ORIGINAL ARTICLE

Fremanezumab in Children and Adolescents with Episodic Migraine

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ABSTRACT

BACKGROUND

Fremanezumab, a humanized monoclonal antibody that selectively targets calcitonin gene–related peptide, is approved for the prevention of migraine in adults. Evidence from randomized, controlled trials in children and adolescents is needed.

METHODS

We randomly assigned participants 6 to 17 years of age with a diagnosis of episodic migraine (defined as migraine for ≥6 months and a history of ≤14 headache days per month) to receive monthly subcutaneous injections of fremanezumab (120 mg for participants with a body weight of <45 kg and 225 mg for those with a body weight of ≥45 kg) or matched placebo for 3 months. Participants were allowed to use migraine-specific medications to treat acute headaches. The primary end point was the change from baseline in the average number of migraine days per month. Key secondary end points included the change in the number of days per month with headache of at least moderate severity and a reduction of 50% or more in the number of migraine days per month.

RESULTS

Of 237 participants who underwent randomization, 234 were included in the full analysis population: 123 in the fremanezumab group (36 received the 120-mg dose and 87 received the 225-mg dose) and 111 in the placebo group. Fremanezumab reduced the number of migraine days per month by 2.5 as compared with 1.4 with placebo (difference, 1.1; P=0.02) and the number of days per month with headache of at least moderate severity by 2.6 as compared with 1.5 with placebo (difference, 1.1; P=0.02). The percentage of participants who had a reduction of 50% or more in the number of migraine days per month was 47.2% with fremanezumab and 27.0% with placebo (P=0.002). Injection-site erythema was the most common adverse event with fremanezumab (9.8% of participants, vs. 5.4% with placebo).

CONCLUSIONS

Among children and adolescents with episodic migraine, fremanezumab resulted in greater reductions in the number of migraine days and headache days than placebo. Injection-site erythema was the most common adverse event with fremanezumab. Longer follow-up is required to further understand the efficacy and safety of the drug in this population. (Funded by Teva Pharmaceuticals; ClinicalTrials.gov number, NCT04458857.)

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CME

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Migraine is a common neurologic disorder in childhood and adolescence, with an estimated overall prevalence of 11%.[1] Children and adolescents with migraine, as well as their families, face a substantial burden due to their attacks, including lost schooling and workdays, poor educational performance, and missed social activities.[2,3] Although lifestyle modifications and treatment of acute attacks represent the mainstay of migraine management in children and adolescents,[4,5] current options for preventive treatment have limited efficacy.[6,7]

Fremanezumab, a humanized monoclonal antibody that selectively targets calcitonin gene–related peptide (CGRP), is approved in adults for the preventive treatment of episodic and chronic migraine in several countries, including the United States, and across Europe, Asia, and South America.[8-12] Fremanezumab has been shown to significantly reduce headache frequency, use of acute headache medication, and headache-related disability in adults with episodic and chronic migraine.[13-15]

The potential of monoclonal antibodies that target the CGRP pathway in children and adolescents has been observed in retrospective cohort studies,[16,17] and although they are recommended by the American Headache Society in certain cases,[18-20] there is a need for evidence from prospective, randomized, controlled trials in this population. As such, we conducted a phase 3, multicenter, randomized, placebo-controlled trial with a 3-month double-blind period to evaluate the efficacy and safety of fremanezumab in children and adolescents with episodic migraine. The results of the trial have led to Food and Drug Administration approval of the drug for the prevention of episodic migraine in children and adolescents.

Methods

Trial Oversight

The protocol (available with full text of this article at NEJM.org) was approved by independent ethics committees or institutional review boards according to national or local regulations. This trial was conducted in full accordance with the International Council for Harmonisation consolidated guideline for Good Clinical Practice (E6), standard ISO 14155 of the International Organization for Standardization (Clinical Investigation of Medical Devices for Human Subjects — Good Clinical Practice), International Headache Society guidelines for controlled trials of preventive treatment of migraine in children and adolescents,[21] and any relevant national and local regulations. The authors assume responsibility for the conduct of the trial and the adherence of the trial to the protocol and for collecting, recording, and reporting the data and adverse events accurately and properly. Written informed consent was obtained from the parent or guardian of each participant, and assent was obtained from each participant as appropriate before any trial procedures or assessments were done. The trial sponsor, Teva Pharmaceuticals, provided the trial medication, performed the statistical analysis, and funded the trial. All the authors contributed to writing the manuscript, reviewed and commented on initial drafts, and approved the final version.

Trial Participants

This trial was conducted at 89 sites, 74 of which enrolled at least one participant, in nine countries from August 20, 2020, to March 13, 2024 (see the Supplementary Methods section in the Supplementary Appendix, available at NEJM.org). The trial included participants 6 to 17 years of age with a diagnosis of episodic migraine (defined as migraine for ≥6 months and a history of ≤14 headache days per month), with or without aura (consistent with the International Classification of Headache Disorders, 3rd edition).[22] Participants had to have at least 4 headache days per month in each of the 3 months before screening. Up to 30% of participants using a stable dose of no more than two concomitant migraine-preventive medications for at least 2 months before screening could be included. Key exclusion criteria included clinically significant coexisting conditions (any coexisting condition that the investigator deemed would, in their opinion, place the participant at unacceptable risk or affect the integrity of the data), use of medications containing opioids or barbiturates for the treatment of migraine during the 3 months before screening, a history of hemiplegic migraine, use of monoclonal antibodies targeting the

CGRP pathway within the preceding 6 months, and use of an intervention or device for the treatment of migraine or in the head or neck area for any condition during the 2 months before screening.

TRIAL DESIGN

This multicenter, parallel-group, randomized, placebo-controlled trial consisted of a 28-day baseline period and a 3-month double-blind period. During the baseline period, participants were required to maintain a headache diary with data entry on at least 21 days and were permitted to use acute migraine medication, except for those containing opioids or barbiturates, and migraine-preventive medications that had been taken at a stable dose for at least 2 months before screening. At the start of the double-blind period, participants were randomly assigned in a centralized fashion and in a 1:1 ratio to receive monthly fremanezumab by subcutaneous injection (120 mg for participants with a body weight of <45.0 kg and 225 mg for those with a body weight of ≥45.0 kg) or matched monthly placebo for 3 months. Randomization was performed with the use of interactive response technology and was stratified according to country, sex, puberty status (participant-reported Tanner stage), and use of preventive medication at baseline. The sponsor, investigators, trial staff (except for the clinical supply team and staff involved in the bioanalytical analyses), and participants were unaware of the trial-group assignments. Scheduled visits are outlined in the Supplementary Methods section.

PRIMARY AND KEY SECONDARY END POINTS

The primary end point was the least-squares mean change from baseline in the average number of migraine days per month during the 3-month double-blind period. A migraine day was defined as a calendar day (00:00 to 23:59) in which the participant reported any of the following three events: at least 2 consecutive hours of headache that was accompanied by at least two migraine symptoms (headache of moderate-to-severe intensity, headache worsening with activity, headache in unilateral location, or migraine throbbing in nature) and was associated with either nausea or photophobia and phonophobia; a headache of any duration that was treated with nonsteroidal antiinflammatory drugs, paracetamol, triptans, or ergot compounds; or a headache associated with aura.

Key secondary end points were the least-squares mean change from baseline in the average number of days per month with headache of at least moderate severity (defined as headache of moderate or severe intensity, or any intensity with use of acute headache medications), a reduction of 50% or more in the number of migraine days per month, the least-squares mean change in the average number of days per month in which acute headache medication was used, the least-squares mean change in the Pediatric Migraine Disability Assessment (PedMIDAS) total score (a 6-item questionnaire; scores range from 0 to 270, with a score of 0 to 10 indicating no or little disability, 11 to 30 mild disability, 31 to 50, moderate disability, and >50 severe disability),[23] and the least-squares mean change in the child-reported Pediatric Quality of Life (PedsQL) total score (a 23-item questionnaire; scores range from 1 to 100, with higher scores indicating better quality of life).[24] The least-squares mean change in the average number of days per month with headache of any severity and Patient Global Impression of Improvement (PGI-I) were evaluated as prespecified exploratory end points.

The safety and side-effect profile were evaluated on the basis of adverse-event reports, clinical laboratory tests (serum chemical, hematologic, coagulation, and urinalysis tests), vital signs (blood pressure and pulse), findings on electrocardiography (ECG), findings on physical examination, concomitant medication use, and suicidal ideation and behavior according to the Columbia–Suicide Severity Rating Scale (C-SSRS).

STATISTICAL ANALYSIS

The intention-to-treat analysis population was planned to include all the participants who underwent randomization. The full analysis population included those in the intention-to-treat analysis population who received at least one dose of fremanezumab or placebo and had at least 10 days of postbaseline efficacy assessments (i.e., diary entries) regarding the primary end point; if fewer than 10 days were recorded, the value for that month was considered to be missing.

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Fremanezumab (N=123)	Placebo (N=112)
Age		
Mean — yr	13.3±2.7	13.4±3.0
Distribution — no. (%)		
6–11 yr	32 (26)	32 (29)
12–17 yr	91 (74)	80 (71)
Female sex — no. (%)	66 (54)	64 (57)
Race — no. (%)†		
White	96 (78)	84 (75)
Nonwhite	9 (7)	7 (6)
Unknown or not reported‡	18 (15)	21 (19)
Weight		
Mean — kg	52.6±15.5	52.1±15.8
Distribution — no. (%)		
<45 kg	36 (29)	33 (29)
≥45 kg	87 (71)	79 (71)
Body-mass index§	20.50±3.98	20.57±3.88
Time since initial migraine diagnosis — yr	4.4±3.0	4.4±3.1
Migraine with aura — no. (%)	41 (33)	30 (27)
Migraine days per month	7.8±3.1	7.5±2.8
Days per month with headache of at least moderate severity	8.2±3.1	7.9±2.8
Days per month in which acute headache medication was used	5.8±3.6	5.6±3.4
PedMIDAS total score¶	44.4±26.5	46.5±43.6
Child-reported PedsQL total score‖	72.0±13.1	72.7±13.7

* Plus–minus values are means ±SD.
† Race was reported by the participant, parent, or guardian.
‡ Most participants for whom race was unknown or not reported were from Finland.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ Pediatric Migraine Disability Assessment (PedMIDAS) total scores range from 0 to 270, with a score of 0 to 10 indicating no or little disability, 11 to 30 mild disability, 31 to 50 moderate disability, and more than 50 severe disability.
‖ Pediatric Quality of Life (PedsQL) total scores range from 1 to 100, with higher scores indicating better health-related quality of life.

The potential effect of missing data on the primary analysis was assessed by means of a prespecified sensitivity analysis that used reference-based multiple imputation[25] incorporating both missing-at-random and missing-not-at-random assumptions. Further details on the handling of missing data are included in the Supplementary Methods section. The full analysis population was used for all efficacy analyses, unless otherwise specified. The safety analysis population included all the participants who took at least one dose of fremanezumab or placebo. In the safety analysis population, treatment was assigned on the basis of the intervention that participants received, regardless of the intervention to which they were assigned.

A hierarchical testing procedure was applied to control the type I error rate at 0.05, with a prespecified sequence of comparisons starting with the primary end point and proceeding to key secondary end points in the order listed in the Supplementary Methods section. The hierarchical testing sequence was finalized before database lock. A P value of less than 0.05 was considered to be statistically significant only if all preceding end points in the hierarchy were statistically significant.

Details of the sample-size calculation, interim analysis, and statistical analysis methods are provided in the Supplementary Methods section. The full statistical analysis plan is available with the protocol.

RESULTS

PARTICIPANTS

Of 411 screened participants, 237 were assigned to receive either fremanezumab (123 participants, of whom 36 received the 120-mg dose and 87 received the 225-mg dose) or placebo (112 participants); however, 2 participants were excluded from all analysis populations owing to nonadherence to Good Clinical Practice guidelines (Fig. S1 in the Supplementary Appendix). The most common reasons for screening failure are described in the Supplementary Results section in the Supplementary Appendix. Of the 235 participants, all 123 of those assigned to receive fremanezumab and 111 of 112 (99.1%) of those assigned to receive placebo had data available for analyses of efficacy end points and were included in the full analysis population (234 participants). Of the randomly assigned participants, 96.7% (119 of 123) in the fremanezumab

group and 94.6% (106 of 112) in the placebo group completed the 3-month double-blind period. The primary end-point analysis was based on 84 diary days (28 per month during the 12-week treatment period). Diary completion was generally high. One participant (0.4%) had fewer than 10 postbaseline diary days and was excluded from the full analysis population.

The demographic and clinical characteristics of the participants at baseline were similar in the two groups (Table 1). The mean (±SD) number of migraine days per month was 7.8±3.1 in the fremanezumab group and 7.5±2.8 in the placebo group. Most participants (97.9% [230 of 235]) received migraine- or headache-specific concomitant medications during the trial, with their use being similar in the two trial groups. Previous preventive medication was used by 21.3% of the participants (50 of 235) in the baseline period. Further details on previous and concomitant use of preventive medication are provided in Table S1. Participants' medical history is shown in Table S2. This trial population was reflective of the real-world population of children and adolescents with episodic migraine (Table S3).

EFFICACY

The least-squares mean change from baseline in the average number of migraine days per month during the 3-month double-blind period (primary end point) was significantly greater in the fremanezumab group than in the placebo group (–2.5 days [95% confidence interval {CI}, –3.2 to –1.7] vs. –1.4 days [95% CI, –2.2 to –0.7]; P=0.02). Results for the change in migraine days per month are shown in Table 2, Figure 1A, and Figure S2.

There was a significantly greater reduction in the number of days per month with headache of at least moderate severity with fremanezumab than with placebo (–2.6 days [95% CI, –3.4 to –1.8] vs. –1.5 days [95% CI, –2.3 to –0.7]; P=0.02) (Table 2 and Fig. S3). A significantly higher percentage of participants receiving fremanezumab had a reduction of 50% or more in the number of migraine days per month than those receiving placebo (47.2% [58 of 123] vs. 27.0% [30 of 111]; odds ratio, 2.5 [95% CI, 1.4 to 4.4]; P=0.002) (Table 2 and Fig. 1B). The least-squares mean change in the average number of days per month in which acute headache medication was used was –2.1 days (95% CI, –2.6 to –1.5) with fremanezumab and –1.0 days (95% CI, –1.6 to –0.4) with placebo (P=0.002) (Table 2 and Fig. S4).

The least-squares mean change in the PedMIDAS total score at month 3 was –21.6 points (95% CI, –28.1 to –15.1) with fremanezumab and –15.3 points (95% CI, –22.0 to –8.7) with placebo (difference, –6.3 points; 95% CI, –13.7 to 1.2; P=0.10) (Table 2). Given that this P value did not indicate significance, the hierarchical testing procedure was stopped. At month 3, the least-squares mean change in the child-reported PedsQL total score was 5.7 points (95% CI, 3.1 to 8.3) in the fremanezumab group and 6.2 points (95% CI, 3.5 to 8.9) in the placebo group (difference, –0.5 points; 95% CI, –3.5 to 2.5).

The least-squares mean change in the average number of days per month with headache of any severity was –2.5 days (95% CI, –3.4 to –1.7) with fremanezumab and –1.5 days (95% CI, –2.4 to –0.6) with placebo (difference, –1.0; 95% CI, –2.1 to –0.04). The PGI-I results are shown in Table S4.

SAFETY

In total, 68 of 123 participants (55.3%) receiving fremanezumab and 55 of 112 (49.1%) receiving placebo had at least one adverse event; most adverse events were nonserious and mild to moderate in severity (Table 3 and Table S5). Serious adverse events were reported by 2 participants in the fremanezumab group (hepatitis secondary to infectious mononucleosis and migraine exacerbation resulting in hospitalization in 1 participant each). One participant in the fremanezumab group (0.8%) had an adverse event involving a mild increase in the alanine aminotransferase level from 23 U per liter at baseline to 68 U per liter that led to discontinuation of participation in the trial. Three participants receiving placebo reported a serious adverse event (thrombocytopenia, hemiparesis, and migraine in 1 participant each). No deaths occurred.

General disorders and administration-site conditions occurred in 21.1% of the participants (26 of 123) in the fremanezumab group and 18.8% of the participants (21 of 112) in the placebo group. Injection-site erythema was the most common

Table 2. Primary and Ranked Secondary End Points.*

End Point	Fremanezumab (N=123)	Placebo (N=111)	Difference	P Value
Primary end point				
LS mean change from baseline in average number of migraine days per month during the 3-month double-blind period (95% CI)	−2.5 (−3.2 to −1.7)	−1.4 (−2.2 to −0.7)	−1.1 (−1.9 to −0.2)	0.02
Secondary end points				
LS mean change from baseline in average number of days per month with headache of at least moderate severity during the 3-month double-blind period (95% CI)	−2.6 (−3.4 to −1.8)	−1.5 (−2.3 to −0.7)	−1.1 (−2.1 to −0.2)	0.02
Reduction of ≥50% in number of migraine days per month during the 3-month double-blind period — % of participants	47.2	27.0	20.1	0.002
LS mean change from baseline in average number of days per month in which acute headache medication was used during the 3-month double-blind period (95% CI)	−2.1 (−2.6 to −1.5)	−1.0 (−1.6 to −0.4)	−1.1 (−1.8 to −0.4)	0.002
LS mean change from baseline in PedMIDAS total score at month 3 (95% CI)	−21.6 (−28.1 to −15.1)	−15.3 (−22.0 to −8.7)	−6.3 (−13.7 to 1.2)	0.10†
LS mean change from baseline in PedsQL total score at month 3 (95% CI)	5.7 (3.1 to 8.3)	6.2 (3.5 to 8.9)	−0.5 (−3.5 to 2.5)	

* Least-squares (LS) means are shown from an analysis of covariance. To control the type I error rate at 0.05, a hierarchical testing procedure was applied; end points are shown in the order in which they were evaluated.
† Given that this P value did not indicate statistical significance, the hierarchical testing procedure was stopped.

adverse event, occurring in 9.8% of the participants (12 of 123) receiving fremanezumab and 5.4% of the participants (6 of 112) receiving placebo. No notable differences in adverse events were observed across trial groups when assessed according to age (Table S6).

No safety signals were observed in the adverse events reported or after analyses of clinical laboratory measures, physical examinations, vital signs, and ECG assessments. Evaluation of the C-SSRS results did not show evidence of an increase in suicidal ideation or behavior in participants receiving fremanezumab as compared with placebo.

DISCUSSION

In this randomized, controlled trial assessing fremanezumab for the preventive treatment of episodic migraine in children and adolescents, reductions in the number of migraine days per

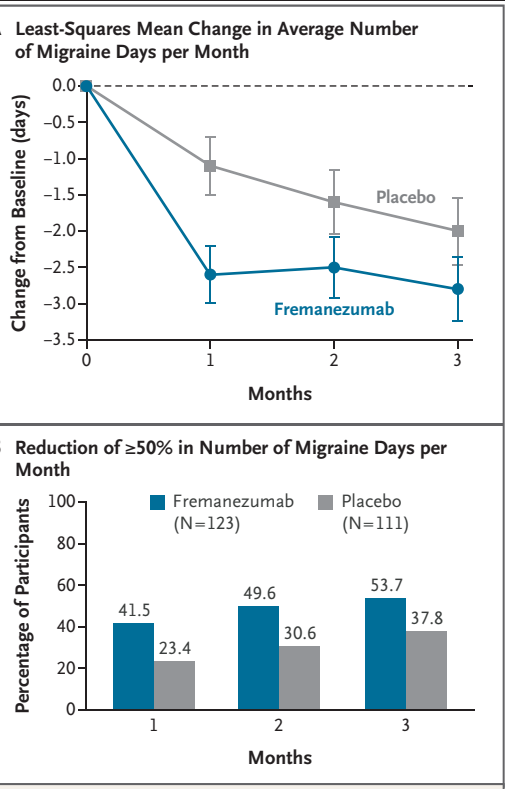

Figure 1. Change in Migraine Days per Month and Reduction of 50% or More in Migraine Days per Month.

Least-squares means (±SE) are shown from a mixed-effects model for repeated measures.

Table 3. Adverse Events According to Trial Group.*

Event	Fremanezumab, 120 mg (N=36)	Fremanezumab, 225 mg (N=87)	All Fremanezumab (N=123)	Placebo (N=112)
	number of participants (percent)			
Any adverse event	20 (56)	48 (55)	68 (55)	55 (49)
Adverse event related to fremanezumab or placebo†	6 (17)	17 (20)	23 (19)	21 (19)
Severe adverse event	2 (6)	2 (2)	4 (3)	4 (4)
Serious adverse event	1 (3)	1 (1)	2 (2)	3 (3)
Blood and lymphatic system disorders	0	0	0	1 (<1)
Immune thrombocytopenia	0	0	0	1 (<1)
Infections and infestations	0	1 (1)	1 (<1)	0
Hepatitis infectious mononucleosis	0	1 (1)	1 (<1)	0
Nervous system disorders	1 (3)	0	1 (<1)	2 (2)
Migraine	1 (3)	0	1 (<1)	1 (<1)
Hemiparesis	0	0	0	1 (<1)
Adverse event leading to discontinuation of participation in the trial‡	1 (3)	0	1 (<1)	0
Adverse event leading to death	0	0	0	0
Adverse events occurring in ≥5% of participants in any group				
General disorders and administration-site conditions	5 (14)	21 (24)	26 (21)	21 (19)
Injection-site erythema	1 (3)	11 (13)	12 (10)	6 (5)
Injection-site pain	0	6 (7)	6 (5)	6 (5)
Injection-site swelling	1 (3)	5 (6)	6 (5)	1 (<1)
Pyrexia	0	4 (5)	4 (3)	1 (<1)
Vaccination-site pain§	2 (6)	0	2 (2)	1 (<1)
Infections and infestations	9 (25)	24 (28)	33 (27)	31 (28)
Nasopharyngitis	3 (8)	8 (9)	11 (9)	8 (7)
Covid-19	2 (6)	5 (6)	7 (6)	6 (5)
Upper respiratory tract infection	2 (6)	4 (5)	6 (5)	5 (4)
Gastroenteritis	0	4 (5)	4 (3)	1 (<1)
Nervous system disorders	3 (8)	6 (7)	9 (7)	6 (5)
Dizziness	0	5 (6)	5 (4)	0
Headache	2 (6)	0	2 (2)	2 (2)

* All adverse events were coded according to system organ class and preferred term with the use of the *Medical Dictionary for Regulatory Activities*, version 26.0 or higher. A more comprehensive list of adverse events reported according to trial group is provided in Table S5. Covid-19 denotes coronavirus disease 2019.
† The relatedness of adverse events to fremanezumab or placebo was determined by the investigators.
‡ One adverse event involving a mild increase in the alanine aminotransferase level led to discontinuation of participation in the trial.
§ Shown are events related to the administration of concomitant medications during the trial.

month, days per month with headache of at least moderate severity, and days per month in which acute headache medication was used were approximately 1 day greater with fremanezumab than with placebo. These findings are consistent with those of the HALO-EM trial of fremanezumab in adults with episodic migraine, in which the reduction in the number of migraine days per

month was 1.5 days greater with fremanezumab than with placebo, with improvements similar to those observed in this trial reported for use of acute headache medication.[13] A reduction of 50% or more in migraine days per month is generally considered to be the benchmark of successful migraine prevention.[26,27] In this trial, 47.2% of the participants in the fremanezumab group and 27.0% of those in the placebo group reached this threshold, which is similar to the 47.7% and 27.9% reported for monthly fremanezumab and placebo, respectively, in the HALO-EM trial.[13]

The most commonly used preventive treatments in children and adolescents, including topiramate, propranolol, and amitriptyline, can have side effects.[28,29] In this trial, the safety and side-effect profile of fremanezumab in children and adolescents were similar to those in a trial of fremanezumab in adults with episodic migraine.[13] Most adverse events were nonserious and mild to moderate in severity. One participant had an increase in the alanine aminotransferase level that led to discontinuation of participation in the trial. General disorders and administration-site conditions, including injection-site erythema, were more frequent with fremanezumab than with placebo, but these events were mild to moderate and did not vary substantially in severity between trial groups. No substantial differences in the safety profile of fremanezumab were identified between children and adolescents.

A high placebo response is a considerable challenge in studies involving children and adolescents with migraine, occurring in up to 30 to 61% of patients.[30] The underlying reasons for this are complex and probably include a combination of expectation response, a standardized treatment plan that includes short-term therapy during a migraine attack and healthy habits, and simply being evaluated by a specialist.[31,32] In this trial, material was developed specifically for the investigative sites to minimize placebo response. As a result, the placebo response was low; the odds of having a reduction of 50% or more in the number of migraine days per month during the 3-month double-blind period were almost twice as high with fremanezumab as with placebo.

The population studied in this trial was reflective of the real-world clinical population of children and adolescents with episodic migraine, and the inclusion of participants across age ranges and geographic regions enhances the generalizability of these results. The generalizability was further enhanced by including participants with a long history of headache as well as those who have had a lack of response to other treatments.[33,34] To allow these persons to participate, this trial permitted up to 30% of the participants using a stable dose of no more than two concomitant migraine-preventive medications for at least 2 months before screening, while limiting inclusion to 30% ensured that the trial was not overweighted with these participants.

Although current evidence suggests that the classification of migraine as episodic migraine and chronic migraine may be artificial,[35] regulatory guidelines for drug development in this indication require demonstration of efficacy and safety in both subgroups independently,[36] and, therefore, a parallel trial involving children and adolescents with chronic migraine has been completed (ClinicalTrials.gov number, NCT04464707). The ongoing open-label extension of both trials will provide additional insights on the long-term use of fremanezumab in children and adolescents.

In this trial, treatment with fremanezumab for 3 months led to significant reductions in the number of migraine days per month, days per month with headache of at least moderate severity, and days per month in which acute headache medication was used, as compared with placebo, in children and adolescents with episodic migraine. Except for injection-site reactions, there were no safety issues identified. These data add to the limited evidence on the efficacy and safety of migraine-preventive treatments in children and adolescents.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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