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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/P46/006

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	27 May 2024	27 May 2024	☐
☐	CHMP Rapporteur Assessment Report	01 July 2024	27 June 2024	☐
☐	CHMP members comments	15 July 2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	18 July 2024	n/a	☐
☒	CHMP adoption of conclusions	25 July 2024	25 July 2024	☐

Table of contents

1. Introduction

On 02 February 2024, 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 stated that **trial 18922A – Extension Period (Part B)** 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; completed)
- 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.

2.3. Clinical aspects

2.3.1. 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 + Extension Period completed).

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.

This trial was performed to identify the paediatric doses that will provide exposures similar to those found to be effective in adults.

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

The data for the Main Study Period are presented in the *Critical Expert Overview* (dated 7 March 2023), which was submitted to EMA in procedure EMA/H/C/ 005287/P46/05 (conclusion adopted by CHMP on 17 August 2023) and to MHRA on 10 April 2023 (initial appraisal step completed 8 December 2023).

2.3.2. Clinical study

Methods

Trial 18922A is an interventional, open-label PK trial with eptinezumab, consisting of a single-dose, 20-week Main Study Period and an optional 44-week multiple-dose Extension Period. The participants were enrolled at 6 sites in the United States.

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.

Main Study Period

• 28 patients were enrolled

• 28 patients were treated – 12 children and 16 adolescents

• 3 patients withdrew from the Main Study – 1 child (withdrawal of consent) and 2 adolescents (lost to follow-up and "other" reason)

• 25 patients completed the Main Study – 11 children and 14 adolescents

• 28 patients were analysed – 12 children and 16 adolescents in the APTS_A and PKS_A

Extension Period

• 2 patients did not continue into the optional Extension Period – 1 child and 1 adolescent

• 23 patients were treated – 10 children and 13 adolescents

• 4 patients withdrew from the Extension Period – 1 child (lost to follow-up) and 3 adolescents (protocol violation of positive urine drug screen [2 adolescents] and lack of efficacy)

• 19 patients completed the Extension Period – 9 children and 10 adolescents

• 23 patients were analysed – 10 children and 13 adolescents in the APTS_B and PKS_B

Treatments

The Main Study Period included a single IV infusion of eptinezumab. The Extension Period included 3 additional eptinezumab infusions (separated by 12 weeks) for a total of up to 4 infusions during the trial.

For patients who continued into the Extension Period, the second IV infusion was given at the Week 20 Visit. The patients returned for a clinic visit at Week 24. The patients' third and fourth IV infusions were given at Week 32 and Week 44, respectively. There was a 20-week follow-up period after the last IV infusion (corresponding to 5 plasma half-lives of eptinezumab), which resulted in a total study duration of 64 weeks after the first IV infusion of eptinezumab (approximately 68 weeks after the Screening Visit).

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

Objectives evaluated for part B included:

- The characterization of the PK profile of eptinezumab after multiple IV administrations in paediatric patients 6 to 17 years of age (Extension Study; Part B)

- The evaluation of 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)
- Exploration of 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).

Study Methodology

• During infusion visits, assessments of safety were performed before and after each infusion. At these visits, adverse events were collected, as well as physical examination, safety laboratory tests, ECG, weight, and vital signs. The PedMIDAS and C-SSRS were administered prior to infusion.

• During infusion visits, patients were monitored during infusion and for a period of 2 hours from the end of infusion. However, patients could have been requested to stay longer should the investigator determine this to be clinically warranted.

• Plasma samples for PK analysis were collected from all patients at Screening, Baseline (immediately after end of infusion and 2 hours after end of infusion), Weeks 4, 8, 12, 20, 24, 32, 44 (pre-dose, immediately after end of infusion, and 2 hours after end of infusion), Week 64, and the Withdrawal Visit, if applicable (pre-dose at all visits except where noted otherwise).

• Serum samples for assessment of ADAs were collected at Screening, Weeks 4, 8, 12, 20, 24, 32, 44, 64, and the Withdrawal Visit, if applicable.

• Efficacy was assessed throughout the study using the PedMIDAS. A subset of patients (those who enrolled under *Clinical Study Protocol,* Edition 2.0) were also asked to complete an electronic headache diary (eDiary) on a daily basis from the Screening Visit until Week 12 or the Withdrawal Visit, whichever came first. The eDiary was used to capture data on disease-related information such as headache frequency, duration, characteristics, severity, as well as use and response to acute headache medication, which was used to evaluate MMDs and MHDs. Three versions of the eDiary were used in the study: one for adolescents and one for children, with the child version accompanied by a caregiver diary to collect detailed information. Only one device was distributed per patient. Children were provided with the simplified child version of the eDiary to capture data on headache frequency, characteristics, severity, and use of medication. Parent(s)/caregiver(s) were asked to report all data related to the child's headache and use of acute headache medication via the caregiver eDiary. Parent(s)/caregiver(s) reports were intended to complement the child reports. Adolescents (12 years of age and older) were to self-report all data.

• If possible, patients who withdrew prior to Week 20 in the Main Study Period or who withdrew prior to Week 64 in the Extension Period were seen for a Withdrawal Visit as soon as possible for scheduled assessments. They were also contacted for a Safety Follow-up Visit 20 weeks after the last investigational medicinal product (IMP) infusion. For patients completing the Main Study Period, safety data were collected at the Main Study Completion Visit. For patients completing the Extension Period, safety data were collected at the Extension Period Completion Visit (also 20 weeks after the last IMP infusion).

• If needed, the individual dose could be adjusted during the study (within weight band) based on PK and safety data.

• Due to recruitment difficulties, an interim popPK analysis was performed *ad hoc* based on data from 16 adolescents and 7 children. Given the robust popPK model and the PK results obtained in the patients already included in the study, 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.

Statistical Methodology

The following analysis sets were used to analyse and present the data:

- *All-patients-treated in Part B set* (APTS_B) – all patients treated with IMP in the Extension Period.
- *PK Part B set* (PKS_B) – all patients in the APTS_B with at least 1 post-infusion PK sample in the Extension Period.
- The PK characterization was primarily performed on the results from Day 1 (the day of the first infusion) through Week 20. Secondary PK characterizations were performed on Extension Period data, from Week 20 through Week 64. The PK analyses were performed using the PKS_A for the Main Study Period and the PKS_B for the Extension Period. PK parameters were determined from the plasma concentration-time data and are summarized for each age group, and for each age group and body weight group, and dose level (if relevant).
- Efficacy, safety, and immunogenicity endpoints are presented descriptively by age group and by age group and weight group.
- The planned sample size for this study was 32 patients with AUC0-inf and Cmax results in the Main Study Period. On the log scale, the standard deviation (SD) of both the AUC0-inf and Cmax measurements were estimated as 0.40. With a sample size of 16 patients in each age group and an SD of 0.40 or less, the resulting 95% CI would have a half width of 0.2 or less, which was expected to be sufficiently precise to draw meaningful conclusions, including a meaningful comparison between paediatric and adult patients in the popPK model.

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

In total, 25 paediatric participants completed the Main Period; of these, 2 paediatric participants did not continue into the Extension Period; hence, 23 participants (10 children and 13 adolescents) were treated with eptinezumab in the Extension Period. Four participants withdrew from the trial during the Extension Period: 1 child (lost to follow up) and 3 adolescents (protocol violation of positive urine drug screen [2 adolescents] and lack of efficacy [1 adolescent]). Nineteen participants (9 children and 10 adolescents) completed the Extension Period.

Results

Baseline data

Demographics and Baseline characteristics were similar in the age groups except for age-specific parameters. The median age of patients in this study was 13.5 years, with a range from 6 to 17 years, and most patients were female (20 patients [71%]) and White or Caucasian (24 patients [86%]). At Baseline, no children weighed ≤20 kg, 11 children (92%) weighed >20 kg and ≤40 kg, and 1 child (8%) weighed >40 kg; all 16 adolescents weighed >40 kg. Patients had a median number of 10 migraine days (range 4 to 20 days) per 28-day period in the 3 months before Screening. 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.

Panel 2: Patient Demographic and Baseline Characteristics in the Extension Period (APTS_B)

	Age Group		
	6 to 11 Years (N=10)	12 to 17 Years (N=13)	Overall (N=23)
Age at Screening (years), median (min, max)	10.5 (6, 11)	16.0 (12, 17)	14.0 (6, 17)
Sex, n (%)			
Male	1 (10.0)	5 (38.5)	6 (26.1)
Female	9 (90.0)	8 (61.5)	17 (73.9)
Ethnicity, n (%)			
Hispanic or Latino	1 (10.0)	3 (23.1)	4 (17.4)
Not Hispanic or Latino	9 (90.0)	10 (76.9)	19 (82.6)
Race, n (%)			
Asian	1 (10.0)	0	1 (4.3)
Black or African American	0	1 (7.7)	1 (4.3)
White or Caucasian	8 (80.0)	12 (92.3)	20 (87.0)
Other	1 (10.0)	0	1 (4.3)
Height (cm) at Baseline, median (min, max)	133.0 (117, 150)	163.0 (153, 181)	156.0 (117, 181)
Weight (kg) at Baseline, median (min, max)	34.0 (22, 39)	64.0 (48, 79)	54.0 (22, 79)
Weight group at Baseline, n (%)			
≤20 kg	0	0	0
>20 kg to ≤40 kg	10 (100)	0	10 (43.5)
>40 kg	0	13 (100)	13 (56.5)
BMI (kg/m^2) at Baseline, median (min, max)	17.60 (14.7, 22.1)	24.60 (17.2, 33.7)	20.20 (14.7, 33.7)

Panel 3: Migraine History in the Extension Period (APTS_B)

	Age Group		
	6 to 11 Years (N=10)	12 to 17 Years (N=13)	Overall (N=23)
Age at diagnosis (years), median (min, max)	7.5 (3, 10)	10.0 (4, 15)	9.0 (3, 15)
Migraine start (female patients), n (%)[a]			
Before menarche	9 (100)	5 (62.5)	14 (82.4)
After menarche	0	3 (37.5)	3 (17.6)
Migraine start (male patients), n (%)[b]			
Before puberty	1 (100)	5 (100)	6 (100)
After puberty	0	0	0
Start of migraine related to an event, n (%)			
Yes	0	0	0
No	10 (100)	13 (100)	23 (100)
Patient suffering from aura, n (%)			
Yes	1 (10.0)	4 (30.8)	5 (21.7)
No	9 (90.0)	9 (69.2)	18 (78.3)
Average number of headache days per 28-day period 3 months before Screening, median (min, max)	5.0 (0, 28)	8.0 (0, 16)	8.0 (0, 28)
Average number of migraine days per 28-day period 3 months before Screening, median (min, max)	7.0 (4, 20)	12.0 (4, 16)	10.0 (4, 20)

a Percentages are based on the number of female patients (N=17).

b Percentages are based on the number of male patients (N=6).

Baseline Efficacy Scores/ Values

Among patients who continued to the Extension Period and were evaluated for shifts in PedMIDAS (9 children, 13 adolescents), the majority had severe or moderate disability at Baseline (6 children and 9 adolescents) and the remaining patients (3 children and 4 adolescents) had mild disability (Panel 4).

Panel 4: PedMIDAS Total Score: Shift from Baseline by Visit in the Extension Period (APTS_B)

				Baseline, n (%)			
Age Group (Years)	Visit	n	Post-Baseline	Little to No Disability	Mild Disability	Moderate Disability	Severe Disability
6 to 11 N=10	Week 32	9	Little to no disability	0	3 (33.3)	2 (22.2)	1 (11.1)
			Mild disability	0	0	0	1 (11.1)
			Moderate disability	0	0	0	0
			Severe disability	0	0	0	2 (22.2)
	Week 44	9	Little to no disability	0	3 (33.3)	2 (22.2)	1 (11.1)
			Mild disability	0	0	0	2 (22.2)
			Moderate disability	0	0	0	0
			Severe disability	0	0	0	1 (11.1)
	Week 64	9	Little to no disability	0	3 (33.3)	2 (22.2)	2 (22.2)
			Mild disability	0	0	0	1 (11.1)
			Moderate disability	0	0	0	1 (11.1)
			Severe disability	0	0	0	0
12 to 17 N=13	Week 32	13	Little to no disability	0	3 (23.1)	0	0
			Mild disability	0	1 (7.7)	2 (15.4)	3 (23.1)
			Moderate disability	0	0	0	3 (23.1)
			Severe disability	0	0	0	1 (7.7)
	Week 44	11	Little to no disability	0	3 (27.3)	0	1 (9.1)
			Mild disability	0	1 (9.1)	2 (18.2)	1 (9.1)
			Moderate disability	0	0	0	2 (18.2)
			Severe disability	0	0	0	1 (9.1)
	Week 64	10	Little to no disability	0	3 (30.0)	0	0
			Mild disability	0	1 (10.0)	2 (20.0)	2 (20.0)
			Moderate disability	0	0	0	0
			Severe disability	0	0	0	2 (20.0)
Overall N=23	Week 32	22	Little to no disability	0	6 (27.3)	2 (9.1)	1 (4.5)
			Mild disability	0	1 (4.5)	2 (9.1)	4 (18.2)
			Moderate disability	0	0	0	3 (13.6)
			Severe disability	0	0	0	3 (13.6)
	Week 44	20	Little to no disability	0	6 (30.0)	2 (10.0)	2 (10.0)
			Mild disability	0	1 (5.0)	2 (10.0)	3 (15.0)
			Moderate disability	0	0	0	2 (10.0)
			Severe disability	0	0	0	2 (10.0)
	Week 64	19	Little to no disability	0	6 (31.6)	2 (10.5)	2 (10.5)
			Mild disability	0	1 (5.3)	2 (10.5)	3 (15.8)
			Moderate disability	0	0	0	1 (5.3)
			Severe disability	0	0	0	2 (10.5)

Medical, Psychiatric, and Neurological Disorders

In the 6-to-11-year age group, 4 female children and no male children were pre-pubertal (Tanner score of 2), and 5 female children and 1 male child were in puberty (Tanner score of 3 to 5). In the 12-to-17-year age group, 5 female and 2 male adolescents were in puberty (Tanner score 6 to 9) and 3 female and 2 male adolescents were post-pubertal (Tanner score 10).

Concomitant Medication

Concomitant medications in the Extension Period, that is, any medication other than IMP that was ongoing at or started on/after the first dose of IMP.

All 23 patients (100%) in the APTS_B took at least 1 concomitant medication in the Extension Period. The most common concomitant medications, taken by ≥2 patients (≥15% of patients) in either age group, were:

- ibuprofen (7 children [70%]; 5 adolescents [39%])
- paracetamol (5 children [50%]; 2 adolescents [15%])
- rizatriptan (2 children [20%]; 5 adolescents [39%])
- naproxen sodium (0 children; 5 adolescents [39%])
- sumatriptan (1 child [10%]; 3 adolescents [23%])
- ondansetron (1 child [10%]; 3 adolescents [23%])
- tozinameran (1 child [10%]; 3 adolescents [23%])
- cetirizine hydrochloride (2 children [20%]; 1 adolescent [8%])
- cyproheptadine (3 children [30%]; 0 adolescents)
- colecalciferol (0 children; 3 adolescents [23%])
- amoxicillin (0 children; 3 adolescents [23%])
- acetylsalicylic acid; caffeine; paracetamol (0 children; 2 adolescents [15%])
- diphenhydramine hydrochloride (2 children [20%]; 0 adolescents)
- fluoxetine hydrochloride (0 children; 2 adolescents [15%])
- melatonin (2 children [20%]; 0 adolescents)
- fluticasone propionate; salmeterol xinafoate (0 children; 2 adolescents [15%])
- montelukast sodium (2 children [20%]; 0 adolescents)
- lidocaine (2 children [20%]; 0 adolescents)

Monthly Migraine Days and Monthly Headache Days (eDiary)

Only the 21 patients who enrolled under *Clinical Study Protocol* Edition 2.0 were asked to use the eDiary.

			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

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"]).

Exposure:

The Extension Period included up to 3 infusions of eptinezumab at 150 mg or 300 mg according to protocol-defined weight-based dosing, unless adjustment was required based upon the individual rolling review after the first infusion in the Main Study. Based on the rolling review, the dose for 1 child was decreased by 25% (to 110 mg) due to high plasma concentrations after an unintentional overdose in the Main Study Period.

Of the 23 patients who were treated with IMP in the Extension Period, 19 patients received 3 infusions in the Extension Period as per the protocol, 1 patient received 2 infusions (Week 20 and Week 32), and 3 patients received a single infusion (Week 20). One adolescent had a temporary 6-min-interruption of the infusion at Week 44. The interruption was not considered related to safety or tolerability as no corresponding adverse event was reported. The eptinezumab infusion was completed in full for all 23 patients (that is, no solution was left in the bag).

Pharmacokinetics

After IV infusions of eptinezumab at Weeks 20, 32, and 44, all available post-dose samples collected and analysed were quantifiable for eptinezumab in all patients through Week 64.

Multiple IV administrations of eptinezumab at Weeks 20, 32, and 44 at 150 mg or 300 mg (section 8) resulted in similar mean eptinezumab concentration-time curves from Week 44 to Week 64, overlapping across dose levels. Peak eptinezumab concentrations at Week 44 were reached within 3 hours after the end of infusion (however, note the limitation of sparse sampling timepoints). Subsequently, plasma concentrations of eptinezumab gradually declined, with plasma concentrations remaining quantifiable at least 20 weeks post-dose (Week 64) in all available patients. Of note, one child had a high concentration of eptinezumab (1094 µg/mL) immediately after infusion at Week 44. A protocol deviation occurred during the collection of this sample which possibly impacted the result. Therefore, the time point for this patient was considered an outlier and excluded from the concentration summary statistics and the PK parameter analysis.

There were no differences when comparing the mean eptinezumab concentration-time curves from Week 44 to Week 64 by age group. The resulting curves overlapped for the age groups

OLE Period: Plasma Concentrations (ug/mL) of Eptinezumab by Dose Level and Visit
(PKS_B)

Dose Level (mg)	Age Group	Visit	Scheduled Time Point	n	<LLOQ, n (%)	Mean (SD)	CV (%)	Median	Q1, Q3	Min, Max
110	6 to 11 years (N=10)	Week 24		1	0	31.18 (-)		31.18	31.18, 31.18	31.2, 31.2
		Week 32		1	0	10.74 (-)		10.74	10.74, 10.74	10.7, 10.7
		Week 44	Pre-dose	1	0	11.92 (-)		11.92	11.92, 11.92	11.9, 11.9
			Immediately after end of Infusion	1	0	90.56 (-)		90.56	90.56, 90.56	90.6, 90.6
			2 Hours after end of Infusion	1	0	83.01 (-)		83.01	83.01, 83.01	83.0, 83.0
		Week 64		1	0	1.571 (-)		1.571	1.571, 1.571	1.57, 1.57

OLE Period: Plasma Concentrations (ug/mL) of Eptinezumab by Dose Level and Visit
(PKS_B)

Dose Level (mg)	Age Group	Visit	Scheduled Time Point	n	<LLOQ, n (%)	Mean (SD)	CV (%)	Median	Q1, Q3	Min, Max
150	6 to 11 years (N=10)	Baseline	Immediately after end of Infusion	10	0	121.0 (37.147)	30.7	116.5	87.57, 131.4	79.9, 206
			2 Hours after end of Infusion	10	0	117.9 (37.668)	32.0	114.9	87.90, 139.3	77.6, 202
		Week 24		7	0	31.26 (5.5228)	17.7	30.01	29.05, 37.08	21.7, 37.7
		Week 32		7	0	8.884 (2.6677)	30.0	7.854	7.608, 10.66	4.89, 13.1
		Week 44	Pre-dose	4	0	8.948 (2.5852)	28.9	8.368	7.086, 10.81	6.57, 12.5
			Immediately after end of Infusion	4	0	195.1 (125.59)	64.4	188.2	86.77, 303.4	86.6, 317
			2 Hours after end of Infusion	5	0	83.96 (11.007)	13.1	85.11	83.85, 90.96	65.8, 94.1
		Week 64		5	0	2.610 (1.0590)	40.6	2.139	1.807, 3.334	1.67, 4.10

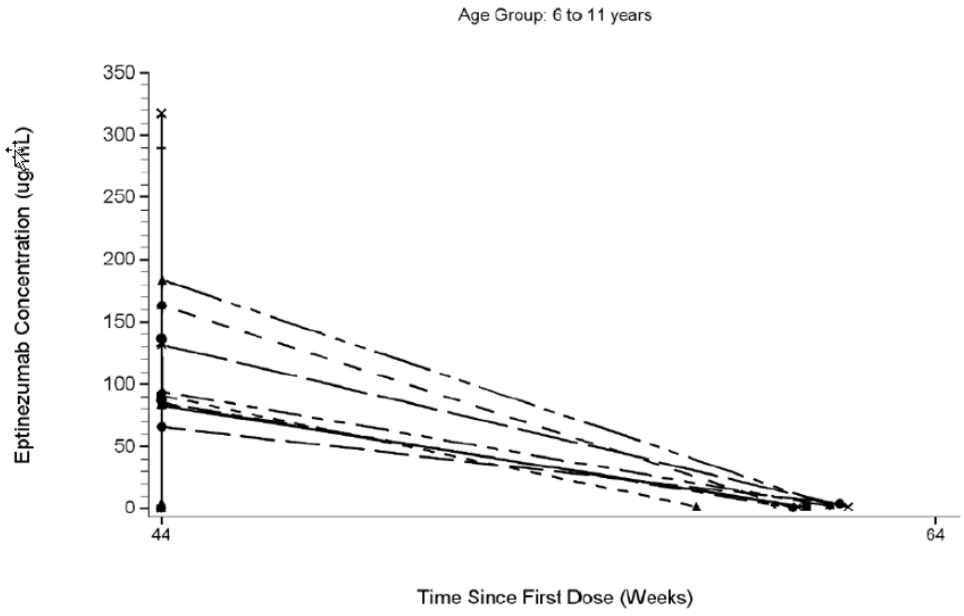
OLE Period: Plasma Concentrations (ug/mL) of Eptinezumab by Dose Level and Visit
(PKS_B)

Dose Level (mg)	Age Group	Visit	Scheduled Time Point	n	<LLOQ, n (%)	Mean (SD)	CV (%)	Median	Q1, Q3	Min, Max
300	6 to 11 years (N=10)	Week 24		2	0	30.61 (4.2285)	13.8	30.61	27.62, 33.60	27.6, 33.6
		Week 32		1	0	3.952 (-)		3.952	3.952, 3.952	3.95, 3.95
		Week 44	Pre-dose	3	0	5.451 (1.3921)	25.5	5.030	4.318, 7.005	4.32, 7.01
			Immediately after end of Infusion	3	0	144.7 (16.566)	11.5	136.8	133.5, 163.7	134, 164
			2 Hours after end of Infusion	3	0	159.7 (26.186)	16.4	163.3	131.9, 183.9	132, 184
		Week 64		3	0	1.692 (1.1474)	67.8	1.456	0.6808, 2.939	0.681, 2.94

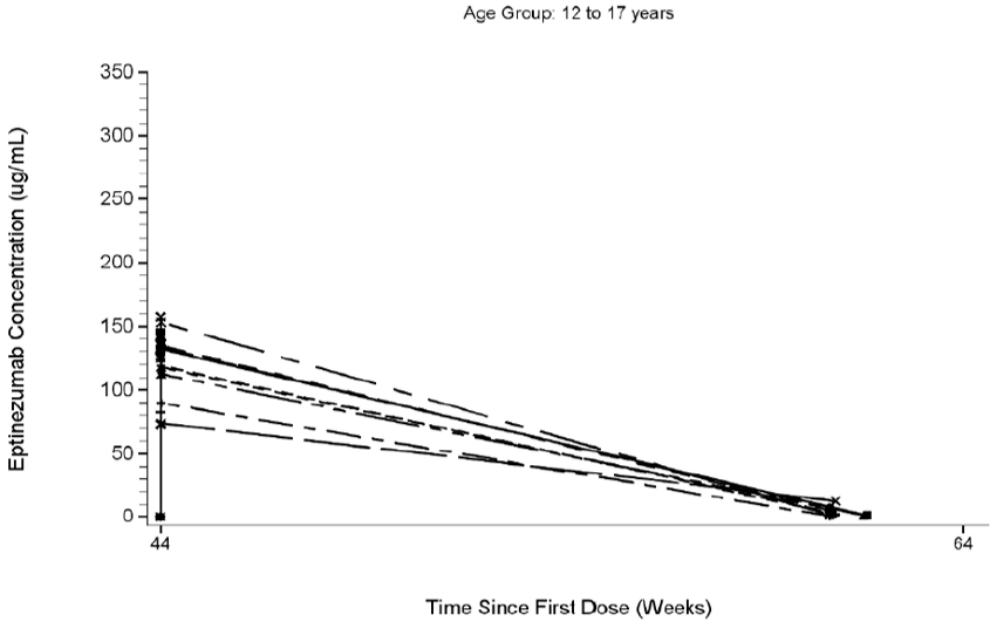
OLE Period: Plasma Concentrations (ug/mL) of Eptinezumab by Dose Level and Visit (PKS_B)

Dose Level (mg)	Age Group	Visit	Scheduled Time Point	n	<LLOQ, n (%)	Mean (SD)	CV (%)	Median	Q1, Q3	Min, Max
300	12 to 17 years (N=13)	Baseline	Immediately after end of Infusion	13	0	132.5 (56.486)	42.6	112.7	106.0, 138.7	75.7, 299
			2 Hours after end of Infusion	13	0	114.7 (27.047)	23.6	112.6	99.97, 123.4	70.3, 176
		Week 24		11	0	39.04 (15.008)	38.4	37.08	31.37, 41.97	16.5, 76.8
		Week 32		11	0	9.041 (3.2887)	36.4	9.254	6.746, 11.90	3.99, 14.7
		Week 44	Pre-dose	10	0	9.882 (3.0615)	31.0	9.331	8.393, 12.52	4.97, 14.7
			Immediately after end of Infusion	10	0	123.9 (26.360)	21.3	130.3	124.3, 139.1	72.9, 157
			2 Hours after end of Infusion	10	0	118.1 (23.024)	19.5	118.6	112.6, 133.5	73.9, 153
		Week 64		9	0	3.992 (3.8269)	95.9	2.192	1.527, 5.096	0.754, 12.6

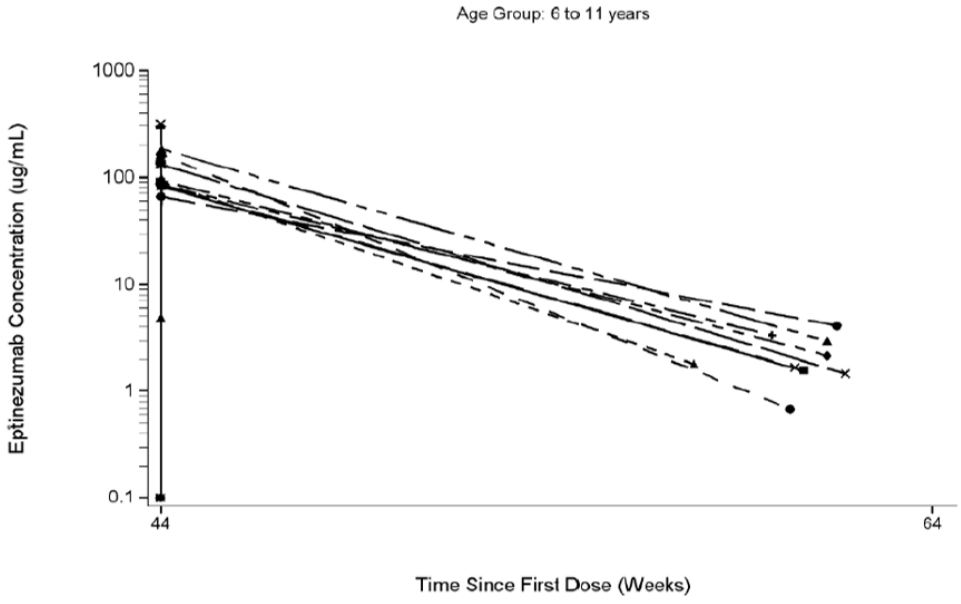
OLE Period: Individual Plasma Eptinezumab Concentration by Age Group – Linear Scale (PKS_B)



OLE Period: Individual Plasma Eptinezumab Concentration by Age Group – Linear Scale
(PKS_B)

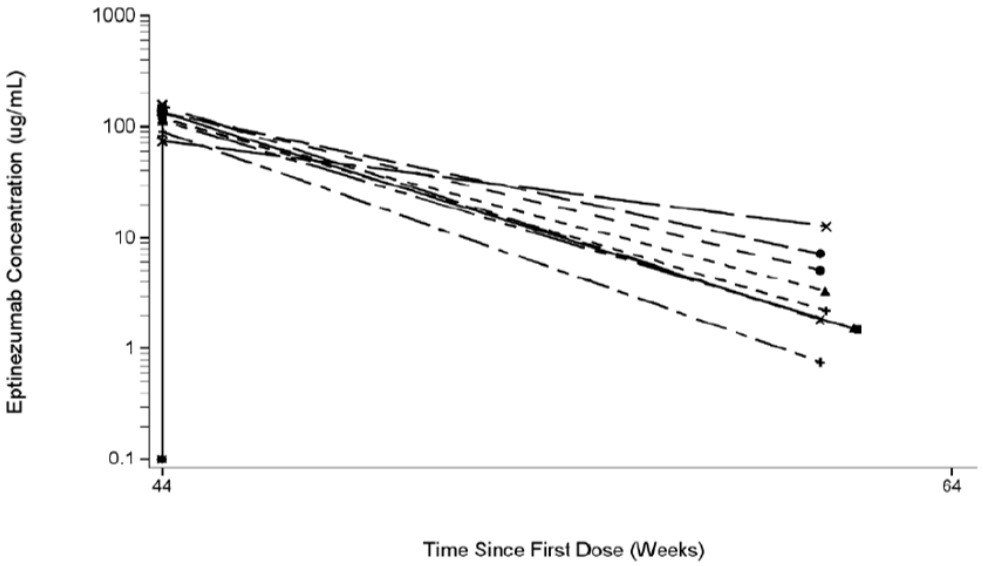


OLE Period: Individual Plasma Eptinezumab Concentration by Age Group – Semi-log Scale
(PKS_B)



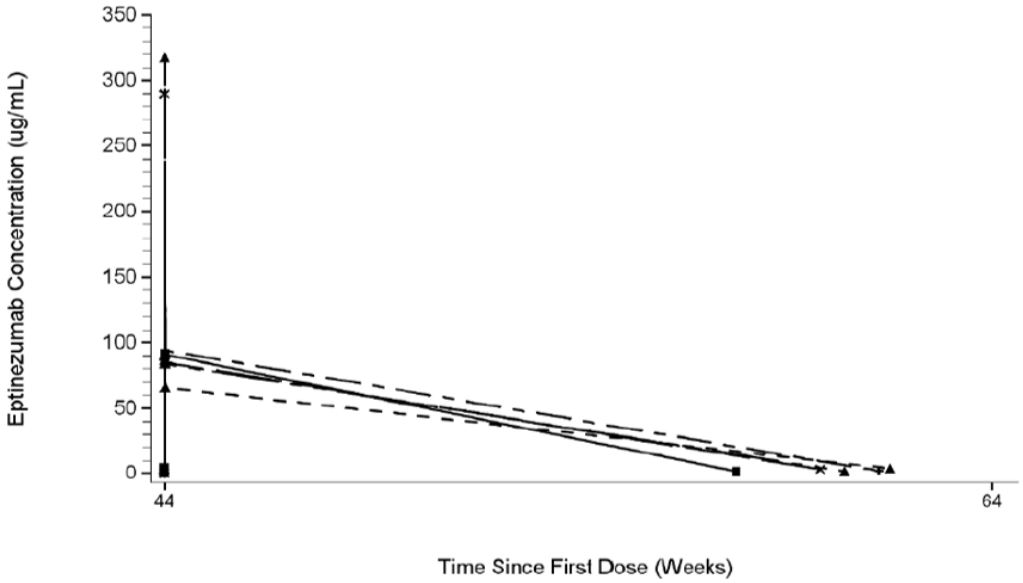
OLE Period: Individual Plasma Eptinezumab Concentration by Age Group – Semi-log Scale
(PKS_B)

Age Group: 12 to 17 years



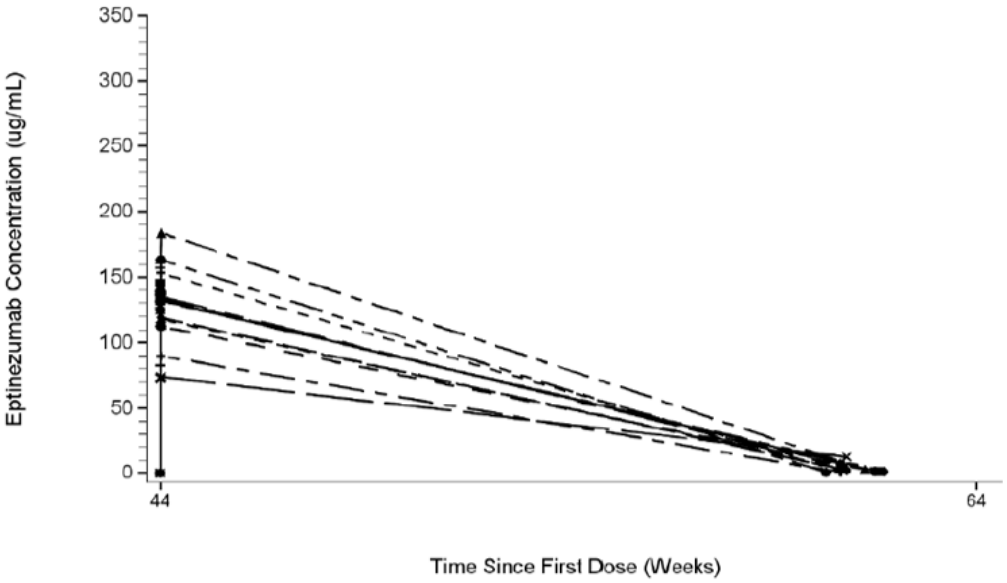
OLE Period: Individual Plasma Eptinezumab Concentration by Dose Level – Linear Scale
(PKS_B)

Dose Level: 150 mg



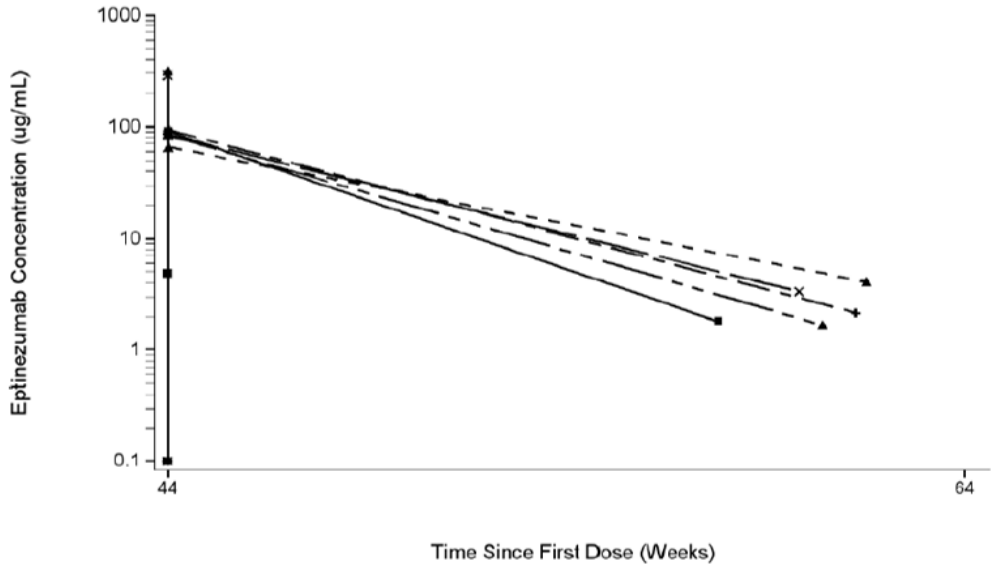
OLE Period: Individual Plasma Eptinezumab Concentration by Dose Level - Linear Scale (PKS_B)

Dose Level: 300 mg

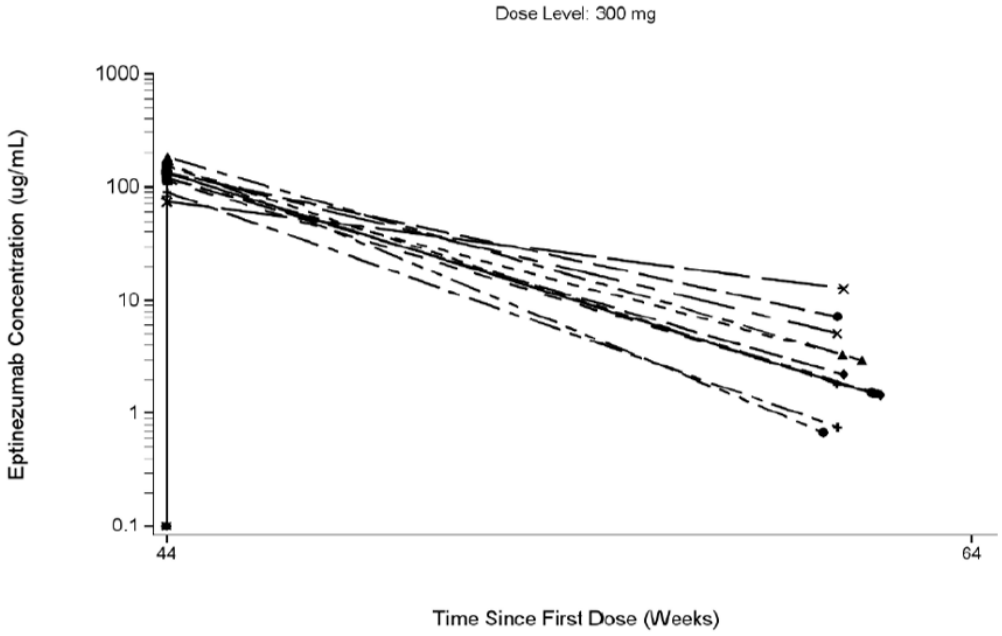


OLE Period: Individual Plasma Eptinezumab Concentration by Dose Level - Semi-log Scale (PKS_B)

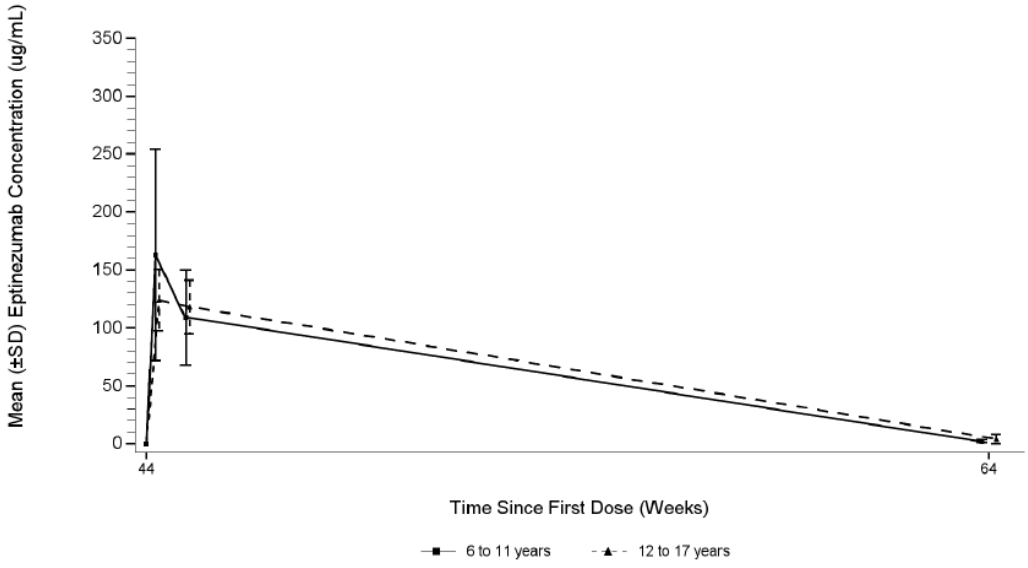
Dose Level: 150 mg



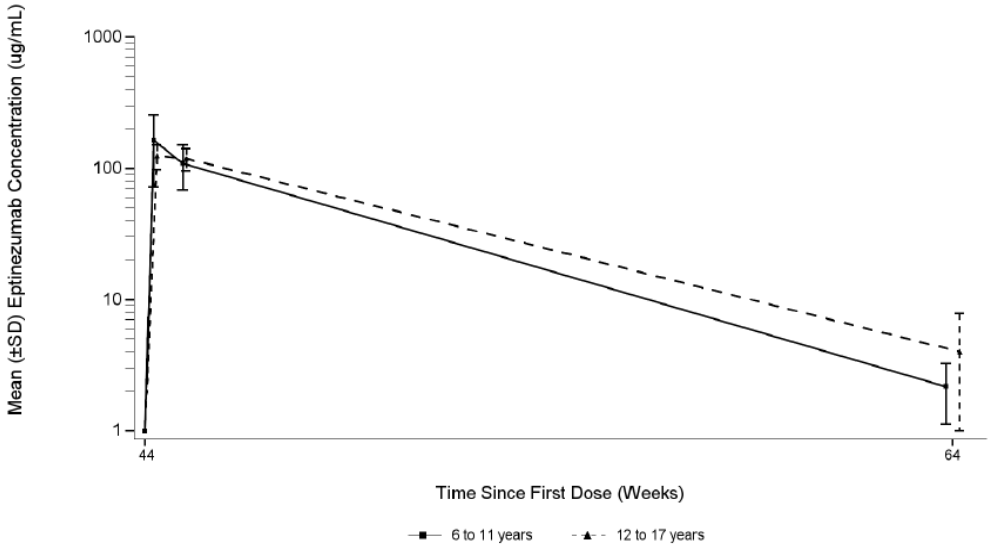
OLE Period: Individual Plasma Eptinezumab Concentration by Dose Level - Semi-log Scale
(PKS_B)



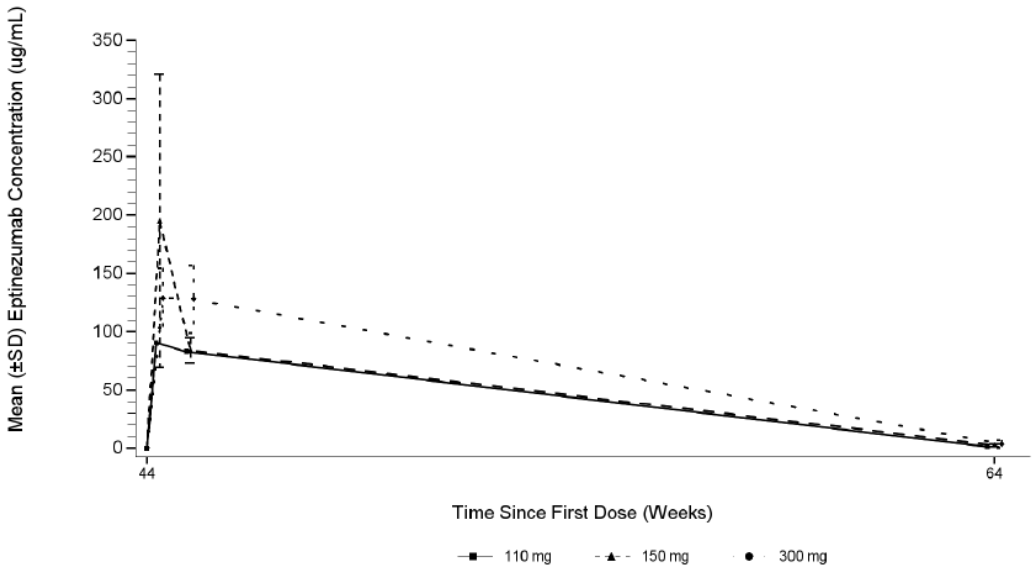
OLE Period: Mean (±SD) Plasma Eptinezumab Concentration by Age Group - Linear Scale
(PKS_B)

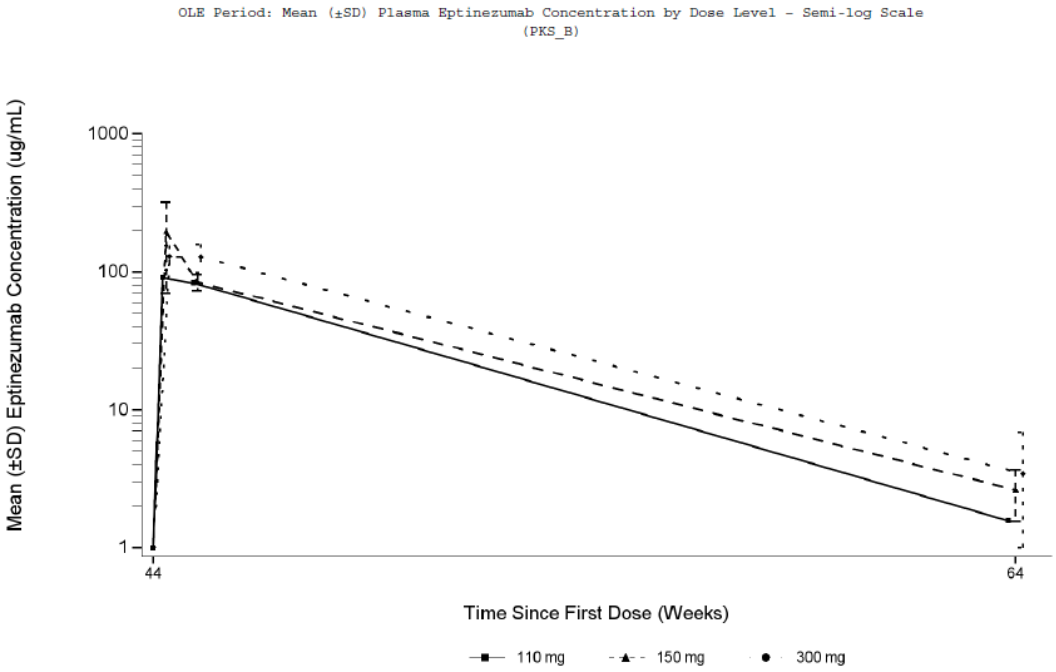


OLE Period: Mean (±SD) Plasma Eptinezumab Concentration by Age Group - Semi-log Scale
(PKS_B)



OLE Period: Mean (±SD) Plasma Eptinezumab Concentration by Dose Level - Linear Scale
(PKS_B)





After multiple IV administrations of eptinezumab to paediatric patients at Weeks 20, 32, and 44, eptinezumab Cmax_w44-w64 was similar between dose levels while AUCw44-w64 was slightly higher at the 300 mg compared with the 150 mg eptinezumab dose level. The eptinezumab C32wk and C44wk were comparable between dose levels. Considering variability and the small number of patients at the 150 mg and 300 mg eptinezumab dose levels, the differences in exposure are considered minor. The child who received 110 mg eptinezumab had slightly lower Cmax_w44-w64 and AUCw44-w64 and slightly higher C32wk and C44wk than the corresponding values at the other dose levels, but the values were within the same range when accounting for variability at the other dose levels. The results were similar in children and adolescents.

Panel 5 PK Parameters of Eptinezumab by Dose Level in the Extension Period (PKS_B)

Parameter (Unit)	Statistics	Dose Level	
		150 mg	300 mg
$AUC_{w44\text{-}w64}$ (h×µg/mL)	n	6	11
	Missing (n)	1	4
	Geo mean (GeoCV%)	161100 (37.2)	213600 (20.2)
$C_{max\ w44\text{-}w64}$ (µg/mL)	n	6	12
	Missing (n)	1	3
	Geo mean (GeoCV%)	152.5 (65.8)	126.5 (22.8)
C_{32wk} (µg/mL)	n	6	13
	Missing (n)	1	2
	Geo mean (GeoCV%)	7.933 (28.4)	8.250 (46.4)
C_{44wk} (µg/mL)	n	5	12
	Missing (n)	2	3
	Geo mean (GeoCV%)	8.321 (26.3)	8.386 (42.4)
$t_{max\ w44\text{-}w64}$ (h)	n	6	12
	Missing (n)	1	3
	Median (Q1, Q3)	1.625 (0.6670, 2.500)	0.7250 (0.6000, 2.475)

CV = coefficient of variation; Geo = geometric; Q1 = lower quartile; Q3 = upper quartile.

Note: One child was dosed with eptinezumab 110 mg and the data for this patient are not displayed in the table. The child's values for $AUC_{w44\text{-}w64}$, $C_{max\_w44\text{-}w64}$, C_{32wk}, C_{44wk}, and $t_{max\_w44\text{-}w64}$ were 142100 h×µg/mL, 90.56 µg/mL, 10.74 µg/mL, 11.92 µg/mL, and 0.6500 h, respectively.

Rapporteur's Comment:

23 participants (10 children and 13 adolescents) were treated with eptinezumab in the Extension Period. Four participants withdrew from the trial during the Extension Period due to lost of follow up (1), positive urine drug test (2), and lack of efficacy (1).

The children (6 to 11 years) and adolescents (12 to 17 years) received 3 additional IV injections at weeks 20, 32, and 44. The dose was either 150 mg or 300 mg eptinezumab, depending on body weight. Obviously, no patients < 20 kg bw were included. Therefore, no data for this weight stratum and for the dosing regimen of 100 mg eptinezumab have been collected.

Unexpectedly, C_{max} mean was higher in the 150 mg group compared to the 300 mg group. This result seems to be driven by 2 "outliers" at week 44 (290 µg/mL und 320 µg/mL). The reason for these increased C_{max} values is not clear but obviously let to the implausible higher C_{max} value in the 150 mg group. With regard to the remaining patients in the 150mg group, Cmax values were well below C_{max} values in the 300 mg group, as expected. Ignoring the 2 "outliers", C max (126.5 µg/mL) was highly comparable with steady state Cmax in the initial model (125 µg/mL).

Overall, mean plasma concentrations after multiple IV administrations ($Cmax_{\_w44\text{-}w64}$) of eptinezumab were in the range observed after administration of 300 mg eptinezumab IV in the pivotal studies in adults (C_{max} 33.1 µg/mL – 368 µg/mL).

As expected, the $AUC_{\_\_w44\text{-}w64}$ was higher after administration of the 300 mg dose compared to the 150 mg dose. AUC results were not comparable with AUC results in adults from the pivotal trials due to differences in intervals and collection time points.

Efficacy results

Analysis of the Exploratory Endpoint 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.

Among patients who continued to the Extension Period, an improvement in disability was seen both in children and in adolescents at all visits, with a median (min, max) score change from Baseline of -21.0 (-53, 115), -27.0 (-59, 98), and -35.0 (-91, -16) to Weeks 32, 44, and 64 for children, respectively, and of -43.0 (-109, -7), -22.0 (-127, 137), and -20.5 (-113, 337) for adolescents, respectively (Table below "*Panel 6*"). Note that a few patients had very high total score values at one or several visits; 1 adolescent had a total score of 435 at Week 64, which is far above the theoretical upper limit of 240.

Improvements in disability were observed in the majority of patients: in 7 of 9 children at Week 32, 8 of 9 children at Week 44, and 9 of 9 children at Week 64; and in 11 of 13 adolescents at Week 32, 9 of 11 adolescents at Week 44, and 7 of 10 adolescents at Week 64.

Few patients (0 to 2 children and 2 to 3 adolescents, depending on the visit) had no change in disability, and no patients had worsened disability.

Panel 6 PedMIDAS Total Score: Shift From Baseline by Visit in the Extension Period (APTS_B)

Age Group (Years)	Visit	n	Post-Baseline	Baseline, n (%)			
				Little to No Disability	Mild Disability	Moderate Disability	Severe Disability
6 to 11 N=10	Week 32	9	Little to no disability	0	3 (33.3)	2 (22.2)	1 (11.1)
			Mild disability	0	0	0	1 (11.1)
			Moderate disability	0	0	0	0
			Severe disability	0	0	0	2 (22.2)
	Week 44	9	Little to no disability	0	3 (33.3)	2 (22.2)	1 (11.1)
			Mild disability	0	0	0	2 (22.2)
			Moderate disability	0	0	0	0
			Severe disability	0	0	0	1 (11.1)
	Week 64	9	Little to no disability	0	3 (33.3)	2 (22.2)	2 (22.2)
			Mild disability	0	0	0	1 (11.1)
			Moderate disability	0	0	0	1 (11.1)
			Severe disability	0	0	0	0
12 to 17 N=13	Week 32	13	Little to no disability	0	3 (23.1)	0	0
			Mild disability	0	1 (7.7)	2 (15.4)	3 (23.1)
			Moderate disability	0	0	0	3 (23.1)
			Severe disability	0	0	0	1 (7.7)
	Week 44	11	Little to no disability	0	3 (27.3)	0	1 (9.1)
			Mild disability	0	1 (9.1)	2 (18.2)	1 (9.1)
			Moderate disability	0	0	0	2 (18.2)
			Severe disability	0	0	0	1 (9.1)
	Week 64	10	Little to no disability	0	3 (30.0)	0	0
			Mild disability	0	1 (10.0)	2 (20.0)	2 (20.0)
			Moderate disability	0	0	0	0
			Severe disability	0	0	0	2 (20.0)
Overall N=23	Week 32	22	Little to no disability	0	6 (27.3)	2 (9.1)	1 (4.5)
			Mild disability	0	1 (4.5)	2 (9.1)	4 (18.2)
			Moderate disability	0	0	0	3 (13.6)
			Severe disability	0	0	0	3 (13.6)
	Week 44	20	Little to no disability	0	6 (30.0)	2 (10.0)	2 (10.0)
			Mild disability	0	1 (5.0)	2 (10.0)	3 (15.0)
			Moderate disability	0	0	0	2 (10.0)
			Severe disability	0	0	0	2 (10.0)
	Week 64	19	Little to no disability	0	6 (31.6)	2 (10.5)	2 (10.5)
			Mild disability	0	1 (5.3)	2 (10.5)	3 (15.8)
			Moderate disability	0	0	0	1 (5.3)
			Severe disability	0	0	0	2 (10.5)

Rapporteur's Comment:

Efficacy was analyzed by changes in PedMIDAS. This analysis was of exploratory nature and indicated a trend to improvement in PedMIDAS disability scores in both age groups.

Safety

In the Extension Period, 14 patients (61%) had at least 1 TEAE; the incidence was 50% in children and 69% in adolescents. Three children (30%) and 1 adolescent (8%) had TEAEs *related* to IMP. None of the patients had TEAEs leading to *death*, *serious* TEAEs, *severe* TEAEs, TEAEs leading to IMP modification, temporary interruption of IMP, withdrawal of IMP, or withdrawal from the study.

The SOCs with the highest incidences of TEAEs (≥2 patients [≥15%] in either age group) were:

- *infections and infestations* (1 child [10%]; 3 adolescents [23%])
- *investigations* (1 child [10%]; 3 adolescents [23%])
- *nervous system disorders* (2 children [20%]; 2 adolescents [15%])
- *respiratory, thoracic and mediastinal disorders* (2 children [20%]; 1 adolescent [8%])
- *injury, poisoning and procedural complications* (2 children [20%])
- *psychiatric disorders* (2 adolescents [15%])

The TEAEs (preferred terms) that were reported for more than 1 patient were:

- hypercholesterolaemia (1 child [10%]; 1 adolescent [8%])
- migraine (1 child [10%]; 1 adolescent [8%])
- nasal congestion (2 children [20%])
- pharyngitis streptococcal (2 adolescents [15%])

While orthostatic hypotension was the only TEAE that was reported for more than 1 patient in the Main Study Period, no patient reported orthostatic hypotension in the Extension Period.

OLE Period: Treatment-Emergent Adverse Events Related to IMP by System Organ Class and Preferred Term
(APTS_B)

System Organ Class Preferred Term	Age Group 6 to 11 Years (N=10) n (%) [Event]	 12 to 17 Years (N=13) n (%) [Event]	 Overall (N=23) n (%) [Event]
Patients with at least one TEAE Related to IMP	3 (30.0) [8]	1 (7.7) [1]	4 (17.4) [9]
Investigations	1 (10.0) [1]	1 (7.7) [1]	2 (8.7) [2]
Eosinophil count increased	0	1 (7.7) [1]	1 (4.3) [1]
Protein urine	1 (10.0) [1]	0	1 (4.3) [1]
General disorders and administration site conditions	1 (10.0) [1]	0	1 (4.3) [1]
Injection site erythema	1 (10.0) [1]	0	1 (4.3) [1]
Nervous system disorders	1 (10.0) [1]	0	1 (4.3) [1]
Dizziness postural	1 (10.0) [1]	0	1 (4.3) [1]
Respiratory, thoracic and mediastinal disorders	1 (10.0) [5]	0	1 (4.3) [5]
Nasal congestion	1 (10.0) [2]	0	1 (4.3) [2]
Respiratory tract congestion	1 (10.0) [1]	0	1 (4.3) [1]
Rhinorrhoea	1 (10.0) [1]	0	1 (4.3) [1]
Sneezing	1 (10.0) [1]	0	1 (4.3) [1]

Main Period and OLE Period: Treatment-Emergent Adverse Events Related to IMP by System Organ Class and Preferred Term (APTS_A)

System Organ Class Preferred Term	Age Group 6 to 11 Years (N=12) n (%) [Event]	 12 to 17 Years (N=16) n (%) [Event]	 Overall (N=28) n (%) [Event]
Patients with at least one TEAE Related to IMP	5 (41.7) [13]	6 (37.5) [8]	11 (39.3) [21]
Nervous system disorders	2 (16.7) [2]	1 (6.3) [1]	3 (10.7) [3]
Dizziness	0	1 (6.3) [1]	1 (3.6) [1]
Dizziness postural	1 (8.3) [1]	0	1 (3.6) [1]
Migraine	1 (8.3) [1]	0	1 (3.6) [1]
Vascular disorders	0	3 (18.8) [4]	3 (10.7) [4]
Orthostatic hypotension	0	3 (18.8) [4]	3 (10.7) [4]
Investigations	1 (8.3) [1]	1 (6.3) [1]	2 (7.1) [2]
Eosinophil count increased	0	1 (6.3) [1]	1 (3.6) [1]
Protein urine	1 (8.3) [1]	0	1 (3.6) [1]
Psychiatric disorders	1 (8.3) [1]	1 (6.3) [1]	2 (7.1) [2]
Adjustment disorder with depressed mood	0	1 (6.3) [1]	1 (3.6) [1]
Sleep terror	1 (8.3) [1]	0	1 (3.6) [1]
Eye disorders	1 (8.3) [1]	0	1 (3.6) [1]
Photopsia	1 (8.3) [1]	0	1 (3.6) [1]

Main Period and OLE Period: Treatment-Emergent Adverse Events Related to IMP by System Organ Class and Preferred Term (APTS_A)

System Organ Class Preferred Term	Age Group 6 to 11 Years (N=12) n (%) [Event]	 12 to 17 Years (N=16) n (%) [Event]	 Overall (N=28) n (%) [Event]
General disorders and administration site conditions	1 (8.3) [1]	0	1 (3.6) [1]
Injection site erythema	1 (8.3) [1]	0	1 (3.6) [1]
Respiratory, thoracic and mediastinal disorders	1 (8.3) [7]	0	1 (3.6) [7]
Cough	1 (8.3) [1]	0	1 (3.6) [1]
Nasal congestion	1 (8.3) [2]	0	1 (3.6) [2]
Respiratory tract congestion	1 (8.3) [1]	0	1 (3.6) [1]
Rhinorrhoea	1 (8.3) [2]	0	1 (3.6) [2]
Sneezing	1 (8.3) [1]	0	1 (3.6) [1]
Skin and subcutaneous tissue disorders	0	1 (6.3) [1]	1 (3.6) [1]
Pruritus	0	1 (6.3) [1]	1 (3.6) [1]

Rapporteur's Comment:

Overall, eptinezumab was well tolerated. There were no serious TEAEs, no severe TEAEs, and no TEAEs leading to IMP or trial withdrawal. No safety signals were identified.

Immunogenicity

In the Main Study Period, 2 adolescents were positive for ADAs in a confirmatory assay, but neither had NAbs. The adolescent who was positive for ADAs in an assay at Week 20 was negative at the Withdrawal Visit in the Extension Period, which was performed 16 days after the Week 20 Visit. The adolescent who was positive for ADAs in a confirmatory assay at Weeks 12 and 20 in the Main Study Period also had positive ADA results in the Extension Period at Weeks 24 and 32. The ADA titres were low (<50, that is, below assay minimum required dilution) at Weeks 12, 20, 24, and 32, and at Week 44 and Week 64, the adolescent had negative ADA results. No TEAEs were reported for this adolescent in the Extension Period. No other adolescent and no children were positive for ADAs in the Extension Period. All patients had negative ADA results at their last visit.

Rapporteur's Comment:

2 adolescents were confirmed ADA positive in the Main Study Period. One of these was also positive for ADAs in the Extension Period. None of the ADAs had neutralizing properties.

2.3.3. Discussion on clinical aspects

The scope of Part B of this study was to evaluate the pharmacokinetic profile and the immunogenicity of eptinezumab after 3 additional intravenous administrations of eptinezumab in pediatric patients 6 to 17 years of age, separated by 12 weeks. The total number of infusions (main study and extension part) was 4.

Eptinezumab was administered at a dose of 150 mg or 300 mg, depending on the participant's body weight. Multiple IV administrations resulted in overlapping mean plasma concentration-time curves from Week 44 to Week 64.

Plasma exposure (Cmax_w44-w64 and AUCw44-w64) was comparable across dose levels, weight groups, and age groups. However, C_{max} mean was higher in the 150 mg group compared to the 300 mg group. This result seems to be driven by 2 "outliers" at week 44 (290 µg/mL und 320 µg/mL). The reason for these increased C_{max} values is not clear but obviously let to the implausible higher C_{max} value in the 150 mg group. With regard to the remaining patients in the 150mg group, Cmax values were well below C_{max} values in the 300 mg group, as expected. Ignoring the 2 "outliers", C max (126.5 µg/mL) was highly comparable with steady state Cmax in the initial model (125 µg/mL).

Overall, mean plasma concentrations after multiple IV administrations ($Cmax_{\_w44\text{-}w64}$) of eptinezumab were in the range observed after administration of 300 mg eptinezumab IV in the pivotal studies in adults (C_{max} 33.1 µg/mL – 368 µg/mL).

As expected, the $AUC_{\_w44\text{-}w64}$ was higher after administration of the 300 mg dose compared to the 150 mg dose. It must be noted that AUC results were not comparable with AUC results in adults from the pivotal trials due to differences in intervals and collection time points.

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.

Overall, eptinezumab was well tolerated in children and adolescents 12 to 17 years of age. No new safety signals were identified.

No participants weighed less than 20 kg and thus no participants received eptinezumab 100 mg. Data from the 150 mg and 300 mg dose groups may not be sufficiently predictive for patients of lower weight/ dose (100 mg eptinezumab) groups. This needs to be accounted for in future pediatric studies, specifically if the inclusion of younger patients/ patients with lower body weight is planned.

No changes to the product information are proposed.

3. CHMP overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.

Annex. Line listing of all the studies included in the development program

Non-clinical studies

Product Name: Vyepti Active substance: Eptinezumab

Study title	Study number	Date of completion	Date of submission of final study report
Study in juvenile rats to determine the potential toxicity of eptinezumab when administered once weekly (IV).	Study 1 ALD403-086-TOX	15-Jan-2020 (date of final report)	The study report was submitted as part of the EU MAA on 16-Nov-2020

Clinical studies

Product Name: Vyepti Active substance: Eptinezumab

Study title	Study number	Date of completion	Date of submission of final study report
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.	18922A The Main Study Period is included as Study 2 in the agreed PIP (EMEA-002243-PIP01-17-M03)	Main Study Period: 20-Oct-2022 Open-Label Extension Period: 21-Aug-2023	Main Study Period: 29-Mar-2023 Extension Period: planned by 13-Feb-2024
Randomised, double blind, placebo-controlled study to evaluate the efficacy and safety of eptinezumab for the prevention of chronic migraine (CM), in paediatric patients 12 to less than 18 years of age	Study 3 19356A	Estimated: 31-Mar-2026	Within 6 months of study completion
Randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of eptinezumab for the prevention of episodic migraine (EM) in paediatric patients from 6 to less than 18 years of age	Study 4 19357A	Estimated: 30-Jun-2027	Within 6 months of study completion
Long-term, open-label (dose-blinded), extension study of eptinezumab in children and adolescents with chronic or episodic migraine (enrolling completers from Study 3 and 4)	19379A	Estimated: 31-Mar-2028	Within 6 months of study completion

Extrapolation, modelling and simulation studies

Product Name: Vyepti Active substance: Eptinezumab

Study title	Study number	Date of completion	Date of submission of final study report
Population PK model to establish the initial paediatric dose to be used in the clinical efficacy and safety Study 3 and 4.	Study 5 ALD403-088-PK	14-Jan-2020 (date of final report)	The study report was submitted as part of the EU MAA on 16-Nov-2020