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REVIEW ARTICLE

# Pharmacokinetics and Pharmacodynamics, Efficacy and Safety of Fremanezumab in Children and Adolescents with Migraine

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## Abstract

Migraine affects up to 11% of children and adolescents, leading to substantial disability through school absenteeism, cognitive impairment, and reduced quality of life. Traditionally, preventive treatment options for this population have been limited to the off-label use of nutraceuticals, antiseizure medications, calcium channel blockers, serotonin modulators, antidepressants, or beta-blockers, with limited efficacy and tolerability data. Monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) pathway have transformed adult migraine prevention, and fremanezumab is the first in this class to receive regulatory approval for pediatric use. In August 2025, the US Food and Drug Administration approved fremanezumab for the preventive treatment of episodic migraine in patients aged 6–17 years weighing at least 45 kg, based on the pivotal phase three SPACE trial. This randomized, placebo-controlled study demonstrated significant reductions in monthly migraine and headache days, with nearly half of treated participants achieving a ≥50% response rate, and a safety profile consistent with adult data. In this review, we provide an integrated, pediatric-focused synthesis of the pharmacokinetic, pharmacodynamic, and regulatory evidence supporting fremanezumab use in children and adolescents. In particular, we contextualize population pharmacokinetic modeling and pediatric phase 1 data to explain the rationale for weight-based dosing, exposure matching with adults, and the selection of the dosing regimens used in clinical trials and regulatory labeling. Pharmacokinetic analyses indicate that fremanezumab follows a two-compartment model with first-order absorption and a terminal half-life of approximately 30 days in pediatric patients, similar to adults, with body weight as the primary determinant of exposure. Finally, we discuss unresolved issues related to long-term CGRP blockade during growth, including theoretical effects on vascular regulation, bone metabolism, and neurodevelopment. Overall, fremanezumab represents a novel, mechanism-based preventive option for older children and adolescents with episodic migraine, while highlighting the need for continued longitudinal studies to define its long-term safety and optimal role in pediatric migraine management.

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**Key Points**

Fremanezumab has been approved by the FDA as the first anti-CGRP preventive treatment for episodic migraine in children and adolescents aged 6–17 years ≥45 kg, on the basis of the phase 3 SPACE trial.

Pharmacokinetics in pediatrics parallels adults when adjusted for weight, supporting a two-tier dosing: 120 mg monthly for < 45 kg (only used in trials) and 225 mg monthly for ≥ 45 kg, with a ~30-day half-life.

The SPACE trial showed fremanezumab significantly reduced migraine and headache days, nearly half of patients achieved ≥ 50% response, and safety was consistent with adults, though long-term developmental effects remain uncertain.

## 1 Introduction

Migraine is a highly prevalent and disabling neurovascular disorder that affects not only adults but also a substantial proportion of children and adolescents [1]. Epidemiological studies estimate that migraine occurs in approximately 8–11% of the pediatric population, with prevalence increasing with age and peaking during adolescence, particularly in females [2]. Migraine in children and adolescents is associated with a substantial disease burden, including school absenteeism, reduced academic performance, impaired social functioning, and decreased quality of life, often comparable to or exceeding the impact observed in adults [3]. Despite this significant burden, therapeutic options for preventive treatment in children and adolescents have historically been limited. Most available medications used in this population, such as nutraceuticals, antiseizure medications, calcium channel blockers, serotonin modulators, antidepressants, and beta-blockers, lack robust evidence of efficacy from controlled pediatric trials, and their use is frequently off-label [4–7]. Importantly, the CHAMP study reported no significant differences in reduction in headache frequency or headache-related disability in childhood and adolescent patients with migraine using amitriptyline, topiramate, or placebo over a period of 24 weeks [8]. Additionally, concerns regarding safety, tolerability, and potential developmental effects have further limited the widespread adoption of preventive medications in young patients with migraine.

The calcitonin gene-related peptide (CGRP) pathway has emerged as a key therapeutic target in migraine pathophysiology [9, 10], and monoclonal antibodies against CGRP (anti-CGRP mAbs) or its receptor have brought a significant change in migraine prevention among adults [11]. However, until recently, these drugs were not available for children and adolescents (≤ 18 years). In August 2025, the US Food and Drug Administration (FDA) [12] approved fremanezumab for the preventive treatment of episodic migraine in patients aged 6–17 years who weigh at least 45 kg, marking the first approval of a CGRP-targeted therapy for a pediatric indication. This decision was based on the pivotal phase 3 SPACE trial [13], which demonstrated substantial reductions in monthly migraine and headache days (MMDs and MHDs, respectively), along with favorable responder rates and a safety profile comparable to that observed in adults [12, 14, 15].

This approval represents a significant advancement in pediatric headache medicine. It offers, for the first time, an evidence-based, mechanism-specific preventive therapy tailored to migraine in young patients. Importantly, it addresses the longstanding gap in pediatric care for migraine by providing an effective option to reduce the frequency and burden of attacks during a critical period of cognitive, emotional, and social development. In this review, we discuss the pharmacokinetic (PK) and pharmacodynamic (PD) features of fremanezumab in the pediatric population, including dosing strategies such as allometric scaling, highlighting differences with the adult parameters and regulatory status.

## 2 Pharmacokinetic

### 2.1 Dose Adjustments and Scaling Strategies

Fremanezumab dosing in pediatric populations was determined using modeling and simulation approaches to account for body size differences. The adult population PK model (a two-compartment with weight as a covariate) was extrapolated to pediatrics and subsequently refined using actual pediatric phase 1 PK data (a summary of the trial is provided in the Supplementary Information section, with detailed data reported below). An initial assumption of a standard 0.75 exponent for clearance and 1.0 for volume (per 70 kg reference) was used to predict pediatric PK. However, after fitting the model to the phase 1 data, the estimated exponents for weight were adjusted accordingly. The clearance exponent decreased slightly, indicating less-than-linear increase in clearance (CL) with weight, and adjustments were required for volume scaling. In fact, the best-fit pediatric model suggested a weight exponent of ~0.83 for CL (compared with about 1.05 in the adult model). This implies that younger children clear fremanezumab a bit faster per kilogram than predicted by simple 0.75 allometry, requiring a proportionally higher dose per kilogram. Similarly, the central volume exponent in the refined model differed from that of the adult,

**Table 1** Weight-banded pediatric dosing versus exposure matching

| | Fremanezumab dose | Steady-state exposure versus adults |
|---|---|---|
| < 45 kg | 120 mg SC monthly (proposed dose, not available) | $AUC_{28d}$ and $C_{max}$ comparable to adults on 225 mg monthly. (Slightly higher peak concentration in children, but within adult range). |
| ≥45 kg | 225 mg SC monthly | Achieves adult-equivalent exposure; pediatric $C_{max}$ and AUC virtually the same as in adults. No dose adjustment needed for ≥ 45 kg. |

*SC* subcutaneous, $AUC_{28d}$ 28-day area under curve, $C_{max}$ peak concentration

reflecting a somewhat different distribution pattern. The outcome of the modeling exercise was the implementation of the two-tier weight-based dosing regimen used in trials: 120 mg monthly for < 45 kg and 225 mg monthly for ≥ 45 kg. This approach was validated through simulations, which showed that 120 mg in a < 45 kg child yields an area under the curve (AUC) nearly identical to an adult on 225 mg. Table 1 summarizes how these doses correspond to adult-equivalent exposure. For reference, the PK data of fremanezumab in adults are reported in previous papers [11, 16].

Notably, the model predicted that using 75 mg monthly would underdose many lighter children (approximately a threefold lower dose than the adult 225 mg, despite their weight being only half to two thirds of that of an average adult) [14]. The exposure-matching analysis strongly supported 120 mg as the appropriate pediatric dose for the < 45 kg group. No further subdivision within this weight range appeared necessary, as simulations indicated that 120 mg covered children between 17 and 45 kg. In fact, even a 17-kg child on 120 mg would remain within the adult exposure range (toward the higher end of peak concentration ($C_{max}$)), providing a safety margin by which efficacy would not be compromised by underdosing.

Regardless of the dose amount, the dosing frequency and route remain the same as in adults (monthly subcutaneous injection). The pediatric program did not explore quarterly dosing (675 mg quarterly) considering weight adjustment and the shorter duration of the trials; thus, all pediatric data with fremanezumab are based on monthly administration. Compared with adults, the pediatric dose per body weight is slightly higher. For example, a 120-mg dose in a 30-kg child results in about 4 mg/kg, as compared with about 3.2 mg/kg with a dose of 225 mg in a 70-kg adult. This marginally higher mg/kg is supported by the PK differences discussed earlier. Additionally, there were no indications that pediatric patients required any initial loading doses or titration; the regimen was started at the full dose.

The phase 1 PK results guided dose selection for subsequent trials. Initially, 75 mg monthly was presumed—by extrapolation—to produce pediatric exposures comparable to efficacious levels in adults. However, observed data revealed that 75 mg in children weighing < 45 kg resulted in underdosing for many patients. After refining the PK model with pediatric data, simulations indicated that a 120-mg monthly dose in children under 45 kg would match the exposure (AUC and trough concentrations) of the adult 225-mg monthly regimen [17]. Consequently, a dose of approximately 4 mg/kg monthly in children under 45 kg is needed to achieve drug exposure equivalent to adults, which is slightly higher on a mg/kg basis than adult dose.

## 2.2 Pharmacokinetics Features

A dedicated open-label phase 1 trial evaluated fremanezumab PK in children aged 6–11 years (body weight 17–45 kg) [17]. In total, 15 patients received a single 75-mg subcutaneous dose. Sparse sampling (five time points over about 113 days) was employed to characterize the concentration–time profile. The median time to reach peak concentration ($T_{max}$) in pediatric patients was approximately 1 week, which was similar to adults (around 5–7 days). Notably, the pediatric PK model indicated no need for an absorption lag time, unlike the adult model, suggesting that drug absorption may be slightly faster or without delay in children [17].

Body weight had a pronounced effect on exposure. Children at the lower end of the weight range achieved higher concentrations from the same dose. For example, after 75 mg in the phase 1 study, children < 30 kg had a mean $C_{max}$ of ~34 µg/mL, versus ~16 µg/mL in those > 30 kg. Correspondingly, the 28-day area under the curve ($AUC_{28d}$) was about 16200 µg h/mL in <30-kg children, doubling the 8840 µg h/mL in 30–45-kg children [17]. This reflects a lower apparent volume of distribution and clearance in smaller children, leading to higher drug exposure for a given dose. A population two-compartment PK model with first-order absorption/elimination and allometric scaling on clearance (CL) and volume ($V$) well described the data. In this phase 1 population [17], the model-estimated clearance for a typical 6–11-year-old was lower in absolute terms than in adults, as expected for smaller body size. For instance, a ~25–30 kg child was predicted to have a CL on the order of 0.06–0.07 L/day (about half the adult value), though weight-normalized clearance was slightly higher than in adults. The elimination half-life in children appears to be on the same order as adults (~30 days). While precise pediatric half-life values were not reported, the modeling did not indicate a major

**Table 2** Comparative pharmacokinetics of fremanezumab

| | Adults | Children-adolescents (6–17 years) |
|---|---|---|
| $T_{max}$ (time to $C_{max}$) | ~5–7 days | ~1 week (similar, possibly slightly faster; no lag time in model) |
| $C_{max}$ (mean, single dose) | 225 mg SC → ~16 µg/mL | 75 mg: ~34 µg/mL (<30 kg) versus ~16 µg/mL (30–45 kg);<br>Steady state 120 mg <45 kg or 225 mg ≥45 kg → adult-equivalent |
| AUC (28 days) | ~8800 µg h/mL (225 mg) | 75 mg: 16,200 (<30 kg) versus 8840 (30–45 kg);<br>Adjusted pediatric dosing yields adult-equivalent exposure |
| Clearance (CL) | ~0.1–0.14 L/day | ~0.06–0.07 L/day at 25–30 kg (lower absolute CL, but slightly higher weight-normalized CL) |
| Volume of distribution (*V*) | ~6 L | Lower absolute *V* in smaller children; ~6 L in ≥ 45 kg adolescents |
| Half-life (t½) | ~30–31 days | ~30 days across ages; no major deviation from adults |
| Accumulation/Steady state | Steady state at ~5–6 months with monthly dosing; ~2.3-fold accumulation | Similar in pediatric patients; steady state ~5–6 months, ~2.3-fold accumulation |
| Dose regimen | 225 mg monthly or 675 mg quarterly | < 45 kg: 120 mg monthly (only in trial, not approved); ≥ 45 kg: 225 mg monthly |

deviation from the adult half-life (~31 days); therefore, a ~4-week terminal half-life is assumed. This long half-life aligns with the dosing interval of once monthly. No significant accumulation or time-dependent clearance changes were noted in pediatric simulations beyond what is seen in adults (steady state ~6 months with monthly dosing) [17].

In the phase 3 pediatric trial (SPACE study, *see below*) of patients aged 6–17 years, dosing was stratified by weight: participants ≥ 45 kg received 225 mg monthly, while those < 45 kg received 120 mg monthly [17]. This strategy was based on the PK modeling described above to equalize exposure across the cohorts.

For patients at or above 45 kg, the PK of fremanezumab mirrors that in adults. The predicted steady-state $C_{max}$ and AUC in patients 6–17 years ≥ 45 kg on 225 mg monthly are similar to adult exposures. The apparent clearance is near adult levels when scaled for weight (no evidence of age-driven metabolic differences beyond size). Likewise, distribution volume (~6 L apparent volume) approaches adult values. Thus, the elimination half-life in patients ≥ 45 kg is ~30–31 days, as in adults. For 12–17-year-olds who are under 45 kg, the PK would align more with the 6–11-year-old profile. Indeed, those patients in the trial were given 120 mg, and their exposure was projected (via the model) to match the adult target. There is no intrinsic difference in drug handling at age 12–17 years versus age 6–11 years beyond body size. The population PK analyses did not identify maturation-related covariates other than weight. For instance, age itself was not a significant independent factor for CL or *V* once weight was accounted for. As in adults, steady state in patients over 45 kg would be reached in ~5–6 months of monthly dosing (owing to the ~30 days half-life). No dose interval adjustments were needed, and a once-monthly schedule was effective and maintained through levels. The PK accumulation ratio in monthly dosing (about 2.3-fold increase from first dose to steady state) is expected to be similar in adolescents as in adults. Comparative differences in PK between pediatric and adult populations are reported in Table 2.

## 2.3 Pharmacodynamics and Clinical Efficacy (SPACE Trial)

The mechanism of fremanezumab in pediatric patients is identical to that in adults; it binds circulating CGRP ligand, preventing CGRP from activating its receptor, primarily in the trigeminovascular system, thereby reducing migraine frequency and severity through suppression of the CGRP pathway. The pivotal phase 3 SPACE trial [13–15] (NCT04458857; the study design and characteristics are reported in the *Supplementary Information*) demonstrated that fremanezumab leads to significant reductions in migraine frequency in children and adolescents, confirming target engagement and downstream effect.

In the SPACE study [13–15], 237 children and adolescents (130 females, 104 males) were randomized; 234 were included in the full analysis population. Of these, 112 were randomized to placebo, 36 to fremanezumab dose A (< threshold weight), and 87 to dose B (≥ threshold weight). A subset of patients (21.3%) was permitted to use up to two additional concomitant preventive medications. Baseline characteristics were well balanced, with a mean age of 13.3 ± 2.7 years and a predominance of female patients (55%). Average baseline migraine frequency was 7.5–7.8 days/month across groups.

A total of 119 on 123 fremanezumab-treated and 106 of 112 placebo-treated participants completed the 3-month double-blind period. Discontinuations were infrequent and mainly due to adverse events or loss to follow-up.

Fremanezumab significantly reduced monthly migraine days (MMDs) compared with placebo. The least squares mean reduction was −2.5 days per month with fremanezumab versus –1.4 with placebo, corresponding to a treatment difference of about 1.1 days ($p = 0.02$). Similarly, monthly headache days (MHDs) of at least moderate severity declined by −2.6 with fremanezumab compared with −1.5 with placebo ($p = 0.02$). Nearly half of patients treated with fremanezumab (47.2%) achieved at least a 50% reduction in MMDs, compared with 27.0% on placebo ($p = 0.002$). Use of acute headache medications was also reduced more in the active treatment group (−2.1 days versus −1.0 days; $p = 0.002$). Migraine-related disability, measured with PedMIDAS, improved by −21.6 points with fremanezumab versus −15.3 with placebo, a difference that, however, was not statistically different ($p = 0.10$), with hierarchical testing stopped at this endpoint. LS mean changes from baseline in MMD favored fremanezumab over placebo, also in subgroups stratified by age (6–11 years: −3.4 versus −1.7; 12–17 years: −2.7 versus −1.8) and sex (male: −3.5 versus −2.2; female: −2.3 versus −1.5) [15].

Regarding safety and tolerability [13–15], 225/235 patients were included in the safety population. The proportion of participants reporting at least one adverse event (AE) was similar across treatment groups, with 55% in the fremanezumab group and 49% in the placebo group. Specifically, treatment-emergent adverse events were reported in 49.1% of placebo, 55.6% of dose A, and 55.2% of dose B participants, with no notable imbalances observed among the groups. Adverse events leading to discontinuation were rare. Immunogenicity analyses revealed low rates of anti-drug antibodies, detected in 2.9% of dose A and 1.1% of dose B participants.

In the safety analysis set, which included all participants who received at least one dose of study medication, serious adverse events (SAEs) were infrequent, occurring in 2.7% of placebo recipients, 2.8% in the low-weight fremanezumab group (dose A), and 1.2% in the high-weight group (dose B). Reported SAEs in the fremanezumab groups included infectious mononucleosis, and migraine, each occurring in isolated instances. Notably, cases of hemiparesis and immune thrombocytopenia reported during the study occurred in the placebo group.

Nonserious adverse events were more common, reported in 23.2% of placebo participants, 22.2% in dose A, and 33.3% in dose B. Most of these events were injection-site reactions and mild infections. Injection-site erythema, pain, or swelling were observed in fremanezumab-treated participants, with a slightly higher incidence in dose B compared with dose A or placebo. Common infections included nasopharyngitis (7-9% across groups), coronavirus disease 2019 (COVID-19) (5-6%), and upper respiratory tract infections (4-6%), with similar incidence between active and placebo groups. Neurological events were infrequent: dizziness was reported only in 5.8% of dose B participants, while headache was noted in 1.8% of placebo and 5.6% of dose A.

Overall, the safety profile of fremanezumab in children and adolescents was consistent with that observed in adults, with no new or unexpected safety signals identified. No significant changes in blood pressure, heart rate, or other systemic biomarkers were reported in pediatric patients, aligning with adult data, indicating that CGRP blockade does not produce notable hemodynamic effects. However, it is important to note that the study excluded patients with clinically significant cardiovascular disease. The safety and effectiveness of fremanezumab for the preventive treatment of episodic migraine in pediatric patients younger than 6 years of age and in pediatric patients with chronic migraine have not yet been established.

### 2.4 Ongoing Trials

Ongoing studies with fremanezumab in the pediatric population include an open-label extension of the phase 3 trial, which is in progress to collect 6–12-month safety and efficacy data (NCT03539393) [18], as well as a completed study on fremanezumab in pediatric patients with chronic migraine for which results are not yet available (NCT04464707) [19]. Additionally, other ongoing studies are investigating different anti-CGRP drugs, including gepants and anti-CGRP mAbs, which are reviewed in [20]. Currently, no other drugs in development for migraine are being tested [21].

### 2.5 Regulatory Status and Labeling

As previously mentioned, fremanezumab was granted an expanded indication by the FDA in August 2025 for the preventive treatment of episodic migraine in pediatric patients aged 6–17 years who weigh ≥ 45 kg [22]. This marked it as the first anti-CGRP therapy approved for any pediatric population. The FDA label recommends 225 mg monthly for those ≥ 45 kg, administered either in-office or at home, mirroring the adult dosing schedule [22]. The label explicitly states that “fremanezumab is not approved in pediatric patients weighing less than 45 kg because of the lack of an appropriate strength presentation” [22]. The approval was based on the results of the phase 3 trial of the SPACE study (reported above). Currently, the indication is limited to episodic migraine; fremanezumab is not yet approved for chronic migraine in pediatrics. The FDA label also specifies that in children aged 6–12 years, fremanezumab injections should be administered by a healthcare provider or adult caregiver [22].

The European Medicines Agency (EMA) or other major regulatory agencies have not approved fremanezumab for pediatric use yet. From a clinical point of view,

recommendations on the use of anti-CGRP mAbs in children and adolescents have already been published by the American Headache Society (AHS) [23].

### 2.6 Blocking CGRP in Children

Blocking CGRP in children may carry theoretical risks owing to its role in vascular regulation, skeletal development, gastrointestinal function, and neuro-immune signaling [23, 24].

Experimental and human data indicate that CGRP pathways are already active during fetal life and childhood, with high CGRP expression in sensory neurons and vascular tissues early in development, followed by age-dependent modulation across adolescence [9]. Clinical studies show that children and adolescents with migraine have elevated circulating CGRP levels compared with controls, supporting a pathophysiological role similar to that observed in adults [9, 25].

While short-term data demonstrate a reassuring safety profile in both adults and children, the absence of long-term developmental data means that potential subtle effects on growth, puberty, or organ maturation cannot be fully excluded [23, 24]. Therefore, longitudinal studies and post-marketing surveillance are essential to confirm the safety of sustained CGRP inhibition during long-term pediatric development.

## 3 Conclusions

Fremanezumab exhibits a PK and PD profile in pediatric patients that closely parallels that observed in adults when adjusted for body size. Key PK parameters , including clearance and half-life, as well as the two-compartment distribution are maintained in children, with body weight being the primary differentiator. Clinically, the PD effect of fremanezumab in inhibiting the CGRP pathway results in significant reductions in migraine frequency in children and adolescents aged 6–17 years. The treatment was generally well tolerated, and its safety profile in pediatric patients mirrors that in adults, with no new concerns identified.

With regulatory approval for older children and adolescents, fremanezumab has the potential to address a significant unmet need in pediatric migraine management.

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**Availability of data and material** All data used for this review are presented in the manuscript and supplementary materials. Any additional documents referenced are available upon request.

## Declarations

**Conflict of interest** LFI received financial support, consulting fees for the participation in advisory boards and support for attending meetings from: Teva, Eli Lilly, Lundbeck, Pfizer, Organon and AbbVie; he is associate editor for the *Frontiers in Neurology* Headache and Neurogenic Pain section and junior editor in *Cephalalgia and Cephalalgia* report. MV received honoraries for talks and papers and consulting fees for the participation in advisory boards from: Teva, Pfizer, Lusofarmaco, and Biogen; he is chief editor of *Pain Research and Management*, associate editor for the *Frontiers in Neurology* Headache and Neurogenic Pain section, *Journal of Clinical Medicine, Life, Brain Sciences*, and *BMC Neurology*; he is in the Editorial Board of *Journal of Headache and Pain*, *European Journal of Pain*, *Clinical Neurophysiology*, and *Neurological Sciences*. LP is a member of the junior editorial board of *The Journal of Headache and Pain*, section board member for Children in the area of *Pediatric Neurology and Neurodevelopmental Disorders*, editorial board member of *Confinia Cephalalgica*, and associate editor for the Pediatric Neurology section of *Frontiers in Neurology*. She has received financial support from TEVA, Eli Lilly, Lundbeck, Pfizer, AbbVie, and Epitech for the organization of scientific meetings and support from attending meetings from MERCK and Biogen. IT is a member of editorial board of of *Headache*; Review Editor of *Frontiers (Epilepsy, Neurogenomics, Pediatric Cardiology, Pediatric Neurology)*; Co-Associate Editors of *Perspectives in Pediatric Neurology*. She has received financial support for the organization of scientific meetings and support for attending meetings from: UCB, JAZZ-Pharmaceuticals, and Italfarmaco. The other Authors have no conflict of interest related to the topic of the review.

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## References

1. Ashina M. Migraine. N Engl J Med. 2020;383(19):1866–76.

2. Victor TW, et al. Migraine prevalence by age and sex in the United States: a life-span study. Cephalalgia. 2010;30(9):1065–72.
3. Lewis DW. Pediatric migraine. Neurol Clin. 2009;27(2):481–501.
4. Termine C, et al. Overview of diagnosis and management of paediatric headache. Part II: therapeutic management. J Headache Pain. 2011;12(1):25–34.
5. Rao R, Hershey AD. An update on acute and preventive treatments for migraine in children and adolescents. Expert Rev Neurother. 2020;20(10):1017–27.
6. Oskoui M, et al. Practice guideline update summary: pharmacologic treatment for pediatric migraine prevention: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2019;93(11):500–9.
7. El-Chammas K, et al. Pharmacologic treatment of pediatric headaches: a meta-analysis. JAMA Pediatr. 2013;167(3):250–8.
8. Powers SW, et al. Trial of amitriptyline, topiramate, and placebo for pediatric migraine. N Engl J Med. 2017;376(2):115–24.
9. Evers S. CGRP in childhood and adolescence migraine: (patho) physiological and clinical aspects. Curr Pain Headache Rep. 2022;26(6):475–80.
10. Russo AF, Hay DL. CGRP physiology, pharmacology, and therapeutic targets: migraine and beyond. Physiol Rev. 2023;103(2):1565–644.
11. Versijpt J, et al. Calcitonin gene-related peptide-targeted therapy in migraine: current role and future perspectives. Lancet. 2025;405(10483):1014–26.
12. Teva Pharmaceutical Inc. FDA Approves Expanded Indication for AJOVY® (fremanezumab-vfrm), The First Anti-CGRP Preventive Treatment for Pediatric Episodic Migraine. 2025 [cited 2025 27 Aug 2025]; Available from: https://ir.tevapharm.com/news-and-events/press-releases/press-release-details/2025/FDA-Approves-Expanded-Indication-for-AJOVY-fremanezumab-vfrm-The-First-Anti-CGRP-Preventive-Treatment-for-Pediatric-Episodic-Migraine/default.aspx.
13. Hershey AD, et al. Fremanezumab in children and adolescents with episodic migraine. N Engl J Med. 2026;394(3):243–52.
14. Teva Pharmaceutical Inc, A study to test if fremanezumab is effective in preventing episodic migraine in patients 6 to 17 years of age. 2020, https://ClinicalTrials.gov/show/NCT04458857.
15. Hershey A, et al. Efficacy and safety of fremanezumab for the preventive treatment of episodic migraine in children and adolescents: a phase 3, randomized, double-blind, placebo-controlled study (PL5.001). Neurology, 2025. **104**.
16. Romozzi M, et al. Pharmacological differences and switching among anti-CGRP monoclonal antibodies: a narrative review. Headache. 2025;65(2):342–52.
17. Cohen-Barak O, et al. Dose selection for Fremanezumab (AJOVY) phase 3 pediatric migraine studies using pharmacokinetic data from a pediatric phase 1 study and a population pharmacokinetic modeling and simulation approach. Cephalalgia. 2021;41(10):1065–74.
18. Teva Pharmaceutical Inc. Fremanezumab compassionate use program for pediatric patients (NCT03539393). 2025 [cited 2025 27 Aug 2025].
19. Clinicaltrial.gov. A study to test if fremanezumab is effective in preventing chronic migraine in patients 6 to 17 years of age. 2020. https://ClinicalTrials.gov/show/NCT04464707.
20. Iannone LF, De Cesaris F, Geppetti P. Emerging pharmacological treatments for migraine in the pediatric population. Life Basel. 2022. https://doi.org/10.3390/life12040536.
21. Silvestro M, et al. Migraine treatment: towards new pharmacological targets. Int J Mol Sci. 2023. https://doi.org/10.3390/ijms241512268.
22. Teva Pharmaceutical Inc, Fremaneuzumab FDA prescribing information. 2025.
23. Szperka CL, et al. Recommendations on the use of Anti-CGRP monoclonal antibodies in children and adolescents. Headache. 2018;58(10):1658–69.
24. Deen M, et al. Blocking CGRP in migraine patients—A review of pros and cons. J Headache Pain. 2017;18(1):96–96.
25. Moore L, Pakalnis A. Calcitonin gene-related peptide inhibitors in the treatment of migraine in the pediatric and adolescent populations: a review. Pediatr Neurol. 2024;157:87–95.