



Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial

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Summary

Background Antibodies targeting calcitonin gene-related peptide (CGRP) or its receptor have shown efficacy in the prevention of migraine attacks. We investigated the efficacy and tolerability of fremanezumab, a fully humanised CGRP antibody, in patients with migraine who had previously not responded to two to four classes of migraine preventive medications.

Methods The randomised, double-blind, placebo-controlled, parallel-group, phase 3b FOCUS trial was done at 104 sites (including hospitals, medical centres, research institutes, and group practice clinics) across Belgium, the Czech Republic, Denmark, Finland, France, Germany, Italy, the Netherlands, Poland, Spain, Sweden, Switzerland, the UK, and the USA. We enrolled participants aged 18–70 years with episodic or chronic migraine who had documented failure to two to four classes of migraine preventive medications in the past 10 years. Failure was defined as no clinically meaningful improvement after at least 3 months of therapy at a stable dose, as per the treating physician's judgment; discontinuation because of adverse events that made treatment intolerable; or treatment contraindicated or unsuitable for the preventive treatment of migraine for the patient. Participants were randomly assigned (1:1:1) by electronic interactive response technology to subcutaneously administered quarterly fremanezumab (month 1, 675 mg; months 2 and 3: placebo), monthly fremanezumab (month 1: 225 mg in episodic migraine and 675 mg in chronic migraine; months 2 and 3: 225 mg in both migraine subgroups), or matched monthly placebo for 12 weeks. The primary outcome was mean change from baseline in the monthly average number of migraine days during the 12-week treatment period. This trial is registered with ClinicalTrials.gov, number NCT03308968, and is now completed.

Findings Between Nov 10, 2017, and July 6, 2018, 838 participants with episodic (329 [39%]) or chronic (509 [61%]) migraine were randomly assigned to placebo (n=279), quarterly fremanezumab (n=276), or monthly fremanezumab (n=283). Reductions from baseline in monthly average migraine days over 12 weeks were greater versus placebo (least-squares mean [LSM] change -0.6 [SE 0.3]) with quarterly fremanezumab (LSM change -3.7 [0.3]; LSM difference vs placebo -3.1 [95% CI -3.8 to -2.4]; $p<0.0001$) and with monthly fremanezumab (LSM change -4.1 [0.34]; LSM difference vs placebo -3.5 [-4.2 to -2.8]; $p<0.0001$). Adverse events were similar for placebo and fremanezumab. Serious adverse events were reported in four (1%) of 277 participants with placebo, two (<1%) of 276 with quarterly fremanezumab, and four (1%) of 285 with monthly fremanezumab.

Interpretation Fremanezumab was effective and well tolerated in patients with difficult-to-treat migraine who had previously not responded to up to four classes of migraine preventive medications.

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Introduction

Migraine is a disease characterised by headache, with specific features and associated symptoms¹ and, in a third of patients, aura.² Migraine ranks as the leading cause of years lived with disability among individuals younger than 50 years.³ Although most patients have the episodic form of migraine, approximately 8% have chronic migraine, with headaches on at least 15 days per month.^{2,4}

Migraine preventive or prophylactic medications do not prevent the illness but can reduce the frequency of migraine attacks.⁵ Conventional migraine preventive medications were all initially developed for other conditions and show little efficacy and often poor tolerability in patients with migraine, frequently leading to early discontinuation of treatment.^{5–11} In a database study of more than 4600 patients, up to 73% had stopped using migraine preventive medications within 6 months

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Research in context

Evidence before this study

Current prescribing of migraine preventive medications is primarily based on trial and error. Only a few studies have investigated whether patients who did not respond to previous migraine preventive medications might benefit from treatment with another migraine preventive medication. In a systematic search of PubMed using the terms “migraine” AND (“refractory” OR “unsuccessful” OR “treatment resistant”) AND “preventive” for clinical studies published in English in the past 10 years, we identified only two reports addressing this topic. In one of these reports, the potential beneficial effects of a migraine preventive medication were assessed in a randomised, placebo-controlled clinical trial, which only included patients with episodic migraine. In that study, documenting of previous preventive medication failure was not mandatory, and failure was defined as failure to two to four individual medications, rather than two to four pharmacological classes. Therefore, study participants could have had no response to multiple medications from a single pharmacological class (eg, different anti-epileptics or different β blockers) rather than to one or more medications from at least two and up to four different pharmacological classes.

Added value of this study

The results of this randomised, double-blind, placebo-controlled, phase 3b trial show that fremanezumab,

administered quarterly or monthly, was effective and well tolerated in a large population of patients with difficult-to-treat episodic or chronic migraine who had documented previous failure to two to four pharmacological classes of migraine preventive medications. The therapeutic gain versus placebo for reductions in days with migraine, headache, or use of acute headache medication was greater than in previous studies of migraine preventive medications. More than a third of participants in both fremanezumab dosing groups achieved a clinically meaningful reduction of 50% or greater in monthly migraine days within 4 weeks of treatment initiation. Similar to the pivotal phase 3 trials, fremanezumab was well tolerated and no safety signals were identified.

Implications of all the available evidence

Fremanezumab, a fully humanised (IgG2 Δ a) monoclonal antibody against CGRP, could provide rapid and clinically meaningful improvements in patients with difficult-to-treat episodic or chronic migraine who previously did not respond to as many as four migraine preventive medication classes.

of treatment.¹¹ Monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) or its receptor, however, were specifically developed for migraine based on an evolving understanding of migraine pathophysiology.^{12,13} These antibodies have all shown sustained efficacy in the prevention of migraine attacks and are well tolerated.^{13,14}

Fremanezumab is a fully humanised monoclonal antibody (IgG isotype 2 Δ a) that potently and selectively binds to both isoforms of CGRP.^{15,16} It can be administered quarterly or monthly by subcutaneous injection. Results from the pivotal, placebo-controlled, phase 3 HALO trials showed that fremanezumab led to significant reductions in migraine and headache days in patients with episodic or chronic migraine.^{17,18} However, as with phase 2 and 3 trials of other monoclonal antibodies targeting CGRP or the CGRP receptor,^{19–22} patients who had previously not responded to two or more migraine preventive medications were excluded from the HALO trials.^{17,18} In fact, most trials of conventional migraine preventive medications excluded patients for this reason. As a result, there is inadequate evidence-based treatment guidance for patients who have previously not responded to migraine preventive medications. Consequently, treatment choices for these patients are mainly based on trial and error.

Fremanezumab has been approved in the USA for the preventive treatment of migraine in adults and in

Europe for the prophylaxis of migraine in adults who have at least 4 migraine days per month. In the FOCUS study, we investigated the efficacy and tolerability of monthly and quarterly fremanezumab compared with placebo in patients with difficult-to-treat episodic or chronic migraine, who had documented failure to two to four pharmacological classes of migraine preventive medications.

Methods

Study design and participants

The FOCUS study was an international, multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 3b trial done at 104 sites (including hospitals, medical centres, research institutes, and group practice clinics) across Belgium, the Czech Republic, Denmark, Finland, France, Germany, Italy, the Netherlands, Poland, Spain, Sweden, Switzerland, the UK, and the USA. Participant enrolment and randomisation by country is summarised in the appendix (p 3).

Eligible participants were aged 18–70 years, had a diagnosis of migraine with onset at or before age 50 years, and were otherwise in good health. Participants were required to have a history of migraine for at least 12 months before screening. Eligible participants could have either episodic or chronic migraine at baseline, as defined in the protocol and based on prospectively collected information during the 28-day run-in period.

See Online for appendix

Participants with episodic migraine had a headache on at least 6 days (but <15 days) per month, with at least 4 days fulfilling any of the following criteria: International Classification of Headache Disorders 3 beta version (ICHD-3 beta) criteria²³ for migraine with aura or without aura, probable migraine (a migraine subtype where only one migraine criterion is missing), or use of triptans or ergot derivatives to treat an established headache. Participants with chronic migraine had a headache on at least 15 days per month, with at least 8 days fulfilling the ICHD-3 beta criteria²³ for migraine with aura or without aura, probable migraine, or use of triptans or ergot derivatives to treat an established headache. Participants with and without overuse of acute headache medication²³ were both included.

At the time of screening, all participants were required to have had documented failure within the past 10 years to two to four of the following pharmacological classes of migraine preventive medications: β blockers (propranolol, metoprolol, atenolol, or bisoprolol), anticonvulsants (topiramate), tricyclic antidepressants (amitriptyline), calcium channel blockers (flunarizine), angiotensin II receptor antagonists (candesartan), onabotulinumtoxinA, or valproic acid. Failure was defined as no clinically meaningful improvement after at least 3 months of therapy at a stable dose, as per the treating physician's judgment; discontinuation because of adverse events that made treatment intolerable; or treatment contraindicated or unsuitable for preventive treatment of migraine for the patient. Documentation of previous failure to migraine preventive medication was generally based on the participant's medical record, with the medication name, treatment duration, dose level, and reason for discontinuation, or an affidavit confirming previous treatment failures, as described in the appendix (p 1).

At the time of screening, participants could not be using migraine preventive medications. Participants continuing treatment with migraine preventive medications were excluded from the study. Participants were also excluded if they had used onabotulinumtoxinA for migraine or any medical or cosmetic reason requiring injections in the head, face, or neck during the 3 months before screening; used opioid-containing or barbiturate-containing treatments on more than 4 days during the run-in period; used interventions or devices for migraine during the 2 months before screening; used triptans or ergots as migraine preventive treatment; or used non-steroidal anti-inflammatory drugs as a preventive treatment for migraine or on an almost daily basis for other indications, with the exception of low-dose aspirin for cardiovascular disease prevention. Participants with previous exposure to a monoclonal antibody targeting the CGRP pathway were also excluded. Additional exclusion criteria included clinically significant disease or psychiatric issues that could, in the opinion of the investigator, compromise patient safety or ability to participate in the study, or a history of clinically

significant cardiovascular disease or vascular ischaemia or thromboembolic events (eg, cerebrovascular accident, deep vein thrombosis, or pulmonary embolism). The full list of study inclusion and exclusion criteria is summarised in the appendix (pp 4, 5).

This study was done in full accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines for Good Clinical Practice and any applicable national and local laws and regulations. All participants provided written informed consent before participation in the study. The final study protocol and informed consent form were reviewed and approved by an independent ethics committee or institutional review board at all participating study sites.

Randomisation and masking

Participants were randomly assigned (1:1:1) to quarterly fremanezumab, monthly fremanezumab, or placebo by electronic interactive response technology. Randomisation was stratified by migraine classification (chronic or episodic migraine), sex, country, and failure to two to three migraine preventive medication classes plus valproic acid or valproate. The last stratification factor was included to ensure that the most difficult-to-treat participants were evenly distributed across the treatment groups, because in some countries (eg, Germany), valproic acid or valproate is considered last-line treatment. The sponsor, investigators, study staff, and participants were masked to treatment assignment during the double-blind period. Both fremanezumab doses and placebo were packaged in identical prefilled syringes.

Procedures

The study consisted of a screening visit, a run-in period (28 days), a 12-week double-blind, placebo-controlled treatment period, a 12-week open-label period, and a follow-up visit 6 months after the last dose of fremanezumab. Only the results of the 12-week double-blind, placebo-controlled period are presented here.

At baseline, participants were randomly assigned (1:1:1) to subcutaneously administered fremanezumab, monthly or quarterly, or matched placebo over 12 weeks of double-blind treatment. For all participants, quarterly fremanezumab treatment consisted of subcutaneously administered fremanezumab 675 mg as a first dose, followed by matched monthly placebo for 2 months. For participants with episodic migraine, monthly subcutaneously administered fremanezumab treatment consisted of fremanezumab 225 mg plus two matching placebo injections as a first dose, followed by monthly fremanezumab 225 mg for 2 months. For participants with chronic migraine, monthly subcutaneously administered fremanezumab treatment consisted of fremanezumab 675 mg as a first dose, followed by monthly fremanezumab 225 mg for 2 months (appendix p 16). Participants with overuse of acute

headache medication were not instructed to withdraw from the study or discontinue the overused medication, nor were they provided with information or education about the risk of headache medication overuse.

For efficacy assessments, participants were asked to record information about headaches during the previous 24-h period in an electronic headache diary device. Participants who reported a headache on the previous day were asked to answer questions about the headache, including use of acute migraine medications. Subjective ratings of headache severity (mild, moderate, or severe) and total hours of headache for each day were also recorded in the electronic diary.

Outcomes

The primary efficacy outcome was the mean change from baseline (28-day run-in period) in the monthly average number of migraine days during the entire 12 weeks after the first dose of study drug. In this study, a migraine day was defined as a calendar day with at least four consecutive hours of a migraine with or without aura as per ICHD-3 diagnostic criteria²³ (no more than one ICHD-3 migraine criterion missing), or a headache of any duration treated with migraine-specific acute medications (triptans or ergot compounds).

Secondary outcomes included the change from baseline in the monthly average number of migraine days during the 4-week period after the first dose of study drug and the proportions of participants with a 50% or greater response (ie, participants achieving a $\geq 50\%$ reduction in the monthly average number of migraine days during the 4-week and 12-week periods after the first dose of study drug). Additional secondary outcomes were the change from baseline in the monthly average number of headache days of at least moderate severity during the 4-week and 12-week periods after the first dose of study drug and the change from baseline in the days of use of any acute headache medications during the 12-week period after the first dose of study drug.

Prespecified exploratory outcomes included the proportions of participants with a 75% or greater response (ie, participants achieving $\geq 75\%$ reduction in the monthly average number of migraine days) and those with a 100% response (no migraine days) during the 12-week period after the first dose of study drug; the proportion of participants with a 100% response (no migraine days) for at least 1 month over 12 weeks; and the proportions of participants who achieved a 50% or greater and 75% or greater response during the first 4 weeks and maintained that response through 12 weeks. Additional prespecified exploratory outcomes included mean changes from baseline during the 12-week period after the first dose of study drug in the monthly average number of headache hours of at least moderate severity, days with nausea or vomiting, days with photophobia and phonophobia, and days of use of migraine-specific

acute headache medications (triptans and ergot compounds). Mean changes from baseline in the number of migraine days during the 12 weeks after the first dose of study drug were assessed as prespecified exploratory outcomes for participants who had previously not responded to topiramate, onabotulinumtoxinA, valproic acid, and valproic acid plus two to three other classes of migraine preventive medications. For participants who had previously not responded to valproic acid plus two to three other classes of migraine preventive medications, proportions of participants with a 50% or greater response during the 12-week double-blind treatment period were evaluated. Mean changes from baseline at 4 weeks after administration of the third dose of study drug in the following patient-reported outcomes were also assessed as prespecified exploratory outcomes: disability scores (measured by the Migraine Disability Assessment [MIDAS] and Headache Impact Test [HIT-6]), Migraine-Specific Quality of Life (MSQOL) score, EurQol-5 Dimension (EQ-5D) health status score, 9-item Patient Health Questionnaire (PHQ-9), and Work Productivity and Activity Impairment (WPAI) questionnaire. Patient Global Impression of Change (PGIC) at 4 weeks after administration of the third dose of study drug was also assessed.²⁴

Adverse events, serious adverse events, and adverse events leading to discontinuation were summarised by treatment group. All adverse events were coded with the Medical Dictionary for Regulatory Activities (MedDRA), version 18.1. Routine laboratory assessments, vital signs measurements, and physical examinations were also assessed.

The timing of study procedures and assessments is summarised in the appendix.

Statistical analysis

A sample size of 705 participants (235 per treatment group) completing the study was required for 90% power to show a difference of 1.8 in migraine days (assuming a common SD of 6 days) at an alpha level of 0.05. Assuming a 12% discontinuation rate, 268 participants per treatment group were planned for randomisation. The intention-to-treat analysis set comprised all randomly assigned participants. The safety analysis set comprised all randomly assigned participants who received at least one dose of study drug. Participants in the intention-to-treat analysis set who received at least one dose of study drug and had at least 10 days of post-baseline efficacy assessments for the primary outcome (modified intention-to-treat analysis set) were included in all efficacy analyses. The per-protocol analysis set was a subset of the modified intention-to-treat analysis set, including only participants who completed the study without important protocol deviations or any deviations or omissions in study drug administration.

Demographic and baseline characteristics were summarised descriptively. The primary efficacy outcome

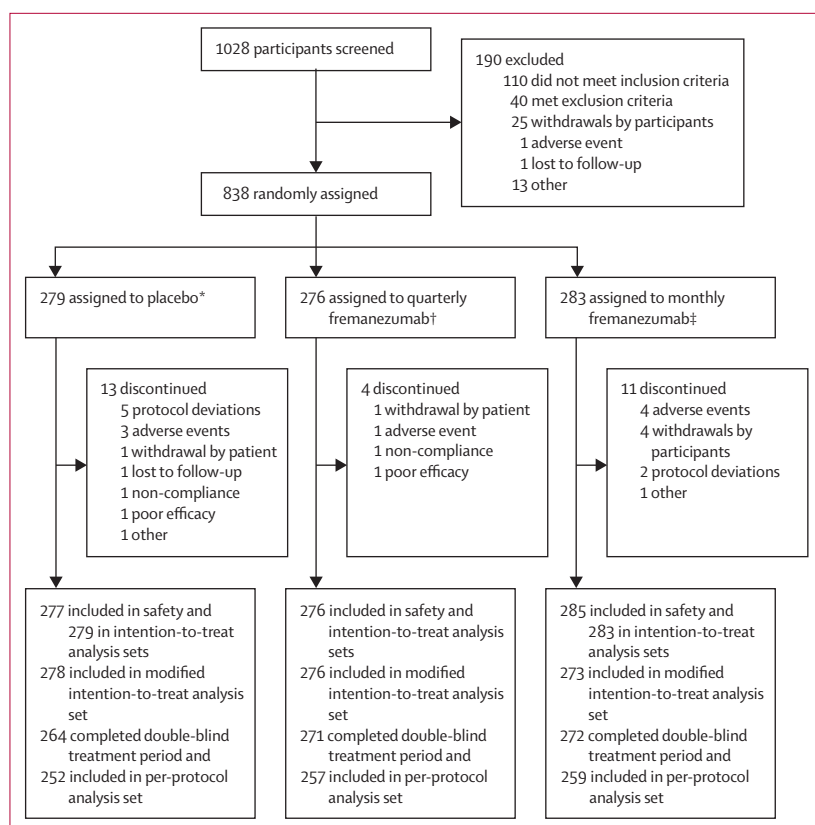


Figure 1: Trial profile

*Two patients randomly assigned to placebo received an active injection during the study; one was analysed in the monthly fremanezumab chronic migraine subgroup and the other in the monthly fremanezumab episodic migraine subgroup for all safety analyses. †675 mg in month 1 and placebo in months 2 and 3. ‡Chronic migraine: 675 mg in month 1, 225 mg in month 2, and 225 mg in month 3. Episodic migraine: 225 mg in months 1, 2, and 3.

was analysed with an analysis of covariance (ANCOVA) method, with treatment, sex, region, special group of treatment failure, migraine classification, and treatment-by-migraine classification interaction as fixed effects; and baseline number of migraine days and years since onset of migraine as covariates. Sensitivity analyses were done with a mixed-effects repeated measures analysis model, including treatment, sex, region, special group of treatment failure, migraine classification, month, treatment-by-migraine classification interaction, treatment-by-month interaction, and treatment-by-migraine classification-by-month interaction as fixed effects; baseline value and years since onset of migraine as covariates; and participant as a random effect. The least-squares mean (LSM) change from baseline with standard error (SE) is presented for each treatment group, and the LSM difference versus placebo with 95% CI is presented for both fremanezumab dosing groups. Continuous secondary and exploratory efficacy outcomes were analysed similarly to the primary efficacy outcome. For the proportion of responders, a logistic regression model was used with the following effects: treatment, sex, region, special group of treatment failure

(yes or no), and migraine classification (chronic or episodic). Stratification factors (as randomised) were used in the model. Participants who discontinued treatment early were considered non-responders for the overall analysis and for each month after discontinuation. Odds ratios (ORs), 95% CIs for ORs, and p values are presented for each fremanezumab dosing group (quarterly and monthly doses). Adjustments for multiple comparisons are described in the appendix (p 1). Adverse events were summarised by counts and percentages. Changes in laboratory, electrocardiogram (ECG), and vital signs measurements data were summarised descriptively. All values were compared with predefined criteria to identify potentially clinically significant values or changes.

Role of the funding source

Employees of the funding source were involved in study design, data collection, data analysis, and data interpretation. As authors on this manuscript, some of these employees were involved in the writing of this report and in the decision to submit the report for publication. All authors had access to the final data, participated in the analysis and interpretation of data, vouched for data accuracy and completeness, and were responsible for the decision to submit for publication.

Results

Between Nov 10, 2017, and July 6, 2018, 838 participants were randomly assigned to placebo (n=279), quarterly fremanezumab (n=276), or monthly fremanezumab (n=283), and received at least one dose of study drug (figure 1). One participant in the placebo group who did not have at least 10 days of post-baseline diary entries for the primary outcome was excluded from efficacy analyses (modified intention-to-treat analysis set). 28 participants discontinued double-blind study treatment (13 [5%] in the placebo group; four [1%] in the quarterly fremanezumab group; and 11 [4%] in the monthly fremanezumab group). Important protocol deviations were reported for 73 (26%) of 276 participants in the quarterly fremanezumab group and for 75 (27%) of 283 in the monthly fremanezumab group, as described in the appendix (p 2). The per-protocol analysis set comprised 768 participants (252 in the placebo group, 257 in the quarterly fremanezumab group, and 259 in the monthly fremanezumab group).

Demographic and baseline characteristics were similar across treatment groups (table 1). The mean age was 46.2 (SD 11.0) years and range 18–71 years. Most participants were female (700 [84%] of 838) and white (786 [94%]). The mean time since migraine diagnosis was 24.2 (SD 13.4) years, and more participants in this study had chronic migraine (509 [61%]) than episodic migraine (329 [39%]). Overall, 415 (50%) participants had previously not responded to two migraine preventive medications, 265 (32%) had not responded to three, and

153 (18%) had not responded to four. Anticonvulsants, β blockers, and tricyclic antidepressants were the most common previous classes of migraine preventive medications that participants had not responded to (table 1). The most common reason for failure was poor efficacy in the placebo, quarterly fremanezumab, and monthly fremanezumab groups, accounting for 58% (106 of 184), 57% (122 of 215), and 59% (128 of 217) of anticonvulsant failures; 64% (102 of 159), 63% (91 of 145), and 66% (108 of 164) of β blocker failures; and 64% (90 of 140), 70% (87 of 125), and 67% (86 of 129) of tricyclic antidepressant failures (appendix p 8). Failure was documented in the medical records of most participants. The mean monthly number of migraine days (approximately 14 days), headache days of at least moderate severity (approximately 12 days), and days of acute headache medication use (approximately 12 days) were similar across treatment groups (table 1). 435 (52%) of 837 participants in the efficacy analysis population had overuse of acute headache medication. The results for these participants will be presented separately in a subsequent publication.

The mean reduction from baseline in the monthly average number of migraine days during the 12 weeks after the first dose of study drug (the primary outcome) was greater versus placebo (LSM change from baseline -0.6 [SE 0.3]) in participants treated with quarterly fremanezumab (LSM change from baseline -3.7 [0.3]; LSM difference vs placebo -3.1 [95% CI -3.8 to -2.4]; $p < 0.0001$) and with monthly fremanezumab (LSM change from baseline -4.1 [0.3]; LSM difference vs placebo -3.5 [-4.2 to -2.8]; $p < 0.0001$) in the modified intention-to-treat analysis set (figure 2A, B, appendix p 9). The mean percentage change from baseline in the monthly average number of migraine days during the 12-week treatment period was -8.5% (SD 31.3) in the placebo group, -34.9% (31.7) in the fremanezumab quarterly group, and -36.8 (32.1) in the fremanezumab monthly group. Similar results were observed for the sensitivity analysis of the primary outcome with the mixed-effects repeated measures analysis model and the per-protocol analysis of the primary outcome (appendix p 2). Based on a prespecified subgroup analysis, the therapeutic gain versus placebo was similar in participants with episodic migraine (quarterly fremanezumab: LSM difference -3.1 [95% CI -3.9 to -2.2], $p < 0.0001$; monthly fremanezumab: -3.1 [-4.0 to -2.3], $p < 0.0001$) and chronic migraine (quarterly fremanezumab: -3.2 [-4.2 to -2.2], $p < 0.0001$; monthly fremanezumab: -3.8 [-4.8 to -2.8], $p < 0.0001$; figure 2B). Reductions from baseline in the monthly average number of migraine days were greater with quarterly fremanezumab versus placebo as early as 4 weeks after starting study treatment (-3.6 [95% CI -4.3 to -2.8]; $p < 0.0001$) and monthly fremanezumab (-3.5 [-4.2 to -2.8]; $p < 0.0001$).

The proportions of participants with a 50% or greater response were higher versus placebo (24 [9%] of 278) over

	Placebo (n=279)	Quarterly fremanezumab (n=276)	Monthly fremanezumab (n=283)
Age (years)	46.8 (11.1)	45.8 (11.0)	45.9 (11.1)
Age range			
18–45 years	121 (43%)	125 (45%)	128 (45%)
46–65 years	149 (53%)	144 (52%)	149 (53%)
>65 years	9 (3%)	7 (3%)	6 (2%)
Sex			
Male	46 (16%)	47 (17%)	45 (16%)
Female	233 (84%)	229 (83%)	238 (84%)
Race			
White	262 (94%)	262 (95%)	262 (93%)
Black or African-American	2 (<1%)	2 (<1%)	4 (1%)
Asian	1 (<1%)	0	3 (1%)
American Indian or Alaska native	0	0	1 (<1%)
Other	1 (<1%)	2 (<1%)	1 (<1%)
Not reported	13 (5%)	10 (4%)	12 (4%)
Weight (kg)	71.4 (13.7)	70.7 (13.4)	71.0 (13.7)
Height (cm)	167.7 (9.0)	167.7 (8.1)	167.3 (7.7)
Body-mass index (kg/m ²)	25.3 (4.1)	25.1 (4.1)	25.3 (4.3)
Time since initial migraine diagnosis (years)	24.3 (13.6)	24.3 (12.8)	24.0 (13.7)
Migraine classification			
Episodic	112 (40%)	107 (39%)	110 (39%)
Chronic	167 (60%)	169 (61%)	173 (61%)
Migraine preventive medications failed in the past 10 years			
β blockers	160 (57%)	146 (53%)	165 (58%)
Anticonvulsants	186 (67%)	213 (77%)	216 (76%)
Tricyclic antidepressants	137 (49%)	124 (45%)	127 (45%)
Flunarizine	59 (21%)	41 (15%)	45 (16%)
Candesartan	51 (18%)	53 (19%)	46 (16%)
OnabotulinumtoxinA	76 (27%)	75 (27%)	71 (25%)
Valproic acid	83 (30%)	86 (31%)	92 (33%)
Number of previous preventive medication classes failed			
2	142 (51%)	140 (51%)	133 (47%)
3	82 (29%)	85 (31%)	98 (35%)
4	54 (19%)	49 (18%)	50 (18%)
Monthly number of migraine days at baseline	14.3 (6.1)	14.1 (5.6)	14.1 (5.6)
Monthly number of headache days of at least moderate severity at baseline	12.8 (5.9)	12.4 (5.8)	12.7 (5.8)
Monthly days of use of any acute headache medication at baseline	12.3 (6.3)	12.8 (6.2)	12.2 (6.0)
Data are mean (SD) or n (%).			

Table 1: Demographics and baseline characteristics of participants

12 weeks with quarterly fremanezumab (95 [34%] of 276; OR 5.8 [95% CI 3.6 to 9.6]; $p < 0.0001$) and with monthly fremanezumab (97 [34%] of 283; 5.8 [3.6 to 9.5]; $p < 0.0001$; appendix p 9). The proportions of participants with a 50% or greater response were higher versus placebo (28 [10%] of 278) at 4 weeks for quarterly fremanezumab (105 [38%] of 276; OR 5.8 [95% CI 3.6 to 9.3]; $p < 0.0001$) and monthly fremanezumab (101 [36%] of 283; 5.3 [3.3 to 8.4]; $p < 0.0001$; appendix pp 9, 17). Based on a 50% or greater response

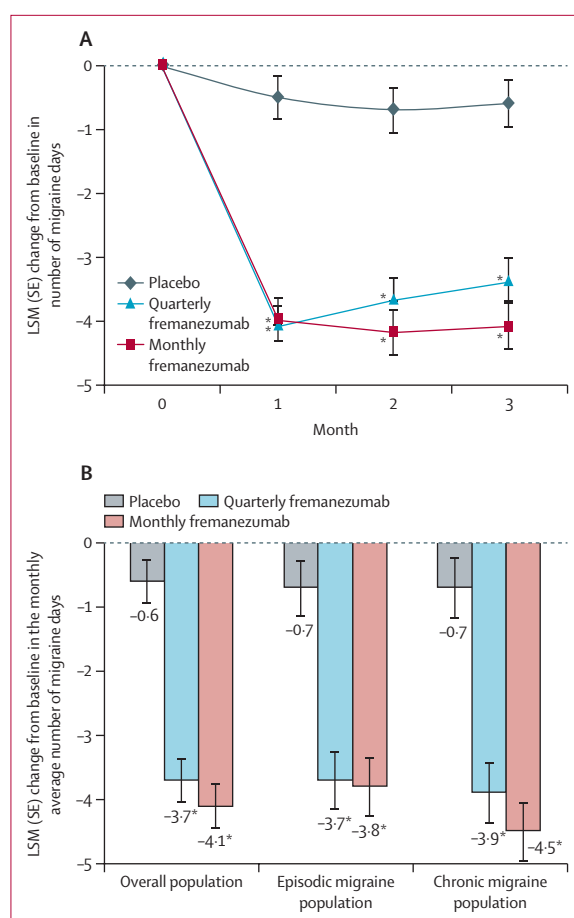


Figure 2: Primary outcome analysis

(A) LSM change from baseline in monthly number of migraine days during the double-blind treatment period. (B) LSM change from baseline in monthly average number of migraine days during the 12-week double-blind treatment period. LSM=least-squares mean. SE=standard error. * $p<0.0001$ versus placebo.

over 12 weeks, the proportion of non-responders was 91% (254 of 278) with placebo and 66% with both quarterly fremanezumab (181 of 276) and monthly fremanezumab (186 of 283). The proportions of participants with a response of 75% or greater over 12 weeks and 100% responders for 1 month or more during 12 weeks were also greater versus placebo for both dosing regimens of fremanezumab ($p=0.0021$ for quarterly fremanezumab and $p=0.0076$ for monthly fremanezumab; appendix p 10). The proportions of participants who achieved a 50% or greater response at 4 weeks and sustained that response through 12 weeks were greater versus placebo for both fremanezumab dosing regimens (both $p<0.0001$), whereas the proportion of participants with a sustained response of 75% or greater from 4 weeks to 12 weeks was significantly greater versus placebo for the monthly fremanezumab group only ($p=0.0045$). The proportion of participants with a 100% response during 12 weeks did not differ significantly between the placebo and fremanezumab groups ($p=0.99$ for quarterly

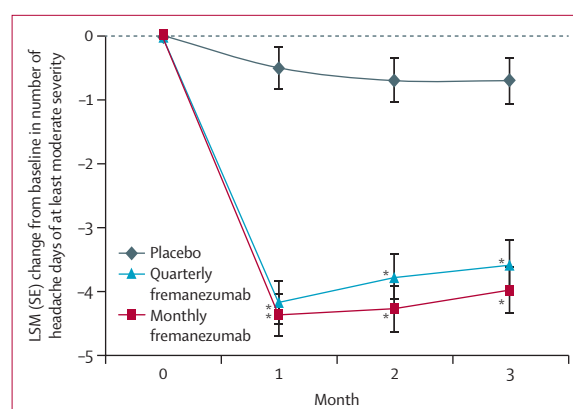


Figure 3: LSM change from baseline in monthly number of headache days of at least moderate severity

LSM=least-squares mean. SE=standard error. * $p<0.0001$ versus placebo.

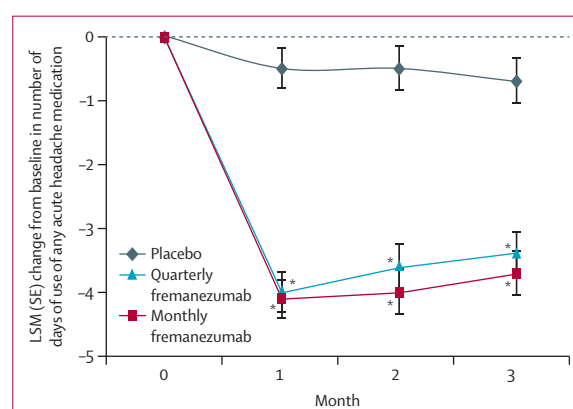


Figure 4: LSM change from baseline in monthly number of days of use of any acute headache medication

LSM=least-squares mean. SE=standard error. * $p<0.0001$ versus placebo.

fremanezumab and $p=0.94$ for monthly fremanezumab; appendix p 10).

Reductions in monthly headache days of at least moderate severity were greater versus placebo over 12 weeks for quarterly fremanezumab (LSM difference -3.2 [95% CI -3.9 to -2.5]; $p<0.0001$) and monthly fremanezumab (-3.6 [-4.3 to -2.9]; $p<0.0001$; figure 3). These reductions were greater versus placebo within 4 weeks for quarterly fremanezumab (LSM difference -3.7 [95% CI -4.4 to -3.0]; $p<0.0001$) and monthly fremanezumab (-3.9 [-4.6 to -3.2]; $p<0.0001$; appendix p 9). Reductions in monthly headache hours of at least moderate severity were also greater versus placebo over 12 weeks for both fremanezumab dosing regimens (both $p<0.0001$; appendix p 11).

Participants who received fremanezumab showed greater reductions from baseline in the monthly average number of days of use of any acute headache medication than did those receiving placebo (quarterly fremanezumab: LSM difference -3.1 [95% CI -3.8 to -2.4]; $p<0.0001$; monthly fremanezumab:

−3.4 [−4.0 to −2.7]; $p<0.0001$; figure 4; appendix p 9), as well as greater reductions from baseline in the monthly average number of days of use of migraine-specific acute headache medication (triptans and ergot compounds) with both fremanezumab regimens (both $p<0.0001$; appendix p 11). Participants receiving fremanezumab also had significantly greater reductions in the monthly average number of days with non-headache migraine symptoms (nausea or vomiting and photophobia and phonophobia) over 12 weeks than did those receiving placebo (all $p<0.0001$; appendix p 11).

As part of prespecified exploratory analyses, the primary efficacy outcome was evaluated in subgroups of participants who had previously not responded to topiramate, onabotulinumtoxinA, valproic acid, and valproic acid plus two to three classes of preventive medications (appendix p 12). Reductions in the monthly average number of migraine days were greater versus placebo in participants who had previously not responded to topiramate with quarterly fremanezumab (LSM difference −2.8 [95% CI −3.7 to −2.0]; $p<0.0001$) and monthly fremanezumab (−2.9 [−3.7 to −2.0]; $p<0.0001$). Across all other evaluated subgroups, reductions in the monthly average number of migraine days were also greater with both dosing regimens of fremanezumab versus placebo ($p=0.0086$ with quarterly fremanezumab and $p=0.0005$ with monthly fremanezumab; appendix p 12). The proportions of participants with a 50% or greater response who had previously not responded to valproic acid and two to three other classes of migraine preventive medications were also significantly greater for both dosing regimens of fremanezumab versus placebo ($p=0.0010$ with quarterly fremanezumab and $p=0.0012$ with monthly fremanezumab; appendix p 12).

All evaluated patient-reported outcomes improved with fremanezumab treatment versus placebo (appendix p 13). Reductions from baseline at 4 weeks after administration of the third dose of study drug in both HIT-6 and MIDAS disability scores were greater with both fremanezumab dosing regimens versus placebo ($p=0.0002$ for quarterly fremanezumab and $p<0.0001$ for monthly fremanezumab; appendix p 13). For both fremanezumab dosing regimens versus placebo, greater improvements from baseline at 4 weeks after administration of the third dose of study drug were reported in quality of life (based on the MSQOL; $p<0.0001$ for both dosing regimens) and health status (based on the EQ-5D; $p=0.0426$ for quarterly fremanezumab and $p=0.0002$ for monthly fremanezumab). Patient satisfaction (based on the PGIC) was also greater at 4 weeks after the third dose of study drug with both fremanezumab dosing regimens versus placebo ($p<0.0001$ for both dosing regimens). Significantly greater improvements with monthly fremanezumab versus placebo were reported for patient-reported depression status (based on the PHQ-9;

	Placebo (n=277)	Quarterly fremanezumab (n=276)	Monthly fremanezumab (n=285)
≥1 adverse event	134 (48%)	151 (55%)	129 (45%)
≥1 serious adverse event	4 (1%)	2 (<1%)	4 (1%)
≥1 treatment-related adverse event	55 (20%)	57 (21%)	55 (19%)
Adverse events leading to discontinuation	3 (1%)	1 (<1%)	4 (1%)
Adverse events			
Injection-site erythema	15 (5%)	19 (7%)	16 (6%)
Injection-site induration	12 (4%)	12 (4%)	13 (5%)
Injection-site pain	8 (3%)	11 (4%)	9 (3%)
Nasopharyngitis	11 (4%)	13 (5%)	7 (2%)
Fatigue	3 (1%)	9 (3%)	9 (3%)
Insomnia	2 (<1%)	6 (2%)	7 (2%)
Upper respiratory tract infection	3 (1%)	4 (1%)	9 (3%)
Diarrhoea	3 (1%)	7 (3%)	2 (<1%)
Dizziness	3 (1%)	5 (2%)	4 (1%)
Constipation	2 (<1%)	7 (3%)	1 (<1%)
Influenza	2 (<1%)	2 (<1%)	6 (2%)
Injection-site pruritus	3 (1%)	3 (1%)	5 (2%)
Back pain	5 (2%)	5 (2%)	2 (<1%)
Injection-site bruising	2 (<1%)	2 (<1%)	5 (2%)
Injection-site paraesthesia	3 (1%)	4 (1%)	3 (1%)
Increased weight	1 (<1%)	4 (1%)	3 (1%)
Upper abdominal pain	0	4 (1%)	2 (<1%)
Gastroenteritis	7 (3%)	3 (1%)	3 (1%)
Injection-site rash	2 (<1%)	3 (1%)	3 (1%)
Nausea	6 (2%)	4 (1%)	2 (<1%)
Urinary tract infection	5 (2%)	3 (1%)	3 (1%)
Anxiety	0	3 (1%)	2 (<1%)
INR increased	2 (<1%)	3 (1%)	2 (<1%)
Migraine	9 (3%)	2 (<1%)	3 (1%)
Neck pain	0	2 (<1%)	3 (1%)
Pain in extremity	3 (1%)	2 (<1%)	3 (1%)
Alopecia	2 (<1%)	2 (<1%)	2 (<1%)
Arthralgia	3 (1%)	2 (<1%)	2 (<1%)
Asthenia	3 (1%)	1 (<1%)	3 (1%)
Hypertension	2 (<1%)	3 (1%)	1 (<1%)
Injection-site warmth	0	1 (<1%)	3 (1%)
Rash	2 (<1%)	1 (<1%)	3 (1%)

Data are n (%). All adverse events occurring in four or more participants receiving active treatment. INR=international normalised ratio.

Table 2: Participants with adverse events during 12-week double-blind treatment period

$p=0.0037$) and work productivity and activity impairment (based on the WPAI; $p=0.0302$) scores.

Incidences of adverse events, serious adverse events, and adverse events leading to discontinuation were similar with both dosing regimens of fremanezumab compared with placebo (table 2). The most common adverse events across all groups were injection-site erythema, injection-site induration, and nasopharyngitis. No severe hypersensitivity reactions or cases of anaphylaxis were reported.

No deaths were reported. Serious adverse events were reported for four (1%) of 277 participants receiving placebo, two (<1%) of 276 receiving quarterly fremanezumab, and four (1%) of 285 receiving monthly fremanezumab. No individual serious adverse event occurred in more than one participant, and no serious adverse events were considered treatment related by investigators. In participants receiving placebo, serious adverse events were thoracic vertebral fracture, uterine leiomyoma, vulval cancer, hypoaesthesia, and metrorrhagia. In participants receiving fremanezumab (either dosing regimen), serious adverse events were atrial fibrillation, cholelithiasis, clavicle fracture, foot fracture, respiratory fume inhalation, rib fracture, road traffic accident, back pain, nephrolithiasis, and vocal cord thickening.

No individual adverse event led to discontinuation in more than one participant. Adverse events leading to discontinuation were reported for three (1%) participants in the placebo group, one (<1%) in the quarterly fremanezumab group, and four (1%) in the monthly fremanezumab group. In the placebo group, adverse events leading to study discontinuation were chest discomfort, injection-site pain, and vulval cancer. In the fremanezumab groups (either dosing regimen), adverse events leading to discontinuation were palpitations, fatigue, cholelithiasis, road traffic accidents, and temporal arteritis.

Individual cardiovascular or hepatobiliary adverse events were reported by no more than two (<1%) participants in any treatment group. Specific cardiovascular and hepatobiliary adverse events reported are summarised in the appendix (p 14). There were no occurrences of anaphylaxis or moderate or severe hypersensitivity and no significant findings in clinical laboratory, ECG, vital signs, or physical examination analysis (appendix p 15). Overall, no safety signals were identified in this study.

Discussion

Results of this study show that patients with difficult-to-treat episodic or chronic migraine, who previously did not respond to up to four pharmacological classes of migraine preventive medications, can still achieve clinically significant improvement with fremanezumab. Fremanezumab was more effective in preventing migraine than placebo across all primary and secondary outcomes and was well tolerated with a similar frequency of adverse events to placebo. Reductions from baseline in monthly days with migraine, moderate to severe headache, or use of acute headache medications were about 3·5 days (30 percentage points) greater with fremanezumab than with placebo. The odds of achieving a 50% or greater reduction in migraine days as early as 4 weeks after starting study treatment were approximately six times higher with fremanezumab than with placebo.

Participants treated with fremanezumab had greater reductions (3·1–3·8 days) in migraine days (from 9·4–17·1 days at baseline) across dosing and migraine classification subgroups than did those receiving placebo. This therapeutic gain (26–39 percentage points) was clinically meaningful and substantially larger than that seen in clinical studies of other migraine preventive medications.^{19–22,25,26} In a prespecified subgroup analysis among participants who had previously not responded to topiramate and up to three other classes of migraine preventive medications, the therapeutic gain for fremanezumab versus placebo was nearly three migraine days (20 percentage points). Topiramate has proven efficacy and is recommended in treatment guidelines for preventive treatment of migraine attacks; thus, topiramate is considered a standard of comparison for newer migraine treatments, including monoclonal antibodies targeting CGRP or the CGRP receptor.²⁴ The improvements in clinical symptoms of migraine with fremanezumab compared with placebo were accompanied by improvements in patient-reported disability, quality of life, health status, depression status, and work productivity and activity impairment.

In comparison with the only other randomised, placebo-controlled trial of difficult-to-treat migraine that we are aware of,²⁷ the FOCUS study has several strengths. The sample size was considerably larger (838 vs ≤246), and the study included not only patients with episodic migraine but also those with chronic migraine, thereby covering a range of headache frequencies that is more representative of clinical practice.^{6,28} Moreover, the inclusion criteria for previous failure of migraine preventive medications were stricter: study participants were required to have documented failure to up to four pharmacological classes of preventive medications, rather than relying on self-reporting failure of individual medications, which could belong to the same pharmacological class. Finally, the placebo response was remarkably low, which was probably related to the strict trial design and severity of the migraine population. Collectively, these attributes suggest that the FOCUS study population was even more difficult to treat than the study populations in two uncontrolled trials that assessed the efficacy of memantine or onabotulinumtoxinA in patients with difficult-to-treat migraine.^{29,30}

Fremanezumab was well tolerated. No safety signals were identified, and the frequency of adverse events and serious adverse events was similar to that of placebo. Less than 1% (five of 561) of patients in the fremanezumab group had an adverse event leading to discontinuation. This finding compares favourably with discontinuation rates related to adverse events in studies with topiramate^{25,26} and onabotulinumtoxinA. In clinical practice, next to poor efficacy, adverse events are a major reason for discontinuation of migraine preventive medications.^{9,11} Patients with major cardiovascular²⁴ and other major comorbid diseases were excluded from

participation in this study, thus limiting full extrapolation of the safety data to the general population. However, patients with cardiovascular risk factors—such as hypertension, diabetes, hyperlipidaemia, overweight, and concomitant use of hormonal birth control—were included. Overall, this study population is representative of the migraine population, which is generally healthy. Another limitation was the relatively short duration of double-blind treatment (12 weeks), precluding assessment of the long-term effects of fremanezumab. Such data are, however, available from the phase 3 (HALO) pivotal registration trials^{17,18} and will also become available from the 12-week open-label FOCUS extension study by June, 2020. Additionally, the average age of the current study population was 46 years, whereas migraine is most common among individuals aged 30–39 years.³¹ The older age of this population is in keeping with the selection criteria, which required failure of up to four previous migraine preventive treatments for enrolment in the current study; however, these patients might have more prolonged and refractory illness than the general population with migraine. The use of triptans or ergot derivatives to treat an established headache was included as a criterion for establishing the presence of episodic and chronic migraine during the baseline period; although this was considered a clinically relevant measure, it is not an ICHD-3 criterion for migraine²³ and might restrict comparability of these results. Finally, valproic acid was considered as a separate class of preventive medication, as it is generally considered as the last-line treatment for migraine prevention in many countries. Thus, patients not responding to topiramate and valproic acid were considered to have not responded to two classes of previous migraine preventive medications, even though these medications could be considered members of the same class (anticonvulsants) for epilepsy treatment.

In conclusion, quarterly and monthly doses of fremanezumab were rapidly effective and well tolerated in the prevention of migraine attacks in patients with particularly difficult-to-treat episodic and chronic migraine who had previously not responded to up to four pharmacological classes of migraine preventive medications. The therapeutic gain versus placebo was higher than in previous studies with fremanezumab^{17,18} or other migraine preventive medications,^{19–22,25–27} despite, or perhaps as a result of, the severity of the migraine study population.

Contributors

MDF contributed to development of the study design; data collection, data analysis, and data interpretation; and writing and critical revision of the manuscript. HCD contributed to data interpretation and providing critical input on the manuscript. XN led the development of the study design and protocol, served as study director to oversee the study conduct and data collection, and led data interpretation. MG served as a study co-lead and was involved in data interpretation. JMC was involved in all aspects of the study, including the study design, protocol preparation, study execution, data analysis, and writing and editing of the manuscript. RY contributed to development of the study design and data analysis. MM contributed to development of the study design,

data analysis, and reporting of study results. AHA contributed to oversight of study conduct, completion, and database lock; helped lead the initial interpretation of top-line data and construction of key conclusions; and had a role in drafting and editing the manuscript. YCS contributed to study execution, data collection, and monitoring. MG-W contributed to study execution and data collection and monitoring. LJ contributed to data analysis. MA was involved in interpretation of the data and providing critical input on the manuscript. All authors approved the final version of the manuscript for submission.

Declaration of interests

MDF, HCD, and MA were investigators on the FOCUS study, sponsored by Teva Pharmaceuticals. XN, MG, JMC, RY, MM, AHA, YCS, MG-W, and LJ are employees or shareholders, or both, of Teva Pharmaceuticals. In the past 3 years, HCD has received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from Alder, Allergan, Amgen, Autonomic Technology, Bristol-Myers Squibb, CoLucid, electroCore, Ipsen Parma, Lilly, Medtronic, MSD, Novartis, Pfizer, Schaper and Brümmer, Teva, and Weber & Weber. Financial support for HCD's research projects was provided by Allergan, electroCore, MSD, and Pfizer. HCD's headache research at the Department of Neurology in Essen is supported by the German Research Council, the German Ministry of Education and Research, and the European Union. HCD has no ownership interest and does not own stocks of any pharmaceutical company. HCD serves on the editorial boards of *Cephalalgia* and *The Lancet Neurology*. HCD chairs the Clinical Guidelines Committee of the German Society of Neurology and is member of the Clinical Trials Committee of the International Headache Society. MA has received personal fees from Alder BioPharmaceuticals, Allergan, Amgen, Eli Lilly, Novartis, and Teva. MA participated in clinical trials as the principal investigator for Alder, Amgen, electroCore, Novartis, and Teva trials. MA has no ownership interest and does not own stocks of any pharmaceutical company. MA serves as associate editor of *Cephalalgia*, co-editor of the *Journal of Headache and Pain*, and associate editor of *Headache*. MA is president-elect of the International Headache Society and general secretary of the European Headache Federation.

Data sharing

Qualified researchers can request access to patient-level data and related study documents, including the study protocol and the statistical analysis plan. Patient-level data will be de-identified and study documents will be redacted to protect the privacy of trial participants and to protect commercially confidential information. Please email USMedInfo@tevapharm.com to make your request. The protocol and statistical analysis plan will be available through ClinicalTrials.gov (NCT03308968) in September, 2019.

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