Fremanezumab for preventive treatment of migraine

Functional status on headache-free days

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Abstract

Objective

To evaluate the effect of fremanezumab on the functional status on headache-free days in phase 2 episodic migraine (EM) and chronic migraine (CM) studies.

Methods

Functional status data were collected prospectively via the electronic headache diary on all headache-free days by patients answering questions regarding work/school/household chore performance, speed of work completion, concentration, and feeling of fatigue. Individuals with EM receiving monthly doses of fremanezumab 225 mg (n = 96) or 675 mg (n = 97) or placebo (n = 104) were compared. Individuals with CM receiving fremanezumab 675 mg followed by monthly 225 mg (n = 88) and 900 mg (n = 86) were also independently compared to those receiving placebo (n = 89).

Results

In patients with EM, compared to patients receiving placebo, those receiving fremanezumab experienced an increased number of headache-free days with normal function in work/school/household chore performance and concentration/mental fatigue measures compared to their baseline over the entire treatment period (all $p < 0.005$). An increased number of headache-free days with normal functional performance for some measures was also found in the CM group in those treated with fremanezumab.

Conclusion

There was an increased number of headache-free days with normal functional performance on all measures for the patients with EM and some measures for patients with CM in the fremanezumab-treated groups. Further research is required to confirm these findings in a prospective study and to clarify the underlying mechanism(s).

ClinicalTrials.gov identifier:

NCT02025556 and NCT02021773.

Classification of evidence

This study provides Class II evidence that for patients with migraine, fremanezumab increases normal functional performance on headache-free days.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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Glossary

ANCOVA = analysis of covariance; **CGRP** = calcitonin gene-related peptide; **CM** = chronic migraine; **EM** = episodic migraine; **HFEM** = high-frequency episodic migraine; **MMRM** = mixed-effects model repeated measurement.

Episodic migraine (EM) affects 12% of the general population, and ≈1% of the general population experiences chronic migraine (CM), defined as headaches occurring on at least 15 d/mo, with at least 8 days of migraine per month.^{1–4} On the basis of disability associated with the headache attacks, migraine is ranked seventh highest among medical causes of disability worldwide.⁵

Headache-related disability may incompletely capture the burden of migraine because growing evidence suggests that the effect of migraine extends beyond the headache. In a recent large study⁶ investigating 2,959 patients with EM, 10.6% reported interictal anxiety, 14.8% reported avoidance and lifestyle compromise, and 26% reported interictal symptoms. Rather than the conventional view of migraine as an episodic or paroxysmal headache disorder with attacks that are divided into discrete phases in between which patients are symptom-free, migraine may be best conceptualized as a chronic neurologic disorder with persistent interparoxysmal physiologic compromise, exemplified by persistent symptoms punctuated by recurrent attacks of headache and other attack-related symptoms that may include overlapping phases of prodrome (commonly referred to as premonitory), aura, headache, and postdrome.^{7–9} Prodrome and postdrome symptoms are indeed common, affecting up to 80% of the migraine population.^{10–12} Accounting for phase-related and interictal nonheadache symptoms, in addition to the symptoms of frequent comorbid diseases, is important in fully describing the burden of migraine.

Fremanezumab, formerly known as TEV-48125, is a fully humanized immunoglobulin G2a monoclonal antibody that potently and selectively binds to calcitonin gene-related peptide (CGRP), thereby preventing its binding to receptors. Phase 2 and pivotal phase 3 trials assessing its efficacy and safety have been completed for EM and CM.^{13–17} In the trials, patients completed a daily headache calendar; in days that they did not experience headaches, patients answered questions focused on functional performance for the day. Here, we take advantage of the phase 2 fremanezumab trials to evaluate its effect on functional performance on headache-free days.

Primary research question

Do patients with migraine taking fremanezumab have improved functional performance on headache-free days? This study provides Class II evidence that for patients with migraine, fremanezumab increases headache-free days with normal functional performance.

Standard protocol approvals, registrations, and patient consents

The high-frequency EM (HFEM) and CM phase 2 studies were conducted in accordance with the Good Clinical Practice and the US Food and Drug Administration guidelines for safety monitoring and were registered at clinicaltrials.gov as NCT02025556 and NCT02021773. All patients provided written informed consent before enrolling in the study, and all protocols were approved by institutional review committees for each site. The studies were conducted from January 2014 to January 2015 at 62 sites in the United States, including headache centers, neurology clinics, and primary care facilities.

Study design and patients

The current study is a post hoc analysis of data from the phase 2 trials assessing fremanezumab in the preventive treatment of HFEM and CM.^{13,14} In each study, 2 doses of fremanezumab were administered as 4 subcutaneous injections once a month for 3 months: monthly 225 or 675 mg fremanezumab in the HFEM study and 675 mg (1 initial loading dose) followed by monthly 225 or 900 mg fremanezumab in the CM study.

Both studies evaluated patients 18 to 65 years of age. Eligible patients in the HFEM trial had HFEM, defined as 8 to 14 headache days per month, and were allowed to use 1 standard migraine preventive drug at stable doses for at least 3 months before study onset and acute migraine medications up to 14 d/mo (maximum of 4 days of opioids or barbiturates). Eligible patients in the CM trial met International Classification of Headache Disorders III beta criteria for CM (defined as >15 headache days per month and could even have daily headache).⁴ They were allowed to use 2 different migraine preventive drugs at stable doses for at least 3 months before study entry and were allowed to treat their acute migraine headaches as usual. In both studies, patients needed to have ≥80% compliance with the recording of daily headache information using the electronic headache diary during the 28-day run-in phase. Patients were excluded if they received onabotulinumtoxinA during the 6 months before study entry, used opioids or barbiturates for >4 days during the run-in phase, or failed ≥3 migraine preventive drugs in the past.

Randomization and masking

After meeting eligibility requirements in the 28-day run-in period, patients in the HFEM and CM trials were stratified on the basis of sex and preventive medication use, and then randomization (1:1:1) was done into either the placebo or

1 of the 2 active treatment arms via an electronic interactive web response system that was accessed by the study coordinators through the eClinical Operating System portal, a Code of Federal Regulations–compliant permissions-based system. The randomization schema was developed centrally by a dedicated staff at the contract research organization who had no further role in the study.

Study sites were asked to have 2 blinded study coordinators at each clinic visit, 1 for clinical assessment and 1 for treatment administration. Patients were masked to treatment allocation; they all received 4 injections at each 28-day treatment visit that were identical in packaging and appearance regardless of treatment group from blinded study coordinators.

Procedures

Daily information on the occurrence and nature of headaches was captured by the patient using the electronic diary. For each day, patients recorded data for the previous 24-hour period. The interactive web response system allowed 1 day of back-entering information and was locked thereafter. Headache information was recorded during the run-in phase and each of the three 28-day treatment periods.

Outcomes and analyses

For these post hoc analyses, headache-free days were defined as days in which a patient answered “no” to the question, “Did you experience a headache of any severity?” Functional performance data were collected prospectively via the electronic diary and were categorized into 1 of 2 categories: work/school/household chore performance and concentration/mental fatigue.

To assess performance at work, school, or home, patients were asked the following 2 questions and could answer by choosing normal, <50% impaired, or ≥50% impaired: (1) Best describe your work/school performance yesterday; and (2) best describe your ability to perform household chores. To assess concentration/mental fatigue, patients were asked the following 3 questions and could choose none of the time, some of the time, most of the time, or all of the time: (1) How much of the time did you feel that you were working more slowly or taking longer to complete tasks? (2) How much of the time yesterday did you find it difficult to concentrate on what you needed to do? (3) On average, how much of the time yesterday were you very tired, asleep, or feeling drained?

Using analyses of covariance (ANCOVAs) and a mixed-effects model repeated measurement (MMRM) analyses (SAS version 9.2, SAS Institute, Cary, NC), we analyzed the change from baseline in the mean number of days each possible response was given per survey question. ANCOVAs measured the change in the mean number of days for each possible response from baseline to the entire treatment period (weeks 1–12). The MMRM analyses evaluated the change in the mean number of days for each possible response from baseline to the end of each monthly treatment period. The

best possible responses indicating optimal status included being able to work/study normally, performing household chores normally, reporting no time working more slowly or taking longer to complete tasks, reporting no time with difficulty concentrating, and reporting no time feeling very tired, asleep, or feeling drained. All efficacy variables were analyzed by the modified intent-to-treat principle, which included all randomized participants who received at least 1 dose of study drug and provided at least 1 endpoint measurement. The ANCOVA model included treatment, sex, region, and baseline preventive medication use (yes/no) as fixed effects and baseline value and years since onset of migraine as covariates. The MMRM model included month and treatment-by-month interaction additionally. Because these were post hoc analyses, adjustments for multiple comparisons are not appropriate,¹⁸ and the results of the inference statistics should be considered exploratory in nature.

Data availability

The data for the post hoc analyses described in this report are available by request from the author investigators or Teva Pharmaceuticals Ltd, the company sponsoring the clinical development of fremanezumab for the treatment of migraine.

Results

Patient disposition

The HFEM and CM studies were conducted in parallel at the same sites, and a total of 1,170 patients were screened overall for both studies. For the HFEM study, 297 individuals met eligibility criteria and were randomized to receive placebo (n = 104) or fremanezumab 225 mg (n = 96) or 675 mg (n = 97). For the CM study, 264 patients with CM were randomized to receive placebo (n = 89) or fremanezumab 675/225 mg (n = 88) or 900 mg (n = 87). The demographic characteristics of both studies are presented in table 1. Patient disposition and reasons for withdrawal have been described previously.^{13,14}

Safety and efficacy

Detailed results of the HFEM and CM phase 2 studies are described elsewhere.^{13,14} In brief, fremanezumab was shown to have a favorable safety profile and to be well tolerated, with no serious safety signals or clinically relevant changes in vital signs, ECG parameters, or laboratory findings. There were no differences in the rate of treatment-emergent adverse events with fremanezumab compared with placebo, with the exception of mild injection-site pain and pruritus. The rate of injection-site pain for the placebo groups in the HFEM and CM studies was 6% and 3%, respectively, and for the fremanezumab groups was 6.8% and 8.0% respectively. The rate of pruritus was 0% for the placebo groups and 2% and 3.4% for the fremanezumab groups in the HFEM and CM study.

As previously described, fremanezumab significantly improved headache parameters such as the number of headache days and the number of migraine days for the duration of the

Table 1 Baseline demographic and disease characteristics of patients in the HFEM and CM studies

Characteristics ^a	HFEM study			CM study		
	Placebo (n = 104)	Fremanezumab		Placebo (n = 89)	Fremanezumab	
		225 mg (n = 96)	675 mg (n = 97)		675/225 mg (n = 88)	900 mg (n = 86)
Age, y	42.0 (11.6)	40.8 (12.4)	40.7 (12.6)	40.7 (11.5)	40.0 (11.6)	41.5 (12.9)
Body mass index kg/cm²	27.2 (5.2)	26.9 (5.2)	27.4 (5.1)	25.7 (4.5)	27.0 (5.2)	26.6 (5.3)
Sex n (%)						
Male	12 (12)	9 (9)	15 (15)	13 (15)	12 (14)	12 (14)
Female	92 (88)	87 (91)	82 (85)	76 (85)	76 (86)	75 (86)
Ethnic origin, n (%)						
White	85 (82)	74 (77)	74 (76)	76 (85.4)	70 (79.6)	73 (83.9)
Black/African American	13 (13)	19 (20)	18 (19)	9 (10.1)	12 (13.6)	9 (10.3)
Asian	2 (2)	1 (1)	1 (1)	1 (1.1)	0 (0)	0 (0)
Other	0	0	0	3 (3.4)	6 (6.8)	5 (5.8)
Hours of headaches of any severity per month	82.1 (49.3)	76.1 (36.7)	80.4 (36.6)	169.1 (13.9)	159.1 (9.7)	157.7 (11.7)
Headache days of any severity per month	12.4 (2.3)	12.6 (3.1)	12.5 (2.6)	16.5 (6.3)	16.5 (6.7)	15.9 (6.5)
Headache days of at least moderate severity per month	9.8 (2.7)	10.0 (3.1)	9.6 (2.9)	13.9 (5.6)	13.8 (6.3)	13.1 (5.9)
Days of acute medication use	10.4 (3.6)	10.4 (3.6)	9.8 (4.0)	15.7 (6.2)	15.1 (7.0)	16.2 (6.7)
Years of migraines, mean (SD)	21 (14.1)	18.9 (12.9)	16.9 (12.3)	20.4 (13.1)	15.8 (11.2)	18.8 (12.2)
Preventive medicine use, n (%)						
Yes	28 (27)	32 (34)	26 (27)	38 (42.7)	35 (39.7)	33 (37.9)
No	76 (73)	64 (66)	71 (73)	51 (57.3)	53 (60.2)	54 (62.1)

Abbreviations: CM = chronic migraine; HFEM = high-frequency episodic migraine.

^a Mean (SD) values are provided unless otherwise noted.

study and at early endpoints with significant efficacy compared with placebo after 1 week of treatment.^{16,17} In the HFEM study, the mean number of headache-free days at month 3 is 19.7 (SD 4.9) for the placebo group, 22.1 (SD 4.7) for fremanezumab 225 mg group, and 21.8 (SD 4.9) for the fremanezumab 675 mg group. For the CM study, the mean number of headache-free days at month 3 is 12.5 (SD 7.9) for placebo, 15.0 (SD 8.2) for fremanezumab 675/225 mg, and 15.7 (SD 8.2) for fremanezumab 900 mg.

Functional status

The results of the ANCOVA least square mean (standard error) post hoc analyses on the changes from baseline to the end of the treatment period for the responses to questions on functional status on headache-free days are shown in table 2. In the HFEM study group, we found differences between the fremanezumab groups and placebo group in the change from baseline to end of treatment in the number of headache-free days in which patients reported that they worked/studied normally and performed household chores normally (all $p < 0.005$). There were treatment differences in the number of

headache-free days in which patients reported no time working more slowly, no time with difficulty in concentrating, and no time feeling very tired, asleep, or feeling drained (all $p < 0.005$).

In the CM study, for those receiving the 900-mg dose, we found consistent differences compared to those receiving placebo in the number of headache-free days with responses indicating optimal status (worked/studied normally $p = 0.011$, performed household chores normally $p = 0.0007$, and reported no time working more slowly $p = 0.0076$, having difficulty concentrating $p = 0.0162$, or feeling very tired $p = 0.0322$). For the patients in the 675/225-mg dose group, there were differences compared to placebo in the number of headache-free days in which patients performed household chores normally ($p = 0.0465$) and reported having no time having difficulty concentrating ($p = 0.0284$). Although changes in the number of headache-free days in which patients reported having work/study and household chore performance impaired by $\geq 50\%$ or reported having difficulty in concentrating most of the time were minimum (i.e., <1 day for all groups), there were increases in the 675/225-mg group

Table 2 Changes in patient-reported measures from baseline to end of the 3-month treatment period on headache-free days for the 2 domains of functional performance

Change from baseline in number of headache-free days with:						
ANCOVA: LSM (SE) (minimum-maximum), <i>p</i> value, placebo vs fremanezumab dose	HFEM study			CM study		
	Placebo (n = 104)	Fremanezumab		Placebo (n = 89)	Fremanezumab	
		225 mg (n = 95)	675 mg (n = 96)		675/225 mg (n = 87)	900 mg (n = 85)
Change from baseline number of headache-free days at month 3	4.0 (0.47)	6.8 (0.50)	6.4 (0.52)	5.4 (0.69)	8.1 (0.78)	8.3 (0.74)
Work/study/chore performance						
Worked/studied normally	1.60 (0.72) (0.18 to 3.02)	4.76 (0.71) (3.37 to 6.14), <i>p</i> = 0.0002	4.34 (0.69) (2.99 to 5.70), <i>p</i> = 0.0012	3.48 (0.77) (1.97 to 5.00)	4.34 (0.85) (2.66 to 6.03), <i>p</i> = 0.3801	6.05 (0.84) (4.39 to 7.71), <i>p</i> = 0.0111
Work/studied impaired <50%	0.71 (0.43) (−0.14 to 1.57)	0.08 (0.42) (−0.76 to 0.91), <i>p</i> = 0.1942	0.37 (0.41) (−0.44 to 1.18), <i>p</i> = 0.4951	0.71 (0.40) (−0.07 to 1.50)	1.49 (0.44) (0.62 to 2.37), <i>p</i> = 0.1271	1.08 (0.44) (0.22 to 1.94), <i>p</i> = 0.4731
Work/studied impaired ≥50%	0.45 (0.16) (0.14 to 0.75)	0.20 (0.15) (−0.10 to 0.49), <i>p</i> = 0.1555	0.48 (0.15) (0.19 to 0.77), <i>p</i> = 0.8733	0.08 (0.13) (−0.17 to 0.32)	0.43 (0.14) (0.15 to 0.70), <i>p</i> = 0.0302	0.15 (0.14) (−0.12 to 0.43), <i>p</i> = 0.6241
Performed household chores normally	1.73 (0.67) (0.42 to 3.04)	4.98 (0.68) (3.65 to 6.32), <i>p</i> < 0.0001	4.54 (0.65) (3.26 to 5.83), <i>p</i> = 0.0003	3.22 (0.67) (1.90 to 4.54)	4.88 (0.69) (3.53 to 6.23), <i>p</i> = 0.0465	6.07 (0.69) (4.71 to 7.42), <i>p</i> = 0.0007
Ability to perform household chores was impaired by <50%	0.51 (0.39) (−0.27 to 1.29)	−0.21 (0.40) (−1.00 to 0.58), <i>p</i> = 0.1109	0.20 (0.37) (−0.56 to 0.96), <i>p</i> = 0.4878	1.13 (0.36) (0.43 to 1.84)	1.26 (0.36) (0.54 to 1.97), <i>p</i> = 0.7753	0.68 (0.37) (−0.03 to 1.40), <i>p</i> = 0.3058
Ability to perform household chores was impaired ≥50%	0.18 (0.12) (−0.06 to 0.42)	−0.04 (0.13) (−0.29 to 0.20), <i>p</i> = 0.1114	0.14 (0.12) (−0.10 to 0.38), <i>p</i> = 0.7658	−0.18 (0.11) (−0.40 to 0.05)	0.15 (0.12) (−0.08 to 0.39), <i>p</i> = 0.0211	0.20 (0.12) (−0.43 to 0.04), <i>p</i> = 0.8884
Could not perform household chores	0.03 (0.06) (−0.09 to 0.14)	0.07 (0.06) (−0.05 to 0.19), <i>p</i> = 0.5059	0.10 (0.06) (−0.02 to 0.22), <i>p</i> = 0.2769	0.10 (0.08) (−0.05 to 0.25)	0.22 (0.08) (0.06 to 0.37), <i>p</i> = 0.2075	0.00 (0.08) (−0.15 to 0.16), <i>p</i> = 0.30
Difficulty in concentration or mental fatigue						
No time working more slowly or taking longer to complete tasks	1.51 (0.71) (0.11 to 2.91)	5.33 (0.69) (3.96 to 6.70), <i>p</i> < 0.0001	5.34 (0.68) (4.01 to 6.67), <i>p</i> < 0.0001	3.39 (0.72) (1.98 to 4.80)	4.97 (0.79) (3.40 to 6.53), <i>p</i> = 0.0848	5.91 (0.79) (4.36 to 7.46), <i>p</i> = 0.0076
Some of the time working more slowly or taking longer to complete tasks	1.26 (0.49) (0.29 to 2.23)	−0.28 (0.48) (−1.23 to 0.67), <i>p</i> = 0.0062	−0.36 (0.47) (−1.30 to 0.54), <i>p</i> = 0.0043	0.99 (0.45) (0.10 to 1.88)	1.42 (0.49) (0.43 to 2.40), <i>p</i> = 0.4552	1.02 (0.49) (0.06 to 1.99), <i>p</i> = 0.954
Half of time or more working more slowly or taking longer to complete task	−0.01 (0.12) (−0.25 to 0.23)	−0.09 (0.12) (−0.32 to 0.15), <i>p</i> = 0.586	0.08 (0.12) (−0.15 to 0.31), <i>p</i> = 0.5094	0.01 (0.10) (−0.19 to 0.21)	0.08 (0.11) (−0.15 to 0.30), <i>p</i> = 0.6046	0.23 (0.11) (0.01 to 0.46), <i>p</i> = 0.0897

Continued

Table 2 Changes in patient-reported measures from baseline to end of the 3-month treatment period on headache-free days for the 2 domains of functional performance
(continued)

Change from baseline in number of headache-free days with:						
ANCOVA: LSM (SE) (minimum-maximum), <i>p</i> value, placebo vs fremanezumab dose	HFEM study			CM study		
	Placebo (n = 104)	Fremanezumab		Placebo (n = 89)	Fremanezumab	
		225 mg (n = 95)	675 mg (n = 96)		675/225 mg (n = 87)	900 mg (n = 85)
None of the time have difficulty concentrating	2.17 (0.67) (0.84 to 3.50)	5.53 (0.69) (4.17 to 6.89), <i>p</i> < 0.0001	5.12 (0.67) (3.80 to 6.43), <i>p</i> = 0.0002	3.40 (0.67) (2.08 to 4.72)	5.22 (0.68) (3.87 to 6.56), <i>p</i> = 0.0284	5.40 (0.69) (4.04 to 6.76), <i>p</i> = 0.0162
Some of the time have difficulty concentrating	0.18 (0.44) (−0.69 to 1.06)	−0.64 (0.46) (−1.54 to 0.25), <i>p</i> = 0.1058	−0.31 (0.44) (−1.17 to 0.56), <i>p</i> = 0.3367	1.02 (0.38) (0.26 to 1.77)	0.91 (0.39) (0.14 to 1.68), <i>p</i> = 0.8174	0.85 (0.39) (0.08 to 1.62), <i>p</i> = 0.7229
Most of the time have difficulty concentrating	0.12 (0.098) (−0.07 to 0.31)	−0.07 (0.10) (−0.27 to 0.12), <i>p</i> = 0.0892	−0.01 (0.097) (−0.20 to 0.18), <i>p</i> = 0.2645	−0.14 (0.11) (−0.35 to 0.07)	0.20 (0.11) (−0.01 to 0.42), <i>p</i> = 0.0109	0.01 (0.11) (−0.21 to 0.22), <i>p</i> = 0.2788
All of the time have difficulty concentrating	−0.00 (0.04) (−0.08 to 0.08)	0.03 (0.04) (−0.05 to 0.11), <i>p</i> = 0.5186	0.06 (0.04) (−0.01 to 0.14), <i>p</i> = 0.1728	−0.01 (0.07) (−0.15 to 0.13)	0.10 (0.07) (−0.05 to 0.24), <i>p</i> = 0.2207	1.1 (0.07) (−0.13 to 0.16), <i>p</i> = 0.8065
None of the time feeling very tired, asleep, or feeling drained	3.02 (0.72) (1.60 to 4.43)	6.19 (0.74) (4.74 to 7.64), <i>p</i> = 0.0001	5.95 (0.71) (4.52 to 7.32), <i>p</i> = 0.0005	3.59 (0.68) (2.24 to 4.93)	4.69 (0.69) (3.32 to 6.06), <i>p</i> = 0.1915	5.40 (0.70) (4.01 to 6.78), <i>p</i> = 0.0322
Some of the time feeling very tired, asleep, or feeling drained	−0.38 (0.54) (−1.44 to 0.69)	−0.99 (0.55) (−2.08 to 0.10), <i>p</i> = 0.3218	−0.68 (0.54) (−1.73 to 0.38), <i>p</i> = 0.6331	0.53 (0.44) (−0.34 to 1.40)	1.43 (0.45) (0.54 to 2.32), <i>p</i> = 0.1015	1.01 (0.45) (0.12 to 1.90), <i>p</i> = 0.3765
Most of the time feeling very tired, asleep, or feeling drained	−0.14 (0.15) (−0.44 to 0.15)	−0.48 (0.16) (−0.79 to −0.18), <i>p</i> = 0.0504	−0.44 (0.15) (−0.73 to −0.15), <i>p</i> = 0.0886	0.06 (0.18) (−0.31 to 0.42)	0.14 (0.19) (−0.23 to 0.51), <i>p</i> = 0.7238	−0.12 (0.19) (−0.49 to 0.26), <i>p</i> = 0.4475
All of the time feeling very tired, asleep, or feeling drained	0.01 (0.08) (−0.15 to 0.17)	0.11 (0.08) (−0.05 to 0.28), <i>p</i> = 0.2583	0.19 (0.08) (0.04 to 0.35), <i>p</i> = 0.0472	−0.04 (0.11) (−0.26 to 0.19)	0.06 (0.12) (−0.17 to 0.29), <i>p</i> = 0.4955	0.00 (0.12) (−0.23 to 0.24), <i>p</i> = 0.7569

Abbreviations: ANCOVA = analysis of covariance; CM = chronic migraine; HFEM = high-frequency episodic migraine; LSM = least square mean.

compared to the placebo group ($p = 0.0302$, $p = 0.0211$, and $p = 0.0109$, respectively; table 2).

Functional status during each monthly fremanezumab treatment period

The results of the MMRM analyses on the changes from baseline during each monthly treatment period for responses indicating optimal status are described below and illustrated in figures 1 and 2. The data for the full results for all possible responses are available in table 3.

As shown in figure 1, the change scores indicate that the number of headache-free days in which patients were able to perform work/study and household chores normally relative to their pretreatment baseline increased during each month of fremanezumab treatment. For the CM study, although there were increases in the number of headache-free days with work/study and household chores performed normally for both fremanezumab groups, there were only marginal effects shown for the 900-mg group.

Patients in the HFEM study in the 225- and 675-mg groups reported increased number of headache-free days compared

to placebo in which they were not working more slowly or reported no difficulty in concentrating, not feeling very tired, or not feeling drained during each treatment period (figure 2, all $p < 0.001$, except 675 mg at month 2, $p < 0.01$ for no difficulty in concentrating). For the CM study, there were increases in headache-free days in which patients reported no time with difficulty in concentrating and no time feeling very tired, asleep, or feeling drained during each of the 3 monthly treatment periods for the 900-mg dose (all $p < 0.05$ except for month 3 for no time working more slowly and no time feeling very tired).

Discussion

Patients taking fremanezumab in the HFEM and CM trials reported an increased number of headache-free days with normal functional performance compared to placebo within the domains of work or school, household work, and chores, as well as energy and ability to concentrate. In the HFEM trial, increases in headache-free days with normal functional performance with 225- and 675-mg doses of fremanezumab were seen. In the CM trial, increases in headache-free days with

Figure 1 Patient responses to questions concerning work/school/chores performance

(A) Work/school performance: I worked/studied normally. (B) Best describe your ability to perform household chores: I performed household chores normally. CM = chronic migraine; HFEM = high-frequency episodic migraine. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figure 2 Patient responses to questions on having difficulty in concentration and mental fatigue

(A) How much time did you feel that you were working more slowly or taking longer to complete a task? None of the time. (B) How much of the time yesterday did you find it difficult to concentrate on what you needed to do? None of the time. (C) On average, how much of the time yesterday were you very tired, asleep, or feeling drained? None of the time. CM = chronic migraine; HFEM = high-frequency episodic migraine. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

normal functional performance were seen mostly with the 900-mg dose of fremanezumab.

Because these findings come from post hoc analyses performed to examine functional status on headache-free days for patients treated with fremanezumab during the HFEM and CM phase 2 studies, the results should be considered exploratory. Further research is needed to confirm these preliminary findings and to understand the factors contributing to perceived functional status on headache-free days. Dissecting these factors will be critical to understanding the total

burden of migraine for patients and identifying how treatments like fremanezumab could potentially address some of them. One could postulate that patients had more headache-free days with normal functional performance simply because they had more headache-free days on fremanezumab. With increased headache-free days, patients may have had reduced interictal anxiety and thus reduced avoidance behavior and lifestyle compromise, allowing them to function normally. This is a testable hypothesis for future studies. Notably, we did not see a consistent increase in headache-free days when patients on active treatment reported lower levels of

Table 3 MMRM analyses results on functional performance measures

MMRM analyses: LSM (SE), <i>p</i> value, placebo vs fremanezumab dose	Change from baseline in number of headache-free days with:								
	HFEM study								
	Month 1			Month 2			Month 3		
	Placebo (n = 104)	225 mg (n = 95)	675 mg (n = 96)	Placebo (n = 104)	225 mg (n = 95)	675 mg (n = 96)	Placebo (n = 104)	225 mg (n = 95)	675 mg (n = 96)
Work/study/chore performance									
Worked/studied normally	0.82 (0.74)	4.21 (0.73), <i>p</i> = 0.0001	3.56 (0.71), <i>p</i> = 0.002	1.76 (0.85)	5.04 (0.84), <i>p</i> = 0.0019	4.16 (0.81), <i>p</i> = 0.0232	2.67 (0.83)	5.74 (0.83), <i>p</i> = 0.003	5.87 (0.80), <i>p</i> = 0.002
Worked/studied impaired <50%	0.77 (0.41)	−0.34 (0.40), <i>p</i> = 0.0189	0.18 (0.39), <i>p</i> = 0.2114	0.52 (0.51)	0.39 (0.50), <i>p</i> = 0.8326	0.45 (0.49), <i>p</i> = 0.9076	0.60 (0.53)	0.39 (0.54), <i>p</i> = 0.7534	0.28 (0.52), <i>p</i> = 0.6297
Worked/studied impaired ≥50%	0.46 (0.15)	0.24 (0.15), <i>p</i> = 0.2183	0.48 (0.15), <i>p</i> = 0.9182	0.56 (0.17)	0.10 (0.17), <i>p</i> = 0.0277	0.49 (0.16), <i>p</i> = 0.7346	0.28 (0.17)	0.26 (0.17), <i>p</i> = 0.9086	0.42 (0.17), <i>p</i> = 0.5076
Performed household chores normally	1.03 (0.68)	3.86 (0.69), <i>p</i> = 0.0004	3.65 (0.67), <i>p</i> = 0.001	1.75 (0.74)	5.52 (0.77), <i>p</i> < 0.0001	4.53 (0.74), <i>p</i> = 0.0024	2.77 (0.75)	6.45 (0.78), <i>p</i> < 0.0001	5.82 (0.75), <i>p</i> = 0.001
Ability to perform household chores impaired <50%	0.40 (0.37)	−0.19 (0.37), <i>p</i> = 0.1574	−0.15 (0.36), <i>p</i> = 0.1928	0.49 (0.44)	−0.35 (0.45), <i>p</i> = 0.1258	0.22 (0.44), <i>p</i> = 0.6205	0.19 (0.44)	−0.42 (0.46), <i>p</i> = 0.2717	0.26 (0.45), <i>p</i> = 0.9051
Ability to perform household chores impaired ≥50%	0.20 (0.12)	−0.11 (0.12), <i>p</i> = 0.0322	0.11 (0.12), <i>p</i> = 0.5331	0.16 (0.17)	−0.01 (0.18), <i>p</i> = 0.4377	0.27 (0.17), <i>p</i> = 0.6441	0.22 (0.15)	−0.06 (0.16), <i>p</i> = 0.1565	0.02 (0.16), <i>p</i> = 0.3115
Could not perform household chores	0.02 (0.06)	0.03 (0.07), <i>p</i> = 0.9505	0.09 (0.06), <i>p</i> = 0.3795	−0.02 (0.09)	0.00 (0.09), <i>p</i> = 0.8446	0.16 (0.09), <i>p</i> = 0.1245	−0.03 (0.08)	0.14 (0.08), <i>p</i> = 0.1213	0.03 (0.08), <i>p</i> = 0.6136
Difficulty in concentration or mental fatigue									
No time working more slowly or taking longer to complete tasks	0.79 (0.73)	4.29 (0.72), <i>p</i> < 0.0001	4.27 (0.70), <i>p</i> < 0.0001	1.63 (0.81)	5.86 (0.81), <i>p</i> < 0.0001	5.33 (0.78), <i>p</i> = 0.0003	2.48 (0.82)	6.74 (0.83), <i>p</i> < 0.0001	6.84 (0.79), <i>p</i> < 0.0001
Some of the time working more slowly or taking longer to complete tasks	1.22 (0.49)	−0.13 (0.49), <i>p</i> = 0.0202	−0.35 (0.47), <i>p</i> = 0.0076	1.09 (0.54)	−0.30 (0.54), <i>p</i> = 0.0343	−0.48 (0.52), <i>p</i> = 0.0178	1.09 (0.57)	−0.47 (0.57), <i>p</i> = 0.0275	−0.53 (0.55), <i>p</i> = 0.0217
Half of the time working more slowly or taking longer to complete tasks	0.03 (0.14)	−0.13 (0.14), <i>p</i> = 0.3685	0.07 (0.14), <i>p</i> = 0.79	0.03 (0.19)	−0.21 (0.19), <i>p</i> = 0.3267	0.28 (0.18), <i>p</i> = 0.3096	−0.12 (0.13)	0.09 (0.13), <i>p</i> = 0.1872	−0.05 (0.13), <i>p</i> = 0.6624
None of the time have difficulty concentrating	1.39 (0.66)	4.01 (0.68), <i>p</i> = 0.0008	4.27 (0.66), <i>p</i> = 0.0002	2.35 (0.75)	6.21 (0.77), <i>p</i> < 0.0001	5.07 (0.75), <i>p</i> = 0.0035	3.05 (0.76)	7.45 (0.79), <i>p</i> < 0.0001	6.30 (0.77), <i>p</i> = 0.0007
Some of the time have difficulty concentrating	0.18 (0.43)	−0.28 (0.44), <i>p</i> = 0.363	−0.72 (0.43), <i>p</i> = 0.0735	−0.04 (0.49)	−0.86 (0.51), <i>p</i> = 0.1811	−0.20 (0.495), <i>p</i> = 0.7932	−0.00 (0.51)	−1.34 (0.53), <i>p</i> = 0.0373	−0.18 (0.51), <i>p</i> = 0.778
Most of the time have difficulty concentrating	0.10 (0.09)	−0.05 (0.09), <i>p</i> = 0.1766	−0.00 (0.09), <i>p</i> = 0.3666	0.16 (0.13)	−0.09 (0.13), <i>p</i> = 0.151	0.04 (0.13), <i>p</i> = 0.4992	0.16 (0.13)	−0.06 (0.14), <i>p</i> = 0.222	−0.05 (0.14), <i>p</i> = 0.244

Continued

Table 3 MMRM analyses results on functional performance measures (*continued*)

MMRM analyses: LSM (SE), <i>p</i> value, placebo vs fremanezumab dose	Change from baseline in number of headache-free days with:								
	HFEM study								
	Month 1			Month 2			Month 3		
	Placebo (n = 104)	225 mg (n = 95)	675 mg (n = 96)	Placebo (n = 104)	225 mg (n = 95)	675 mg (n = 96)	Placebo (n = 104)	225 mg (n = 95)	675 mg (n = 96)
All of the time have difficulty concentrating	−0.01 (0.04)	−0.01 (0.04), <i>p</i> = 0.9421	0.03 (0.04), <i>p</i> = 0.45	−0.05 (0.09)	−0.04 (0.09), <i>p</i> = 0.9545	0.16 (0.09), <i>p</i> = 0.0985	−0.06 (0.04)	0.04 (0.04), <i>p</i> = 0.038	−0.02 (0.04), <i>p</i> = 0.3485
None of the time feeling very tired, asleep, or feeling drained	1.99 (0.70)	4.58 (0.72), <i>p</i> = 0.0016	4.37 (0.70), <i>p</i> = 0.0038	3.30 (0.79)	6.93 (0.82), <i>p</i> = 0.0003	6.41 (0.80), <i>p</i> = 0.0017	4.16 (0.79)	8.14 (0.83), <i>p</i> < 0.0001	7.55 (0.80), <i>p</i> = 0.0007
Some of the time feeling very tired, asleep, or feeling drained	−0.07 (0.50)	−0.63 (0.52), <i>p</i> = 0.3422	−0.45 (0.50), <i>p</i> = 0.5228	−0.81 (0.59)	−1.19 (0.61), <i>p</i> = 0.6063	−1.03 (0.59), <i>p</i> = 0.7634	−0.69 (0.60)	−1.60 (0.63), <i>p</i> = 0.229	−0.93 (0.61), <i>p</i> = 0.7473
Most of the time feeling very tired, asleep, or feeling drained	−0.21 (0.16)	−0.35 (0.17), <i>p</i> = 0.4909	−0.39 (0.16), <i>p</i> = 0.8151	−0.02 (0.18)	−0.53 (0.19), <i>p</i> = 0.0316	−0.42 (0.19), <i>p</i> = 0.0886	−0.26 (0.19)	−0.71 (0.20), <i>p</i> = 0.0671	−0.52 (0.19), <i>p</i> = 0.281
All of the time feeling very tired, asleep, or feeling drained	0.01 (0.08)	0.10 (0.08), <i>p</i> = 0.3749	0.21 (0.08), <i>p</i> = 0.0404	0.00 (0.10)	0.02 (0.11), <i>p</i> = 0.8756	0.27 (0.11), <i>p</i> = 0.0489	0.02 (0.12)	0.31 (0.12), <i>p</i> = 0.0672	0.11 (0.12), <i>p</i> = 0.5536
MMRM analyses: LSM (SE), <i>p</i> value, placebo vs fremanezumab dose	Change from baseline in number of headache-free days with:								
	CM study								
	Month 1			Month 2			Month 3		
	Placebo (n = 89)	675/225 mg (n = 87)	900 mg (n = 85)	Placebo (n = 89)	675/225 mg (n = 87)	900 mg (n = 85)	Placebo (n = 89)	675/225 mg (n = 87)	900 mg (n = 85)
Work/study/chore performance									
Worked/studied normally	2.83 (0.73)	3.64 (0.80), <i>p</i> = 0.3834	4.91 (0.81), <i>p</i> = 0.0306	3.98 (0.85)	4.20 (0.93), <i>p</i> = 0.8502	6.10 (0.94), <i>p</i> = 0.0671	3.74 (0.92)	4.61 (1.02), <i>p</i> = 0.4845	6.77 (1.02), <i>p</i> = 0.0181
Worked/studied impaired <50%	0.49 (0.38)	1.20 (0.42), <i>p</i> = 0.148	1.30 (0.43), <i>p</i> = 0.1063	0.61 (0.50)	2.13 (0.55), <i>p</i> = 0.0272	1.38 (0.56), <i>p</i> = 0.2653	1.37 (0.54)	1.96 (0.59), <i>p</i> = 0.4296	1.08 (0.59), <i>p</i> = 0.7044
Worked/studied impaired ≥50%	0.05 (0.11)	0.25 (0.12), <i>p</i> = 0.157	0.07 (0.12), <i>p</i> = 0.8472	−0.06 (0.12)	0.31 (0.13), <i>p</i> = 0.0197	0.12 (0.13), <i>p</i> = 0.2735	0.08 (0.17)	0.58 (0.19), <i>p</i> = 0.042	0.11 (0.19), <i>p</i> = 0.9105
Performed household chores normally	2.13 (0.64)	3.97 (0.65), <i>p</i> = 0.0209	5.31 (0.66), <i>p</i> < 0.0001	3.71 (0.74)	4.98 (0.75), <i>p</i> = 0.1793	6.32 (0.754), <i>p</i> = 0.0061	4.13 (0.823)	5.57 (0.84), <i>p</i> = 0.1875	6.71 (0.85), <i>p</i> = 0.0184
Ability to perform household chores impaired <50%	1.29 (0.36)	1.24 (0.37), <i>p</i> = 0.9095	0.51 (0.37), <i>p</i> = 0.0817	0.90 (0.43)	1.81 (0.44), <i>p</i> = 0.1038	0.92 (0.44), <i>p</i> = 0.9664	1.34 (0.48)	1.18 (0.49), <i>p</i> = 0.7939	0.79 (0.49), <i>p</i> = 0.3808
Ability to perform household chores impaired ≥50%	−0.28 (0.11)	−0.00 (0.12), <i>p</i> = 0.0506	−0.12 (0.12), <i>p</i> = 0.2519	−0.12 (0.13)	0.20 (0.13), <i>p</i> = 0.0721	−0.27 (0.14), <i>p</i> = 0.399	−0.06 (0.17)	0.15 (0.17), <i>p</i> = 0.3742	−0.26 (0.18), <i>p</i> = 0.3922

Continued

Table 3 MMRM analyses results on functional performance measures (*continued*)

MMRM analyses: LSM (SE), <i>p</i> value, placebo vs fremanezumab dose	Change from baseline in number of headache-free days with:								
	CM study								
	Month 1			Month 2			Month 3		
	Placebo (n = 89)	675/225 mg (n = 87)	900 mg (n = 85)	Placebo (n = 89)	675/225 mg (n = 87)	900 mg (n = 85)	Placebo (n = 89)	675/225 mg (n = 87)	900 mg (n = 85)
Could not perform household chores	0.16 (0.09)	0.08 (0.10), <i>p</i> = 0.477	−0.01 (0.10), <i>p</i> = 0.1498	0.01 (0.15)	0.36 (0.15), <i>p</i> = 0.0892	−0.07 (0.15), <i>p</i> = 0.6952	0.04 (0.12)	0.31 (0.13), <i>p</i> = 0.1105	0.05 (0.13), <i>p</i> = 0.9495
Difficulty in concentration or mental fatigue									
No time working more slowly or taking longer to complete tasks	2.68 (0.69)	4.13 (0.76), <i>p</i> = 0.0975	4.92 (0.76), <i>p</i> = 0.014	3.76 (0.80)	5.18 (0.88), <i>p</i> = 0.1822	6.48 (0.89), <i>p</i> = 0.0133	4.22 (0.86)	5.70 (0.95), <i>p</i> = 0.202	6.44 (0.95), <i>p</i> = 0.0621
Some of the time working more slowly or taking longer to complete tasks	0.80 (0.44)	1.13 (0.49), <i>p</i> = 0.553	1.21 (0.49), <i>p</i> = 0.4733	0.97 (0.52)	1.59 (0.57), <i>p</i> = 0.3779	0.75 (0.58), <i>p</i> = 0.7557	1.04 (0.55)	1.25 (0.61), <i>p</i> = 0.7848	1.24 (0.61), <i>p</i> = 0.8014
Half of the time working more slowly or taking longer to complete tasks	0.06 (0.11)	−0.04 (0.12), <i>p</i> = 0.4853	0.16 (0.12), <i>p</i> = 0.5506	−0.06 (0.10)	0.07 (0.11), <i>p</i> = 0.3455	0.27 (0.12), <i>p</i> = 0.0208	−0.00 (0.13)	0.23 (0.14), <i>p</i> = 0.1877	0.30 (0.14), <i>p</i> = 0.0989
No time with difficulty concentrating	2.52 (0.63)	4.20 (0.64), <i>p</i> = 0.0305	4.70 (0.65), <i>p</i> = 0.0052	3.91 (0.73)	5.55 (0.74), <i>p</i> = 0.0305	4.70 (0.65), <i>p</i> = 0.0052	4.21 (0.81)	6.07 (0.83), <i>p</i> = 0.0856	6.34 (0.84), <i>p</i> = 0.049
Some of the time have difficulty concentrating	1.00 (0.36)	0.86 (0.37), <i>p</i> = 0.7636	0.66 (0.37), <i>p</i> = 0.4478	0.79 (0.46)	1.28 (0.47), <i>p</i> = 0.4169	0.94 (0.47), <i>p</i> = 0.8042	1.35 (0.52)	0.70 (0.53), <i>p</i> = 0.3582	0.75 (0.53), <i>p</i> = 0.394
Most of the time have difficulty concentrating	−0.21 (0.11)	0.12 (0.12), <i>p</i> = 0.0267	0.01 (0.12), <i>p</i> = 0.1325	−0.14 (0.13)	0.23 (0.13), <i>p</i> = 0.0347	0.02 (0.13), <i>p</i> = 0.3565	−0.10 (0.13)	0.16 (0.13), <i>p</i> = 0.1205	−0.10 (0.13), <i>p</i> = 0.9994
All of the time have difficulty concentrating	0.05 (0.07)	0.02 (0.07), <i>p</i> = 0.777	0.02 (0.07), <i>p</i> = 0.6987	−0.03 (0.15)	0.25 (0.15), <i>p</i> = 0.1714	0.01 (0.15), <i>p</i> = 0.8761	0.03 (0.12)	0.24 (0.13), <i>p</i> = 0.2089	0.07 (0.13), <i>p</i> = 0.7893
No time feeling very tired, asleep, or feeling drained	2.84 (0.60)	3.43 (0.62), <i>p</i> = 0.4269	4.61 (0.62), <i>p</i> = 0.0179	4.00 (0.74)	5.09 (0.76), <i>p</i> = 0.2604	5.88 (0.76), <i>p</i> = 0.0528	4.61 (0.83)	5.75 (0.85), <i>p</i> = 0.3016	6.31 (0.85), <i>p</i> = 0.1226
Some of the time feeling very tired, asleep, or feeling drained	0.41 (0.44)	1.56 (0.45), <i>p</i> = 0.0355	0.98 (0.45), <i>p</i> = 0.2904	0.33 (0.54)	1.77 (0.55), <i>p</i> = 0.0423	1.01 (0.55), <i>p</i> = 0.3333	0.77 (0.57)	0.96 (0.59), <i>p</i> = 0.805	0.81 (0.59), <i>p</i> = 0.9629
Most of the time feeling very tired, asleep, or feeling drained	−0.06 (0.17)	0.13 (0.18), <i>p</i> = 0.3707	−0.05 (0.18), <i>p</i> = 0.9583	0.17 (0.22)	0.18 (0.22), <i>p</i> = 0.992	−0.12 (0.22), <i>p</i> = 0.3012	0.08 (0.21)	0.03 (0.22), <i>p</i> = 0.8635	−0.22 (0.22), <i>p</i> = 0.2717
All of the time feeling very tired, asleep, or feeling drained	0.07 (0.12)	−0.03 (0.13), <i>p</i> = 0.5428	−0.05 (0.13), <i>p</i> = 0.4612	−0.06 (0.18)	0.17 (0.18), <i>p</i> = 0.3291	0.00 (0.18), <i>p</i> = 0.7989	−0.07 (0.25)	0.38 (0.25), <i>p</i> = 0.1881	0.26 (0.25), <i>p</i> = 0.3404

Abbreviations: ANCOVA = analysis of covariance; CM = chronic migraine; HFEM = high-frequency episodic migraine; LSM = least square mean.

functional performance compared to placebo. This is an important observation because many preventive migraine therapies are known to have a variety of side effects (e.g., cognitive difficulties) that can contribute to interictal symptom burden and reduce medication adherence and persistence.^{19,20}

Acute medications for migraine management are often administered at the onset of headache but in a subset of patients may be taken on headache-free days as a form of anticipatory treatment, especially if prodromal symptoms are experienced, in an attempt to preempt the headache phase. In addition, patients may use an acute treatment in the absence of headache as an anxiety response out of fear of having a headache (cephalalgiphobia).^{21,22} With more headache-free days, patients may have reduced intake of acute treatments, resulting in reduction of any associated side effects that may contribute to impaired functional performance on headache-free days. Overall, patients taking fremanezumab significantly reduced their use of acute medication by 5 and 6.5 d/mo compared to the reduction of 3 and 4 d/mo for those taking placebo during the HFEM and CM studies.^{13,14} We do not know specifically whether the use of acute medications decreased on headache vs headache-free days. A future study should take into account a potential change in acute medications due to the use of a preventive treatment in evaluating functional performance.

Another possibility is that there is an effect on more than just the headache phase of the attack but also prodrome-, postdrome-, or interictal-phase symptoms on headache-free days. The prodrome phase of migraine is believed to be centrally mediated, likely at the level of the hypothalamus.²³ Although CGRP-monoclonal antibodies are not believed to cross the blood-brain barrier because their high molecular weight, it is possible that fremanezumab could directly affect central networks. One possibility is that fremanezumab may reduce CGRP-mediated transmission in the trigeminovascular system and that this reduction in peripheral afferent activity may modulate the central networks that generate the migraine attack.^{24,25} In a study examining saliva CGRP levels throughout migraine phases in patients with EM, a statistically significant increase of CGRP was found during the premonitory, mild headache, and moderate to severe headache phases compared to levels in the baseline and resolution phases.²⁶ Pretreatment interheadache CGRP levels in patients with CM have also been shown to be significantly higher in responders to onabotulinumtoxinA compared to nonresponders, and 1 month after treatment, CGRP decreased in responders but not in nonresponders.²⁷ Our patients were not surveyed for prodrome and postdrome symptoms, so a comparison between such symptoms and their reported functional status is not possible. It would be of interest for future studies to see whether fremanezumab has an effect on these symptoms and how this relates to its proposed mechanism of action and its effect overall on disease burden.

Another explanation is that modulation of CGRP affects comorbid conditions such as depression, anxiety, irritable

bowel syndrome, and other chronic pain disorders that were not assessed. Animal models have shown a role for CGRP in depression-like behaviors and in anxiety-related neural pathways.^{28–31} CGRP has been studied in a variety of pain syndromes, including fibromyalgia³² and visceral pain.³³ β -CGRP has also been reported as modulating the autonomic visceral control in the gut.³⁴ Future studies should evaluate the effect of CGRP-modulating therapies on the symptoms of associated comorbid diseases.

As with all clinical trials, a potential limitation of our study is that patients may have become unblinded during the study because of differences in the side effects between the active treatment and placebo treatment, which may have affected reporting. Given the low rate of reported adverse events that occurred in the HFEM and CM studies, it is very unlikely that any unblinding due to adverse event differences had a substantial effect on the results. Another limitation of our study includes the fact that our assessment of function was not based on standardized questionnaires such as the Headache Impact Test-6 or the Migraine-Specific Quality of Life Questionnaire. However, these measures ask about the last 4 weeks and do not distinguish ictal and interictal burden. We believe that reports from a daily diary asking about the last day provide a face-valid method of assessing self-reported function on a particular day. Daily diary measures are not subject to recall bias and are recommended as an additional measure to retrospective quality-of-life assessments.³⁵ Nonetheless, validation of these measures is needed. The clinical meaningfulness of the increased number of headache-free days with normal function was not evaluated; therefore, direct comparison to other types of health-related quality-of-life assessments in migraine is needed in future studies.^{36,37} However, recognizing that in headache clinical trials a difference of 1 headache day per month is clinically meaningful along with a 30% reduction headache frequency, we can surmise that our findings may be clinically meaningful.³⁸

The strength of this study is that it introduces a novel and potentially clinically meaningful endpoint that, if confirmed in future studies, facilitates the measurement of more comprehensive outcomes for patients and raises a host of questions about the mechanism of action of this class of biologics and the mechanism of disease in migraine.

Our study reports increased headache-free days with normal function for patients on fremanezumab treatment during the HFEM and CM studies. Further prospective research on the effect of CGRP monoclonal antibodies on headache-free days is warranted. Evaluating the effect of CGRP-modulating therapies on functional performance during headache-free days and on nonheadache symptoms may help provide insight into potential pathophysiologic mechanisms of migraine and may assist in determining the role of CGRP monoclonal antibodies such as fremanezumab in the pathophysiology of migraine and on the influence of CGRP and its blockade on migraine-related comorbid diseases.

Author contributions

J.V., D.W.D., R.B.L., P.S.L., Y.M., and M.E.B. designed the post hoc analyses and discussed the interpretation of the results. Y.M. created the statistical analysis plan, analyzed and interpreted data. J.V. and P.S.L. wrote the first draft of the manuscript. All authors participated in the writing and editing of the manuscript and approved its content.

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