (4.541)	-4.74 (4.961)
		Median	-2.30	-5.70	-3.05
		Q1, Q3	-2.30, 2.30	-11.40, -3.80	-8.55, -2.30
		Min, Max	-2.3, 2.3	-12.4, -2.3	-12.4, 2.3

Parameter	Visit	Statistics	Age Group: 6 to 11 Years (N=12)	Age Group: 12 to 17 Years (N=16)	Overall (N=28)
Weeks 1-12 MHD	Weeks 1-12	n	6	6	12
		Mean (SD)	9.63 (8.032)	15.30 (11.351)	12.47 (9.831)
		Median	7.25	16.90	9.65
		Q1, Q3	3.50, 12.30	5.40, 26.30	4.45, 23.55
		Min, Max	3.0, 24.5	0.0, 26.3	0.0, 26.3
	Change from Baseline to Weeks 1-12	n	4	5	9
		Mean (SD)	-0.63 (4.487)	-4.56 (4.547)	-2.81 (4.710)
		Median	-0.25	-4.30	-2.80
		Q1, Q3	-3.95, 2.70	-5.40, -2.80	-5.40, 1.10
		Min, Max	-6.3, 4.3	-11.4, 1.1	-11.4, 4.3

There were operational issues with implementation of the eDiary, especially in the younger age group in which children and parents or caregivers were expected to provide separate reports, and also poor compliance was noted in some patients. In consequence, only about one-third of the patients provided data from the Screening Visit until Week 12 and could be evaluated for the change in number of MMDs and MHDs from Baseline to the monthly averages.

A summary of MMDs and MHDs is provided in Table above. Due to problems with the eDiary data collection and the low number of patients who completed the eDiary from the Screening Visit until Week 12, this exploratory evaluation provided only limited data, and the results for MMDs and MHDs are difficult to interpret.

Safety

The SOCs with the highest incidences of TEAEs (>15% in either age group) were:

· *infections and infestations* (4 children [33%]; 1 adolescent [6%])

· *psychiatric disorders* (3 children [25%]; 1 adolescent [6%])

· *vascular disorders* (0 children; 3 adolescents [19%])

The only TEAE (preferred term) that was reported for more than 1 patient was orthostatic hypotension, which occurred in 3 adolescents (19%) (see section 10.1.4 for details). All other TEAEs occurred as single events in single patients only.

1 child was inadvertently infused with 200 mg instead of 150 mg eptinezumab. For this case a TEAE of accidental overdose was reported.

Thirteen (46%) patients had TEAEs with a maximum intensity of *mild*. Seven (25%) patients had TEAEs with a maximum intensity of *moderate*. None of the patients had a *severe* TEAE.

Nine (32%) patients had at least 1 TEAE *related* to IMP. TEAEs *related* to IMP in the 3 children were migraine and photopsia, sleep terror, and cough and rhinorrhea. TEAEs *related* to IMP in the 6 adolescents were orthostatic hypotension (in 3 adolescents), adjustment disorder with depressed mood, pruritus, and dizziness.

Infusion-related Reactions

Four (14%) patients had at least one *infusion-related reaction*. *Infusion-related reactions* were migraine (verbatim term: worsening migraine) in 1 child, cough and rhinorrhoea in 1 child, and orthostatic hypotension in 2 adolescents. Of note, 2 additional adolescents had TEAEs (1 adolescent had orthostatic hypotension and 1 had adjustment disorder with depressed mood) on the day of the

infusion after the infusion was started, which were assessed as *related* to IMP but not classified as *infusion-related reactions* by the investigators.

The 3 adolescents with orthostatic hypotension all received the IMP infusion at the same study site. All events were non-serious and *related* to IMP. The intensity was *moderate* for 2 adolescents and *mild* for 1 adolescent. Of note, the TEAE of orthostatic hypotension in 1 adolescent is listed twice since a change in intensity from *moderate* to *mild* was recorded for the last minute of the event. Site queries confirmed that patients reported symptoms as "dizzy, sweaty and hot", "dizzy, lightheaded, and hot", and "clammy and nauseous". All events *resolved* on the same day (resolution was reported after 5 min, 9 min, and exact time unknown but on the same day). No other TEAEs were reported for these adolescents on the same day, and the orthostatic hypotension did not lead to IMP modification, temporary interruption of IMP, withdrawal of IMP, or withdrawal from the study.

Clinical Safety Laboratory Test Results

For all laboratory values, the mean changes from Baseline were generally small in both age groups, with no clinically relevant findings.

The urine laboratory tests showed no relevant findings in either age group

Four patients had post-Baseline PCS (potentially clinically significant) haematology values (Listing 16.2.8.1.1.1a):

· One child had PCS low haematocrit values at all study visits, including Screening and Baseline. This child also had PCS low haemoglobin values at Screening, Baseline, and Week 4.

· Two adolescents had PCS high eosinophil values: 1 at Baseline and Week 20, and 1 at Week 20.

Immunogenicity

Two adolescents were positive for ADAs in a confirmatory assay: 1 at Week 20 and 1 at Weeks 12 and 20, but neither had NAbs. No child was positive for ADAs.

3.2.3. Discussion on clinical aspects

The scope of this study 18922A, an open-label, single-dose, pharmacokinetic study to evaluate IV eptinezumab in children and adolescents with migraine, followed by an optional, multiple-dose, open-label extension period (Main Study Period completed, Extension Period ongoing), was to evaluate the pharmacokinetic profile of eptinezumab after a single intravenous administration in paediatric patients 6 to 17 years of age. Secondary objectives were to characterize the PK profile of eptinezumab after multiple IV administrations in the context of an extension study, and to evaluate immunogenicity.

In the study patients weighing >20 to ≤40 kg received a single dose of eptinezumab 150 mg IV and patients weighing >40 kg received a single dose of eptinezumab 300 mg IV. In total, 28 patients with migraine were included and treated in the Main Study Period. Thereof, 11 patients were included in the weight group 20-40 kg (39%) and 17 patients (61%) in the weight group >40kg. The mean age of the patients was 12.6 years and the mean weight 51.1kg.

To characterize the PK profile, blood samples were collected and analysed at screening, baseline (immediately after end of infusion and 2 hours after end of infusion), and at weeks 4, 8, 12, and 20.

The following PK-Parameters were analysed: $AUC_{0\text{-}inf}$, C_{max}, $AUC_{0\text{-}tlast}$, C_{min} (C_{12wk}), t_{max}, $T_{1/2}$, CL, Vz.

The currently provided results for the PK-Parameter C_{max}, $AUC_{0\text{-}inf}$ and $T_{1/2}$ after a single IV administration of eptinezumab appears to be similar between the weight groups >20 kg to ≤40kg and the weight group >40 kg and no major differences between the 150 mg and 300 mg treated group were observed based on the concentration-time curves provided. The $t_{1/2}$ was similar between dose levels with a median of 27.5 days and 29.2 days for the 150 mg and 300 mg respectively. However, differences have been observed in clearance (geometric mean: 0.001709 L/h vs. 0.003190 L/h) and volume of distribution (geometric mean: 1.591 L vs. 3.233 L) between both dose levels/weight groups (150 mg vs. 300 mg). Heavier participants administered 300 mg eptinezumab demonstrating a faster CL and a larger Vz by approximately 2-fold compared to lighter participants administered 150 mg. In addition, small difference was observed for C_{12wk} (geometrical mean for 150 mg: 6.440 µg/mL vs geometrical mean for 300 mg: 9.707 µg/mL) and differences in the median for t_{max} between the lower dose level/lighter weight group (median: 0.6830h) and the higher dose level/weight group (median: 2.483h) were observed, but with overlapping quartiles (Q1, Q3). In addition, the lower dose level/lighter weight group showed a higher intra-subject variability (GeoCV %: between 31.9%-117%) compared to the higher dose level/weight group (GeoCV% between 18.3%-33.9%). Moreover, the number of children (n=11) and adolescents (n=16) included in this study was quite small.

However, based on the data provided, the PK profile of eptinezumab in pediatric participants appears similar overall between the dose levels/weight groups evaluated in this study, except for CL and Vz. Nevertheless, there are currently still concerns regarding the selected dosing regimen and the robustness of the Pop-PK model used in this study. It would have been desirable to select the dose recommended in the SmPC for adults (100 mg) rather than the maximum dose (300 mg) tested in adults, to avoid possible unnecessary overdose. However, eptinezumab was well tolerated in children and adolescents so far and it was already agreed in the PIP [P/0091/2022 European Medicines Agency decision dated 11 March 2022] to cover both doses (100 mg and 300 mg) in the paediatric development program. In addition, as stated by the applicant, the PK-sampling is included in the ongoing efficacy and safety trials (19356A, 19357A, and 19379A), and the paediatric popPK model will be updated accordingly when these data become available. Therefore, the final paediatric doses will be decided based on all available paediatric data (Trials 18922A, 19356A, 19357A, and 19379A).

The efficacy and safety of eptinezumab in this pediatric population was evaluated as an exploratory objective.

There was a trend to clinical improvement in PedMIDAS disability scores across age groups. This result was to some extend supported by MMD and MHD analyses, but due to problems with the eDiary data collection and the low number of patients who completed the eDiary from the Screening Visit until Week 12, this exploratory evaluation provided only limited data which need to be handled with care.

Overall, eptinezumab was well tolerated in children and adolescents. No new safety signals were identified.

No changes to the product information are proposed.

4. Rapporteur's overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.

5. Request for supplementary information

Pharmacokinetics – Modelling and Simulation

1. Please revise the paediatric population PK model and provide model-based simulations for additional doses over a broad dose range (e.g. 10 different doses) targeting both authorized adult doses (100 mg and 300 mg IV). The documentation of this exercise should then also include:
   - Generally provided information on analytical methods including LLOQ, BLQ etc.
   - Exact composition of the dataset (e.g. number per dose and age group, demographics, disease state etc.). Any deviation from the planned dosing should be explained and justified.
   - Covariates: if still the use of covariates identified in adults will be deemed appropriate, these need to be explained and justified for the paediatric population, parameter values and their impact on the paediatric PK need to be presented and explained. Results for the investigation of age and sex on the paediatric PK should be discussed and presented.
   - VPCs should be presented also on semi-log scale.

Pharmacokinetics – Non-compartmental analysis

2. Since the recommended dose for adults according to the SmPC of Vyepti is 100 mg, a comprehensible justification for the dosing regimen chosen in this study and a direct comparison of the observed PK-Parameter between children, adolescents and adults (treated with 100 mg and 300 mg), including figures and tables, should be provided.

Efficacy

3. Please clarify the number of children and of adolescents with chronic migraine and with episodic migraine, respectively.

MAH responses to Request for supplementary information

Question 1

Please revise the paediatric population PK model and provide model-based simulations for additional doses over a broad dose range (e.g. 10 different doses) targeting both authorized adult doses (100 mg and 300 mg IV). The documentation of this exercise should then also include:

- Generally provided information on analytical methods including LLOQ, BLQ etc.
- Exact composition of the dataset (e.g. number per dose and age group, demographics, disease state etc.). Any deviation from the planned dosing should be explained and justified.
- Covariates: if still the use of covariates identified in adults will be deemed appropriate, these need to be explained and justified for the paediatric population, parameter values and their impact on the paediatric PK need to be presented and explained. Results for the investigation of age and sex on the paediatric PK should be discussed and presented.
- VPCs should be presented also on semi-log scale.

Summary of the Applicant's Response

Lundbeck considers the paediatric population PK model (that has been submitted in the population PK report) to be sufficiently robust and hence no revision of the model is deemed necessary. Simulations with several different doses were performed (Table 4). The results of the simulations are shown in

Figure 5, Figure 6, Figure 7, and Figure 8 for $AUC_{0\text{-}Wk12}$ and C_{max}, respectively. The original proposed doses for children and adolescents (for 100 mg adult equivalent 40, 50, and 100 mg [Table 4 scenario A] and for 300 mg adult equivalent 100, 150, and 300 mg [Table 4 scenario G] for weight groups of <20 kg, 20-40 kg, and >40 kg, respectively) were considered as best results.

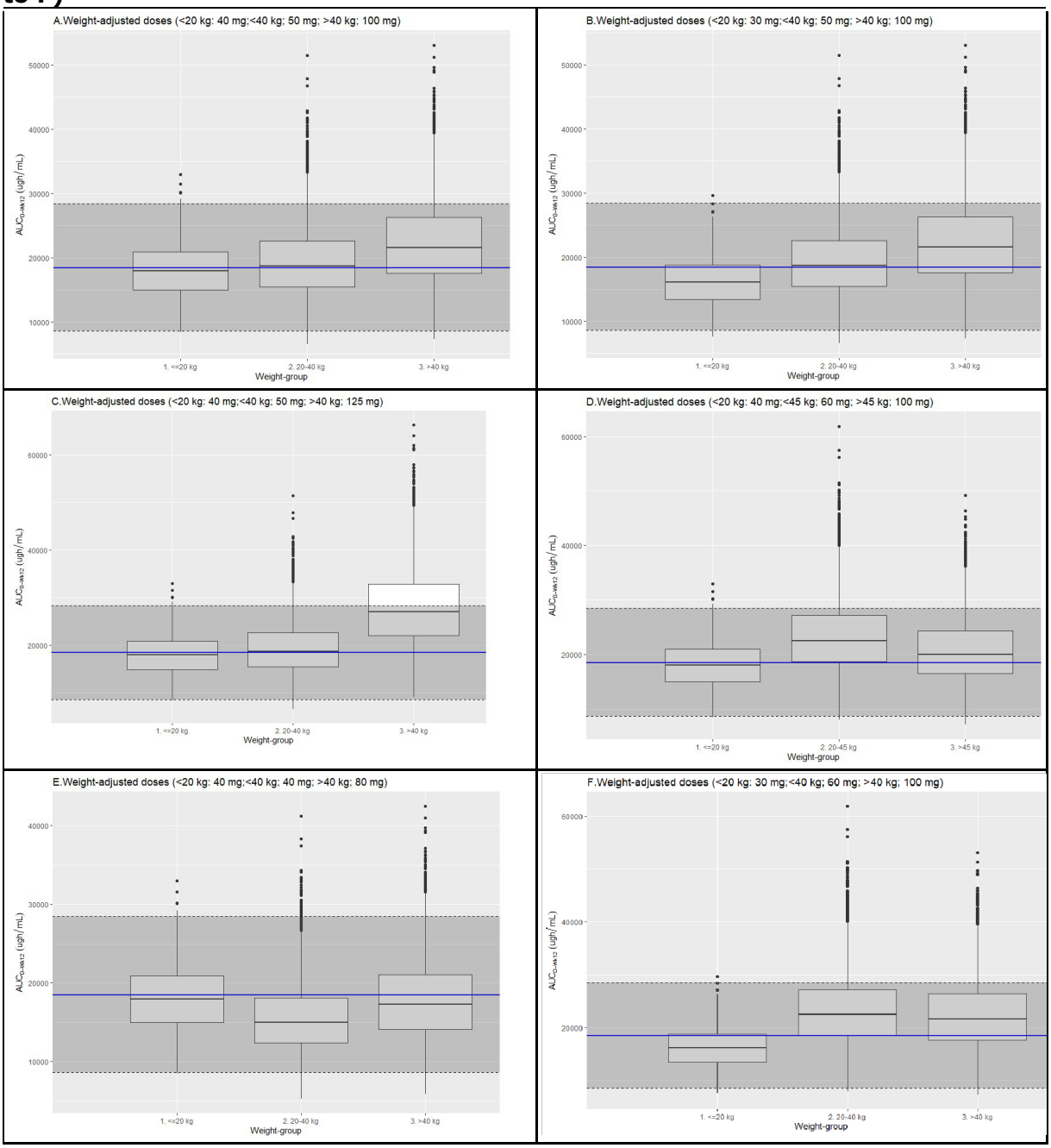
The use of the 60% to 140% criterion was accepted by the EMA/PDCO in PIP modification 03 (P/0341/2022; European Medicines Agency decision dated 10 August 2022).

Table 4: Panel 1 - Simulation Scenarios with Corresponding Weight-adjusted Doses

Simulation Scenario	Weight-adjusted Doses	Adult Reference Dose (mg)
A	<20 kg: 40 mg, 20-40 kg: 50 mg, >40 kg: 100 mg[a]	100
B	<20 kg: **30** mg, 20-40 kg: 50 mg, >40 kg: 100 mg	100
C	<20 kg: 40 mg, 20-40 kg: 50 mg, >40 kg: **125** mg	100
D	<20 kg: 40 mg, 20-**45** kg: **60** mg, >**45** kg: 100 mg	100
E	<20 kg: 40 mg, 20-40 kg: **40** mg, >40 kg: **80** mg	100
F	<20 kg: **30** mg, 20-40 kg: **60** mg, >40 kg: 100 mg	100
G	<20 kg: 100 mg, 20-40 kg: 150 mg, >40 kg: 300 mg[b]	300
H	<20 kg: **125** mg, 20-40 kg: 150 mg, >40 kg: 300 mg	300
I	<20 kg: 100 mg, 20-40 kg: 150 mg, >40 kg: **350** mg	300
J	<20 kg: 100 mg, 20-**45** kg: **175** mg, >**45** kg: 300 mg	300
K	<20 kg: 100 mg, 20-40 kg: **125** mg, >40 kg: **250** mg	300
L	<20 kg: 100 mg, 20-40 kg: **175** mg, >40 kg: 300 mg	300

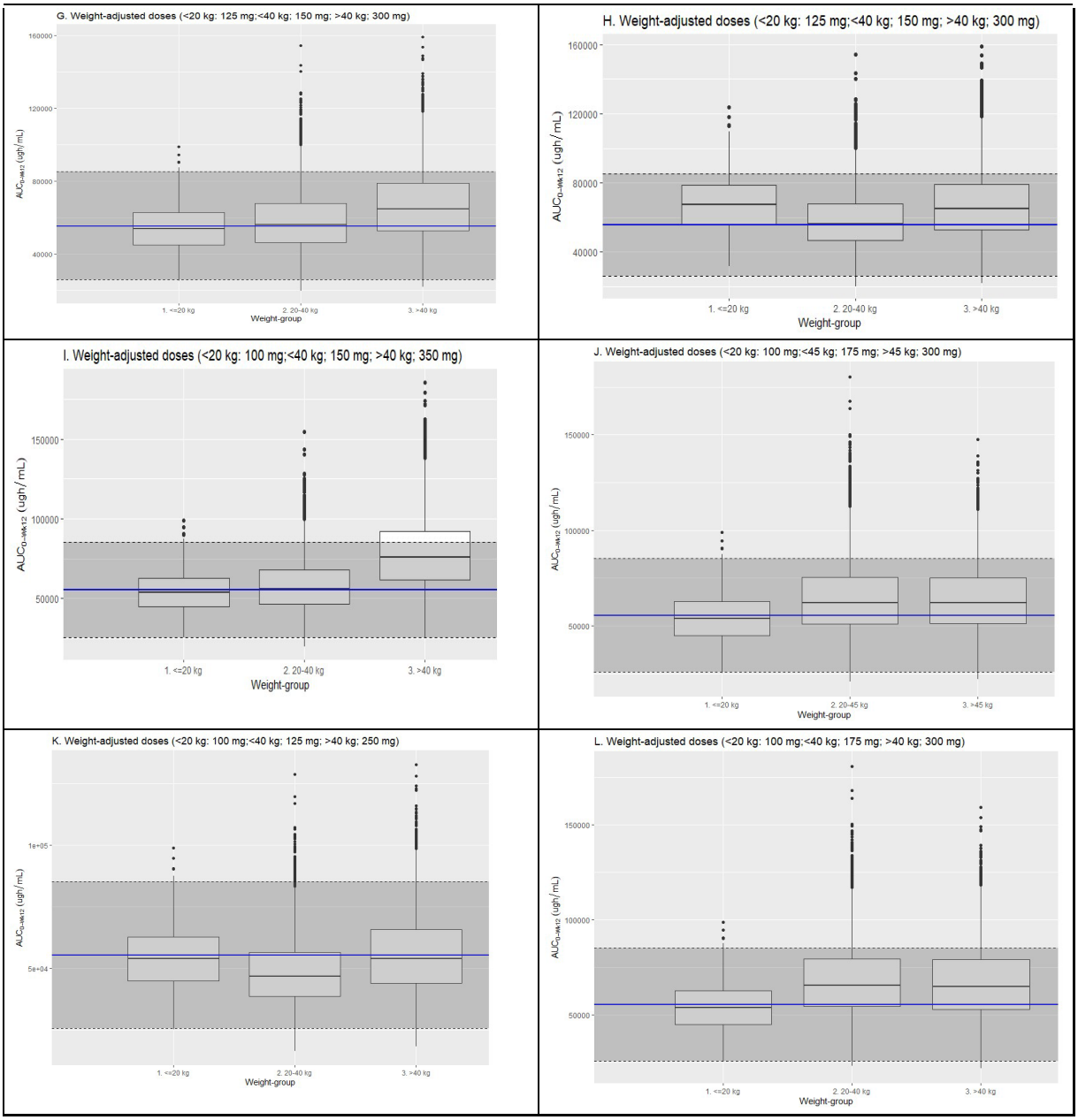
a The doses simulated in the popPK report for comparison with 100 mg adult.
b The doses simulated in the popPK report for comparison with 300 mg adult.
Text in bold refers to changes made to the doses simulated in the popPK report.

Figure 5: Panel 2 - Simulated AUC0-Wk12 Values in a Paediatric Population after a Single Administration of Eptinezumab for 100 mg Adult Dose (Simulations A to F)



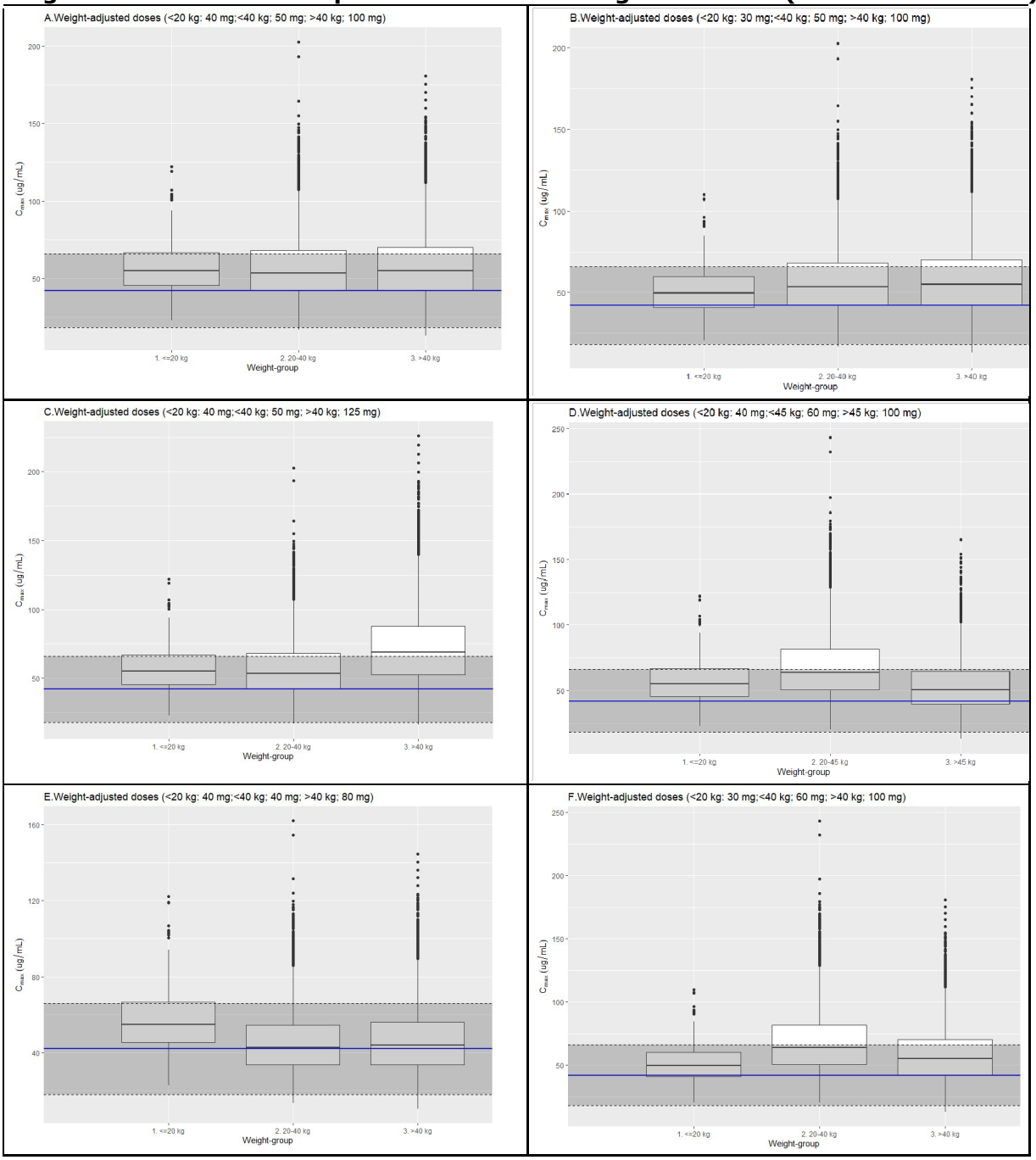
The adult reference range (5th-95th percentiles and median) are highlighted in the background. The paediatric data (N = 13,300) are shown as boxes with median, 25th (Q1) and 75th (Q3) percentiles, whiskers are defined as 1.5*interquartile range (Q3-Q1) and with outliers outside these ranges. For simulation scenarios A and G, the percentage of apparent outliers (out of 13,300 simulations) was <2% and <3% for AUC and C_{max}, respectively.

Figure 6: Panel 3 - Simulated $AUC_{0\text{-}wk12}$ Values in a Paediatric Population after a Single Administration of Eptinezumab for 300 mg Adult Dose (Simulations G to L)



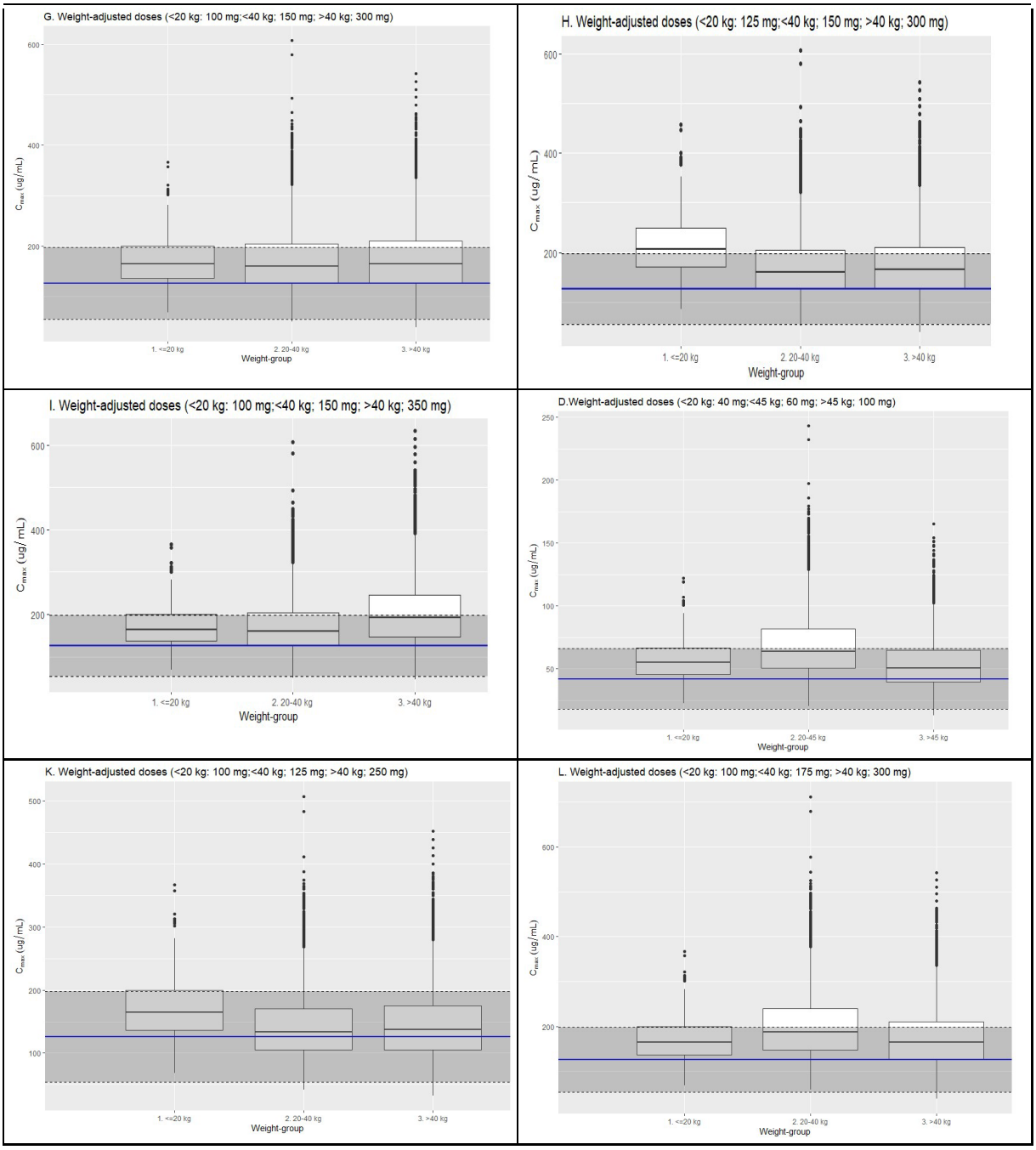
The adult reference range (5th-95th percentiles and median) are highlighted in the background. The paediatric data (N = 13,300) are shown as boxes with median, 25th (Q1) and 75th (Q3) percentiles, whiskers are defined as 1.5*interquartile range (Q3-Q1) and with outliers outside these ranges. For simulation scenarios A and G, the percentage of apparent outliers (out of 13,300 simulations) was <2% and <3% for AUC and C_{max}, respectively.

Figure 7: Panel 4 - Simulated Cmax Values in a Paediatric Population after a Single Administration of Eptinezumab for 100 mg Adult Dose (Simulations A to F)



The adult reference range (5th-95th percentiles and median) highlighted in the background. The paediatric data (N = 13,300) are shown as boxes with median, 25th (Q1) and 75th (Q3) percentiles, whiskers are defined as 1.5*interquartile range (Q3-Q1) and with outliers outside these ranges. For simulation scenarios A and G, the percentage of apparent outliers (out of 13,300 simulations) was <2% and <3% for AUC and C_{max}, respectively.

Figure 8: Panel 5 - Simulated Cmax Values in a Paediatric Population after a Single Administration of Eptinezumab for 300 mg Adult Dose (Simulations G to L)



The adult reference range (5th-95th percentiles and median) are highlighted in the background. The paediatric data (N = 13,300) are shown as boxes with median, 25th (Q1) and 75th (Q3) percentiles, whiskers are defined as 1.5*interquartile range (Q3-Q1) and with outliers outside these ranges. For simulation scenarios A and G, the percentage of apparent outliers (out of 13,300 simulations) was <2% and <3% for AUC and C_{max}, respectively.

Data:

The Lower Limit of Quantification (LLOQ) of free Lu AG09222 in plasma was 50 ng/mL.

The characteristics of the covariates as listed in Table 5 were included in the population PK analysis. Information on disease state was not collected during the trial. Hence, it is not part of the clinical database (see also response to Request 3 - Efficacy).

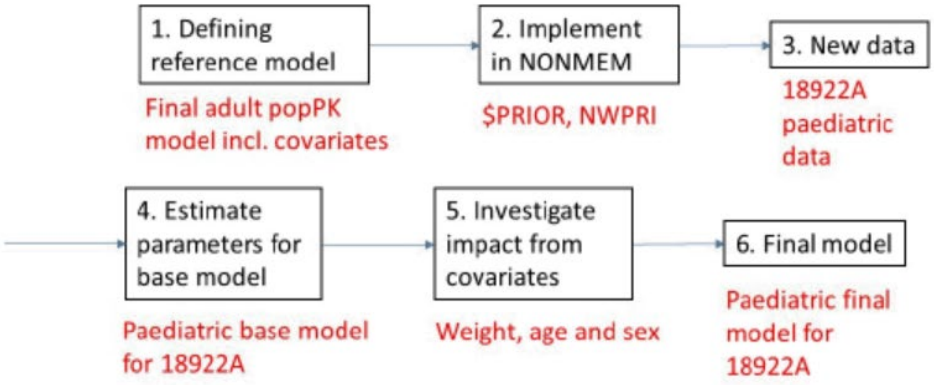
Table 5: Panel 7 - Description of the dataset used for popPK of eptinezumab in paediatrics

	N	Mean	SD	Minimum	Median	Maximum
Age (yr)	28	12.6	3.3	6	13.5	17
Weight (kg)	28	51.1	18.8	20	52	80
Height (cm)	28	152	18.2	117	155	181
BMI	28	21.3	4.6	13.7	20.5	33.7
			Counts (frequency)			
Weight group 20-40 kg			11 (39%)			
Weight group >40 kg			17 (61%)			
Boys			8 (29%)			
Girls			20 (71%)			
Children (6-11 yr)			12 (43%)			
Adolescents (12-17 yr)			16 (57%)			
Asian			1 (4%)			
Black or African American			2 (8%)			
Other			1 (4%)			
White			24 (86%)			
Dose 300 mg			17 (61%)			
Dose 150 mg			11 (39%)			

Model development:

A population PK analysis was used to estimate PK parameters and their variability from concentration data. Due to data sparseness issues, available datasets often do not allow the estimation of all parameters of the suitable model. The $PRIOR subroutine in NONMEM supports the estimation of some or all parameters with values from previous models, as an alternative to fixing them or adding data to the dataset. The flow of the population PK analysis of Trial 18922A using prior information is depicted in Figure 9.

Figure 9: Panel 8 – Flowchart of the popPK analysis for trial 18922A using prior information



NONMEM = software for non-linear mixed-effects modelling; NWPRI = normal inverse-Wishart prior; $PRIOR = subroutine in the NONMEM software that supports the estimation of some or all parameters with values from previous models

In the paediatric population PK analysis of eptinezumab, the $PRIOR functionality in NONMEM was implemented. As prior information for the paediatric population PK analysis, the final adult population PK model was used and that model included the covariates body weight, creatinine clearance capped at a physiological value of 150 mL/min (CLcr_cap), disease state (healthy, CM or EM patients) and baseline MMDs on CL, and body weight, sex, and disease state on the Vc. However, these adult covariates were not included or investigated in the paediatric population PK analysis, and they were just used to describe the average adult PK parameters in the prior part of the model. The same approach/method/conditions was/were used in the interim population PK submitted in PIP modification 03, which was approved by EMA on 10 August 2022 (P/0341/2022; European Medicines Agency decision dated 10 August 2022).

To use parameters from the final adult model as prior information, the medians or most frequent values of the covariates had to be assumed to obtain the "average" for the adult population, but no assumption or values were imputed for the paediatric population PK analysis. For example, the relationship between CL and baseline MMDs for adults is CL = CLbase*(MDbase/13)0.044, and to obtain the average CL (that is, CLbase), baseline MMDs of 13 would have to be assumed.

With regards to covariates and the paediatric population PK analysis, the objective was to investigate the impact of body weight and age. These two covariates, together with sex, were included in the covariate model building for paediatrics. The results of the covariate step in the model building are described in section 4.3.2 of the Population Pharmacokinetic Report and copied as following:

4.3.2 Covariate Model

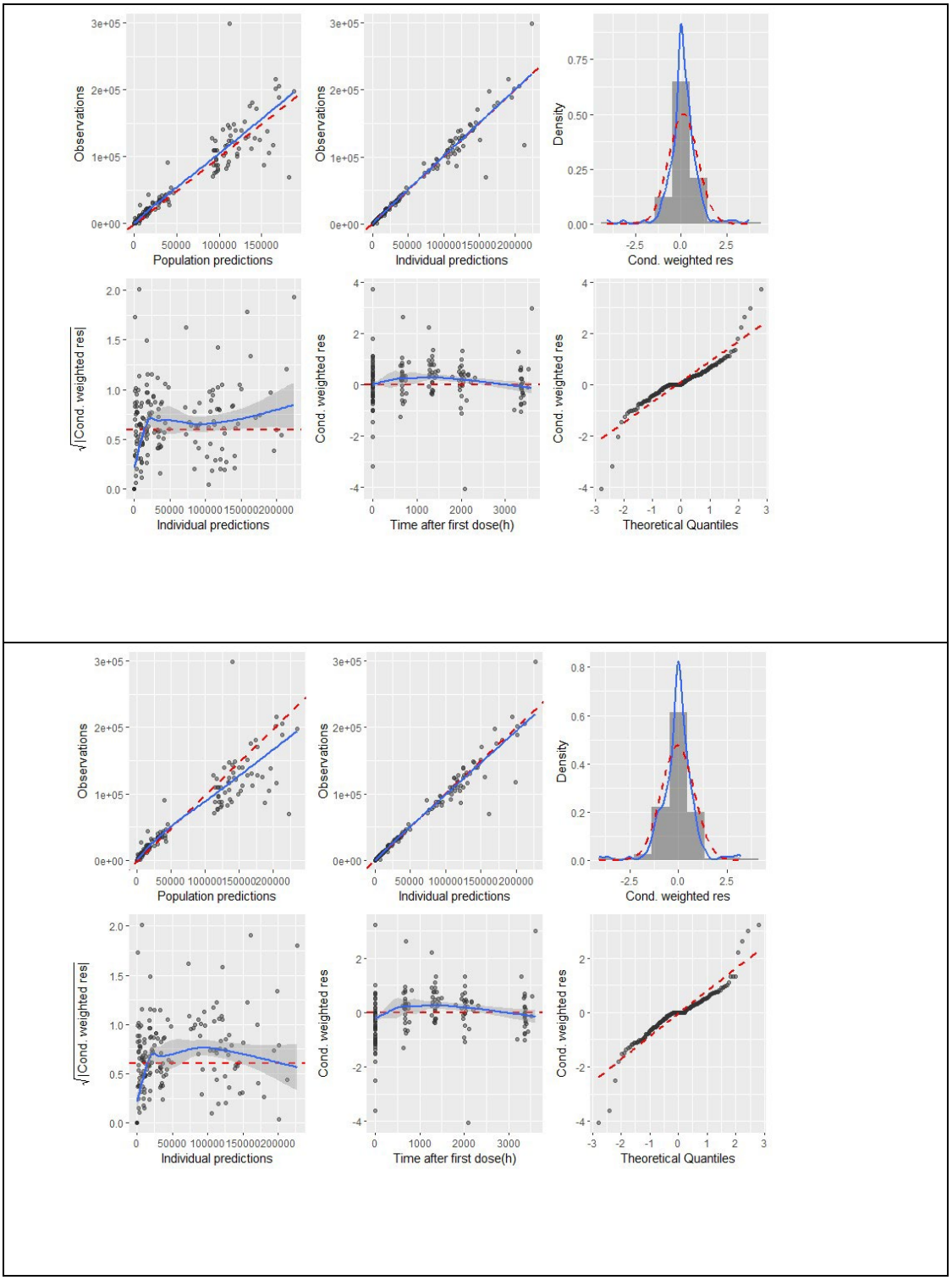
In the first covariate model building step, weight on CL and Q (estimated) was the covariate-parameter relationship with highest decrease in OFV (-53.4), although the difference to the model with weight on CL and Q with a fixed power value of 0.75 was not significant. Weight on V_c and V_p (estimated) gave also a significant drop in OFV (-50.0), but again not significant different from using a fixed power (1). In step 2, fixed values of 0.75 for CL and Q and 1.0 for Vc and Vp was tested a gave a drop in OFV of -60.5 compared to the model with weight on CL and Q (estimated) from step 1. In step 3, no significant impact from age or sex on the PK parameters could be identified, most likely due to weight was already incorporated in the model, and hence the final covariate model consisted of weight on all parameters, scaled to the power 0.75 for CL and Q.

When body weight was included in the model, age or sex had no significant impact on the PK parameters. An alternative (that was not included in the population PK report) to using the final adult model as information for the prior model is to use the base adult model (that is, the structural model without covariates) instead. The paediatric population PK model has been re-run with this other prior information and the results are the same with regards to the covariates and in general very similar. Fixing the power of the weight effect to 0.75 for clearances and 1.0 for volumes of distribution gave the best results (largest decrease in objective function value) and when body weight was included in the model, age or sex had no significant impact on the PK parameters. The results of the covariate step with the base adult model as prior information are summarized in Table 6. Goodness-of-fit plots that use the final adult model and base adult model as prior information are presented in Figure 10.

Table 6: Panel 9 – Covariate model steps for the model using the base adult mode as prior information

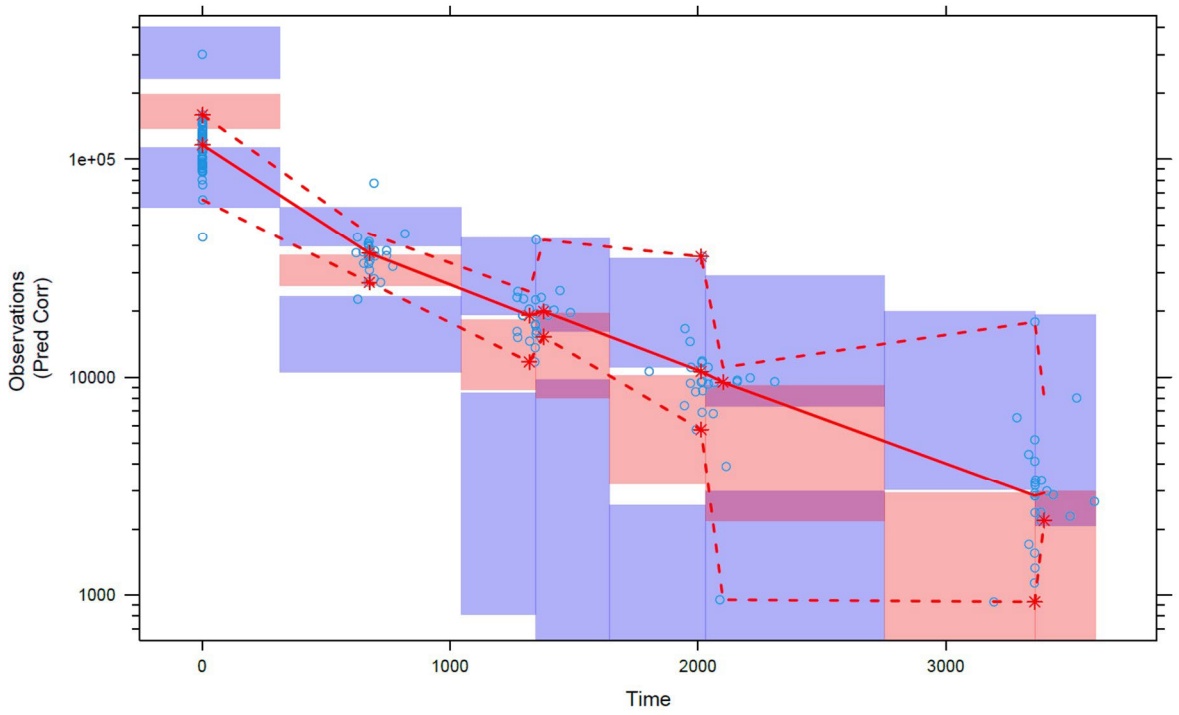
Model #	Step	Desc	OFV	delta-OFV	Minim	Cov
601	0	BASE MODEL	99.35	NA	Yes	Yes
603	1	AGE ON CL POWER	53.48	-45.873	Yes	Yes
605	1	WT ON CL+Q	45.08	-54.273	Yes	Yes
606	1	WT ON V1/V2	25.83	-73.521	Yes	Yes
607	1	WT ON CL+Q FIX 0.75	46.10	-53.251	Yes	Yes
608	1	WT ON V1/V2 FIX 1	25.87	-73.481	Yes	Yes
609	1	SEX ON CL/Q	96.39	-2.959	Yes	Yes
610	1	SEX ON V1/V2	99.23	-0.115	Yes	Yes
602	2	FIXED WT EFFEXTS	-41.56	-140.91	Yes	Yes
701	3	FIXED WT EFF, AGE ON CL/F	-43.39	-1.83	Yes	Yes
702	3	FIXED WT EFF, SEX ON CL/Q	-43.60	-2.038	Yes	Yes
703	3	FIX WT EFF, SEX ON V1/V2	-41.65	-0.083	Yes	Yes

Figure 10: Panel 10 - Goodness-of-fit Plots for the Final Paediatric PopPK Model Using the Base Adult Model (Top) and Final Adult Model (Bottom) As Prior Information



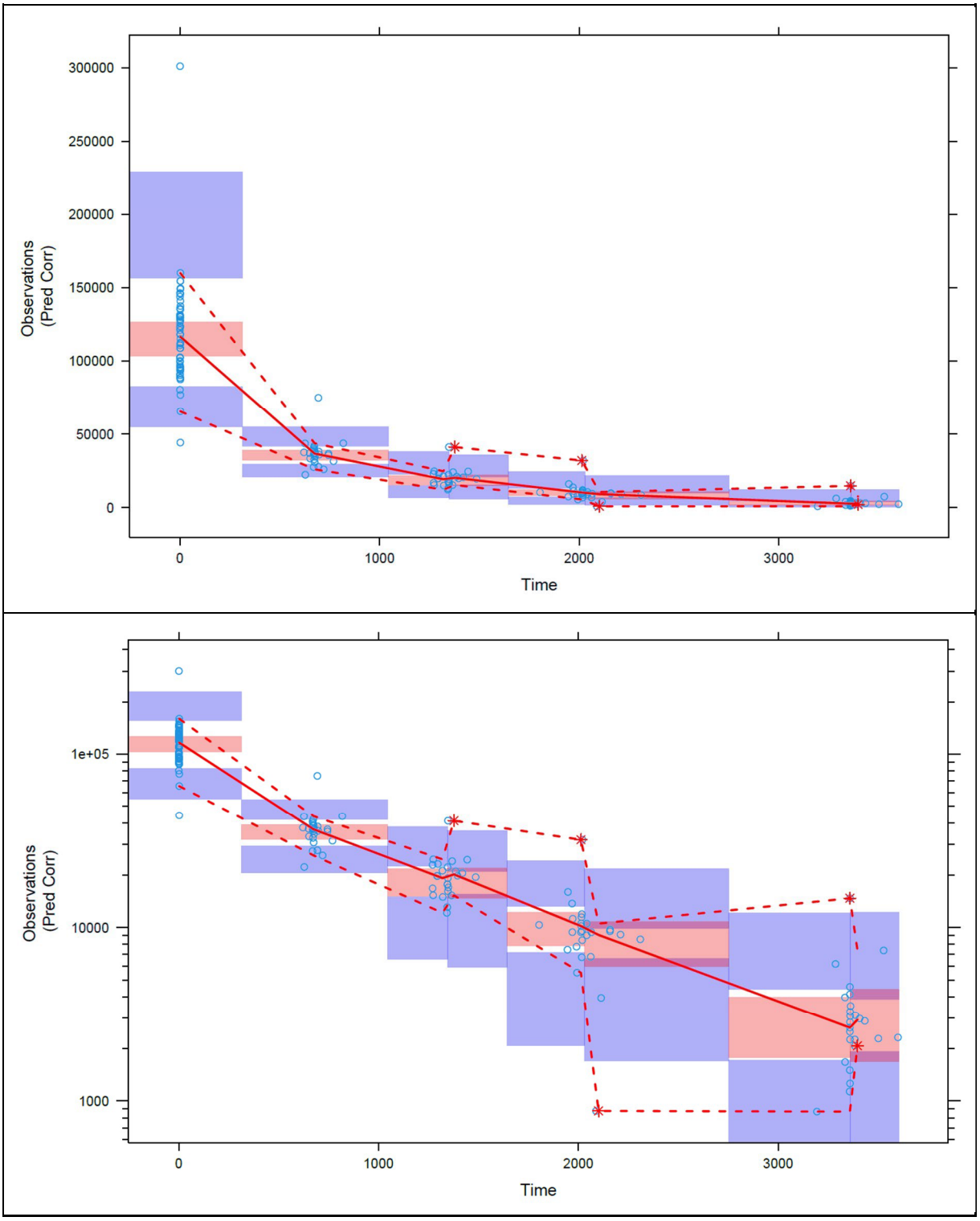
The VPC is presented in semi-log scale in Figure 11. There seems to be an overprediction of Cmax. In addition, there appears to be an underprediction of exposure at later time points (from about 700 h post-infusion). This is not a result of a poor predictive model, but rather, due to limitations in the use of the VPC, since different doses are part of the input dataset. If prediction-corrected VPC (pcVPC) - which accounts for differences in the input dataset - is used instead, the model seems more predictive. The pcVPCs are presented in both linear and semi-log scale in Figure 12.

Figure 11: Panel 11 - Visual Predictive Check Plots for the Final Model on Semi-log Scale



Full and dotted lines show median and the 2.5th and 97.5th percentiles, respectively, for the observed data (blue circles) while the 3 shaded regions show the 95% CIs for the 97.5th percentile, median, and 2.5th percentile for the simulated data.

Figure 12: Panel 12 - Prediction-corrected Visual Predictive Check (pcVPC) Plots for the Final Model on Linear (Top) and Semi-log (Bottom) Scale



Full and dotted lines show median and the 2.5th and 97.5th percentiles, respectively, for the observed data (blue circles) while the 3 shaded regions show the 95% CIs for the 97.5th percentile, median, and 2.5th percentile for simulated data.

Assessment of the Applicant's Response

The requested model revision was not performed. Additional simulations using the previous model were presented. It is acknowledged that the requested information on the LLOQ (50 ng/mL) was provided. Moreover, it was explained that information on disease state (CM and EM) are not available for Study 18922A. And as requested, the VPC was presented on semi-log scale.

Population PK model and simulations:

Additional explanations were provided helping to better understand how the paediatric population PK model was developed. Considering these along with the earlier provided information from the population pharmacokinetic report PLUTO ID CLI_01848467, it is anticipated that the final population PK model for paediatrics consists of the following aspects:

- 2-compartment model
- zero order absorption
- first-order elimination
- IIV on CL, Q, Vc, and Vp
- Covariates: allometric scaling using a population typical body weight of 70 kg
    - body weight on CL and Q (exponent 0.75) → only results for the population typical CL and Q (based on priors from adults) are listed in Table 1 (CL= 0.00469 L/h, Q=0.0420 L/h).
    - body weight on Vc and Vp (exponent 1) → only results for the population typical Vc and Vp (based on priors from adults) are listed in Table1 (Vc= 3.13 L, Vp=1.99 L)
- Residual error: "Residual error was modelled as combined proportional and additive", but the additive error could not be found in the list of final parameter estimates (Table).

A few additional simulations were carried out using this final paediatric population PK model. The following doses were simulated using the same body weight increments as before (<20 kg, 20-40 kg, >40 kg, and >45 kg) and were not tested for smaller increments, which could have been informative. Note: the labelling of graphics Panels 2, 3, 4, and 5 indicate ≤20kg, 20-40 kg, and >40 kg.

Simulated doses per body weight group according to Table 4, Figure 5, Figure 6, Figure 7, and Figure 8

Adult dose equivalent	Paediatric			
	< 20 kg (≤20kg?)	20 - 40 kg	>40 kg	>45 kg
100 mg	30 mg	40 mg	80 mg	100 mg
	40 mg	50 mg	100 mg	Not applicable
	Not applicable	60 mg	125 mg	Not applicable
300 mg	100 mg	125 mg	250 mg	300 mg

	125 mg	150 mg	300 mg	Not applicable
	Not applicable	175 mg	250 mg	Not applicable

These simulations still do not provide a lot of additional information on other potential doses for each body weight cohort. Simulations over broad dose ranges, e.g. 10 different doses per paediatric (body weight) group, were requested and thought to inform on potential other (better / lower) doses. Unfortunately, this was not provided. A few comments are given with respect to the provided simulations:

- Based on the simulations (Panel 3-5), lower doses than currently proposed might be sufficient, given that a flat exposure-response has been described earlier, and because exposures tend to exceed the upper boundary of adults ranges (e.g. for 100 mg adult equivalent: ≤ 20 kg: 30 mg [Panel 2B], >20 kg to <40 kg: 40 mg [Panel 2E], 40 – 45 kg: 80 mg [Panel 2E]. For 300 mg adult dose equivalent, considering AUC, lower doses than the proposed 100 mg were not simulated for the ≤ 20 kg group, which might be of interest).
- It is confusing why for the <20 kg (or ≤ 20 kg?) group receiving 125 mg, exposure is higher in Panel 3H compared to 3G, although the dose is the same according to the labelling.
- C_{max} values are higher for most of the paediatrics and tend to exceed the upper boundary.

Overall comment:

Although the provided overall documentation of this modeling exercise was presented in a minimalistic way, the overall concept of the model development and final composition appears clearer now. Nonetheless, the model´s fit for purpose is still doubted and its ability to relibly predict the PK in paediatrics down to 6 years of age not entirely convincing e.g. due to misspecification in the GOF plots or bootstrap results containing zero for two parameters (refer also to the previous critique). However, besides such aspects, the model-based simulations reveal a trend of generally higher exposure for the paediatric population compared to the adult exposure range. This is not considered acceptable since the large adult exposure range should not be targeted at the upper end. Interestingly, this is also the case for the higher body weight group of > 40 kg (presumably older paediatric ages), which would be expected to be closer to the adult exposures, compared to the lighter and presumably younger paediatric patients. Therefore, it is assumed that the doses are not adequate to match adult exposures or at least this cannot be adequately simualted with the underlying model.

It is acknowleded that only very limited and variable paediatric data for mainly two different doses (150 mg and 300 mg) are available. (Note: one paediatric participant received 200 mg instead of 150 mg and it is not clear if this was adequately flagged in the dataset as this is not listed in Table). Considering this, it is acknowledged that analysing these data may be challenging, e.g. with respect to covariate investigations. However, given that this modelling exercises is used to inform on paediatric dosing of eptinezumab outside the tested doses and body weight ranges (i.e., dose below 150 mg and body weight < 20 kg, down to 6 years of age), a robust and credible model should be aimed. Therefore, the MAH is encouraged to further investigate the PK and PKPD behaviour in the paediatric cohorts, maybe with potentially future emerging data through revision and update of the model.

Conclusion

From the pharmacometrics point of view, the proposed doses are not supported by the presented modelling results and the model is not considered fit for prupose. Given that a flat exposure-response behaviour was concluded earlier, lower doses might be sufficient for most of the proposed body weight / age groups and should be considered. This should be further investigated to prevent exceeding the

previously agreed target exposure range, because this might lead to concerns at time of potential extention of indication for the paediatric population.

The issue will not be further pursued in this P46 submission but will be further discussed during a possibly upcoming extension of indication application.

Question 2: Since the recommended dose for adults according to the SmPC of Vyepti is 100 mg, a comprehensible justification for the dosing regimen chosen in this study and a direct comparison of the observed PK-Parameter between children, adolescents and adults (treated with 100 mg and 300 mg), including figures and tables, should be provided.

MAH Response

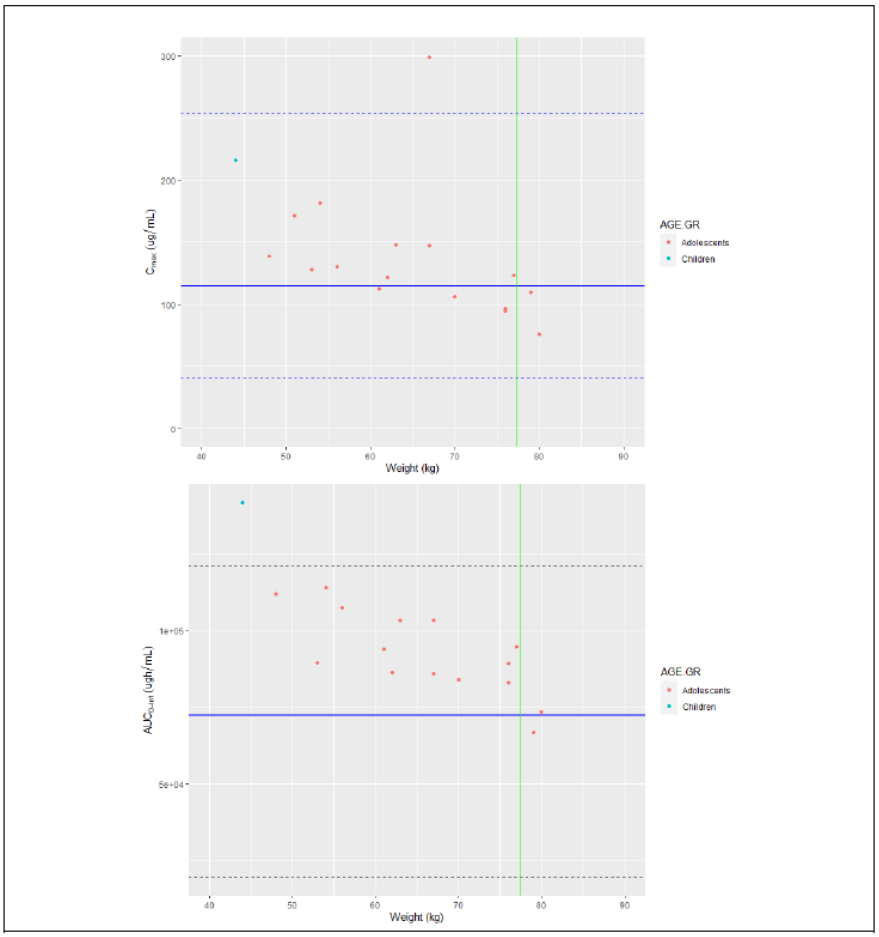
Both the 100 mg and 300 mg doses of eptinezumab are approved in adults. Based on the SmPC, the 100 mg dose is the recommended dose, and the 300 mg dose is indicated as the dose that "some patients may benefit from". Given the availability of the 2 doses in adults, the paediatric development programme was designed to cover both these doses, as agreed in the PIP [P/0091/2022 European Medicines Agency decision dated 11 March 2022]. To evaluate the efficacy and safety of both these eptinezumab doses, 2 paediatric efficacy and safety trials (19356A and 19357A) have been initiated and are currently ongoing.

In addition to these 2 trials, 1 long-term extension trial [Trial 19379A] is ongoing and includes participants from Trials 19356A and 19357A. Trial 18922A is a PK and safety trial, where the highest adult dose of 300 mg was selected, since from a PK perspective – and in particular, from a safety and tolerability perspective - the 300 mg dose (weight-adjusted) could cover both the 100 mg and 300 mg doses (Part A [single-dose] of the trial has been completed and Part B [multiple-dose extension] is ongoing).

In adults, eptinezumab displayed linear PK for doses ranging from 10 to 1,000 mg and the popPK analysis of Trial 18922A also revealed linear and dose-proportional PK between 150 mg and 300 mg in the paediatric population. As part of the popPK analysis for Trial 18922A (Population Pharmacokinetic Report), simulated plasma concentration profiles for 13,300 virtual paediatric patients were undertaken for eptinezumab 100 mg and 300 mg IV (weight-adjusted) and the results were compared with adults. The simulations showed that paediatric plasma exposures (in terms of AUCs) were on average within 10% to 20% above adult levels. Therefore, no adjustments to the PDCO/EMA approved doses (100 mg and 300 mg, weight-adjusted) for children and adolescents in the efficacy and safety trials (19356A and 19357A) are deemed necessary and should remain unchanged throughout the paediatric development programme.

A direct comparison of the observed PK parameters between children (6-11 years), adolescents (12-17 years), and adults (>17 years) is only possible for 300 mg, since no patient in Trial 18922A received eptinezumab 100 mg. In Panel 13, Cmax and AUC0-inf versus weight are shown for children and adolescents from Trial 18922A and compared to adult values from the 300 mg cohort in Trial ALD403-CLIN-005 (single-dose eptinezumab trial in adult patients with CM). Note that in Trial 18922A, only one child was given eptinezumab 300 mg. As can be seen in Panel 13, there is as expected a clear relationship between weight and Cmax and AUC0-inf, but the adult values are very similar to the paediatric values at corresponding weight (green vertical line).

Panel 13 Observed C_{max} and $AUC_{0\text{-inf}}$ Values *versus* Bodyweight for Children and Adolescents and Compared with Adult Values for Patients Given 300 mg



The full blue horisontal line is the mean value for C_{max}/$AUC_{0\text{-inf}}$ for the 300 mg adult cohort in Trial ALD403-CLIN-005 while the dotted lines are the min and max values. The green vertical line is the mean weight of the patients for the 300 mg cohort in Trial ALD403-CLIN-005.

In conclusion, both the 100 mg and 300 mg doses of eptinezumab are approved in adults, and given that 2 doses are approved in adults, the patients in Trial 18922A had received a single dose of eptinezumab IV based on the highest approved dose in adults (300 mg), since from a safety and tolerability perspective, the 300 mg dose (weight-adjusted) could cover both the 100 mg and 300 mg doses. The dosing guideline for Trial 18922A received agreement from EMA/PDCO (EMEA-002243-PIP01-17-M01; Opinion of the Paediatric Committee on the acceptance of a modification of an agreed Paediatric Investigation Plan dated 30 April 2020 [EMA/PDCO/86124/2020 Corr]), which reflects approval of the use of the highest approved adult dose for Trial 18922A. Based on the results of Trial 18922A, the use of the 300 mg dose (weight-adjusted) appears justified, in that it allowed a more robust (as compared to if the 100 mg dose had been used) evaluation of eptinezumab's tolerability profile. Trial 18922A demonstrated that eptinezumab is well tolerated in children and adolescents, with no serious TEAEs, severe TEAEs, or TEAEs leading to the withdrawal of IMP, and with no new safety signals identified. A direct comparison of the PK parameters suggests that paediatric values (based on Trial 18922A) correspond to adult values. In addition, simulations for 13,300 virtual paediatric patients that were performed as part of the popPK analysis for Trial 18922A showed that paediatric plasma exposures (in terms of AUCs) were on average within 10% to 20% above adult levels. Therefore, no adjustments to the PDCO/EMA approved doses (100 mg and 300 mg, weight-adjusted) for children and adolescents in the efficacy and safety trials (19356A and 19357A) are deemed necessary and should remain unchanged throughout the paediatric development programme.

PK-sampling is included in both the efficacy and safety trials (19356A, 19357A, and 19379A), and the paediatric popPK model will be updated accordingly when these data become available. The final paediatric doses will be decided based on all available paediatric data (that is, data from Trials 18922A, 19356A, 19357A, and 19379A).

Assessor's Comment:

Although, concerns currently remain regarding the selected dosing regimen and the robustness of the Pop-PK model used in this study, and although it would have been desirable to use the dose recommended in the SmPC for adults (100 mg) rather than the maximum dose (300 mg) tested in adults, to avoid possible unnecessary overdose, the rationale provided by the applicant can currently be acknowledged, since eptinezumab was well tolerated in children and adolescents and, furthermore, it was already agreed in the PIP [P/0091/2022 European Medicines Agency decision dated 11 March 2022] to cover both doses (100 mg and 300 mg) in the paediatric development program.

In addition, as stated by the applicant, the PK-sampling is included in both the ongoing efficacy and safety trials (19356A, 19357A, and 19379A), and the paediatric popPK model will be updated accordingly when these data become available. Thus, the final paediatric doses will be decided based on all available paediatric data (Trials 18922A, 19356A, 19357A, and 19379A).

Therefore, the issue will currently not be pursued further.

Question 3: Please clarify the number of children and of adolescents with chronic migraine and with episodic migraine, respectively.

MAH Response

The data collected in Trial 18922A did not include the collection of disease state (that is, EM or CM), as, given the nature of the trial, this was considered out-of-scope; the trial's main objective was to characterize the PK profile of eptinezumab, and its target population was migraine patients requiring migraine prevention treatment (specifically, the inclusion criterion was: The patient has a diagnosis of migraine with or without aura as defined by ICHD-3 guidelines (in the opinion of the investigator) of at least 6 months prior to the Screening Visit and is requiring migraine prevention treatment). Trial 18922A had only included the use of eDiaries in a subset of patients (that would have enabled confirmation of the patients' disease states). Efficacy was only included as an exploratory objective in Trial 18922A, and the eDiaries were mainly meant to evaluate the operational aspect of the trial, and in particular, to gain insights that could benefit the 2 large efficacy and safety trials (19356A and 19357A). Although information on disease state is not available, an approximate diagnosis based on the retrospectively self-reported frequencies during the 3 months prior to enrolment ("Average number of headache days per 28 day period in the months prior to screening"; "Average number of migraine days per 28 day period in the 3 months prior to screening") has been used to indicate the disease state. In total, 6 patients (2 children, 4 adolescents) reported a 3-month average of 15 to 28 monthly headache days and at least 8 MMDs, which approximately corresponds to a diagnosis of CM. The rest of the patients (N = 22 [10 children and 12 adolescents]) reported a monthly average of $<$15 headache days, which corresponds to a diagnosis of EM.

Assessor's Comment: Although baseline data is missing, eDiary data indicates that both, EM and CM patients, were included into the evaluation. Issue not further pursued.