Fremanezumab: a disease-specific option for the preventive treatment of migraine, including difficult-to-treat migraine

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Fremanezumab is a fully humanized monoclonal antibody (IgG2a) that targets calcitonin gene-related peptide (CGRP), a key neuropeptide involved in the pathophysiology of migraine. Fremanezumab is approved for quarterly and monthly subcutaneous dosing for the preventive treatment of migraine in adults. The phase 3 clinical development program for fremanezumab aimed to evaluate the efficacy of this preventive treatment across different patient populations, including those with difficult-to-treat migraine. Two pivotal 12-week, phase 3, placebo-controlled studies investigated quarterly and monthly dosing of fremanezumab in participants with chronic migraine (HALO CM) and episodic migraine (HALO EM). The efficacy of fremanezumab was further explored in individuals with difficult-to-treat chronic or episodic migraine in the 12-week FOCUS study, which enrolled participants who had previously experienced an inadequate response to 2–4 pharmacological classes of migraine preventive medications. The long-term efficacy of fremanezumab was assessed in a 12-month long-term study (HALO LTS), which enrolled participants completing the 12-week HALO studies and new participants. Across these studies, treatment with fremanezumab dosed quarterly or monthly provided significant reductions in the frequency of migraine days, headache days of at least moderate severity, and migraine- and headache-related disability compared with placebo. Sustained improvements were seen with long-term fremanezumab treatment. Subgroup analyses of participants with difficult-to-treat migraine (those with comorbid depression, overuse of acute headache medications, and concomitant use of other migraine preventive medications) demonstrated the effectiveness of quarterly or monthly fremanezumab in these populations. Ongoing studies are further exploring the potential benefits of fremanezumab in difficult-to-treat migraine and other headache and pain disorders.

Introduction

Migraine is a prevalent and disabling neurologic disease characterized by attacks of moderate to severe headache, often throbbing or unilateral, that are exacerbated by physical activity and accompanied by symptoms such as photophobia, phonophobia, nausea, and vomiting [1]. Migraine imposes a substantial burden on individuals’ daily activities, which rises with increasing frequency of headache [2]. For certain populations of patients with migraine, including those with comorbid psychiatric conditions or overuse of acute headache medications, the disease burden is especially marked, and successful treatment may be more difficult [3–5]. Episodic migraine (EM), the most common form of migraine, is generally defined by headache occurring <15 days per month, whereas chronic migraine (CM) is defined by headache occurring ≥15 days per month, with ≥8 days of migraine, probable migraine, or use of acute migraine-specific medication [6].
Preventive migraine treatment is recommended for patients who have frequent or disabling headaches, with the goals of reducing attack frequency, intensity, and duration; improving daily functioning; enhancing responsiveness to acute therapy; and preventing overuse of acute medications that can cause progression to CM [1,7]. Various classes of medications originally developed for other conditions have been used for migraine prevention, such as antiepileptic drugs, antidepressants, beta-blockers, calcium channel blockers, angiotensin II receptor antagonists, and onabotulinumtoxinA [1,7,8]. These previously standard preventive treatments often have multiple therapeutic targets, and their off-target actions may lead to undesirable side effects [9]. Although oral preventive therapies have generally been considered the first line, some patients may experience a limited response or adverse events, necessitating a change to a migraine preventive medication from a different class [1].

Advances in the understanding of migraine pathophysiology led to the development of the first disease-specific preventive migraine therapies that target the calcitonin gene-related peptide (CGRP) pathway [9]. CGRP is a potent vasodilator and neuropeptide in the trigeminal vascular system, aberrant activation of which is thought to be involved in the generation of pain and other migraine symptoms [10]. CGRP is released during migraine attacks and is inhibited after acute treatment with triptans; it triggers migraine attacks when infused systemically [8]. After the initial development of oral, small-molecule CGRP receptor antagonists was hampered by associated hepatotoxicity, an alternative approach of developing therapy with monoclonal antibodies (mAbs) targeting CGRP or its receptor proved successful [11]. As mAbs are too large to cross the blood-brain barrier, these drugs are believed to block the action of circulating CGRP on the trigeminal system [11]. Four mAbs, fremanezumab, erenumab, galcanezumab, and eptinezumab, were investigated in clinical trials for CM and EM and are approved for the preventive treatment of migraine in the United States and/or Europe [12–18]. All 4 of these CGRP pathway–targeted mAbs have effectively reduced the frequency of migraine days with a good tolerability profile [1,11,19,20].

Fremanezumab (AJOVY®; Teva Pharmaceuticals), a fully humanized mAb (IgG2Δa) [21], was the first approved mAb targeting the CGRP ligand, thereby preventing the peptide from acting on the CGRP receptor (Figure 1) [11,22]. Fremanezumab is the only CGRP pathway–targeted mAb approved for both quarterly and monthly subcutaneous dosing for the preventive treatment of migraine in adults [12,13]. Fremanezumab has a

![Figure 1. Fremanezumab](https://portlandpress.com/emergiplifesci/article-pdf/doi/10.1042/ETLS20200018/891533/etls-2020-0018c.pdf)

CGRP, calcitonin gene-related peptide.
long half-life (30 days) as well as prolonged absorption, which support the use of quarterly or monthly dosing [23]. Furthermore, a recent exposure-response analysis showed similar responses over time with both quarterly and monthly fremanezumab dosing [24]. In this article, we review the phase 3 clinical development of fremanezumab, highlighting key efficacy outcomes across different populations with migraine, including those with CM and EM, as well as different types of difficult-to-treat migraine.

**Fremanezumab phase 3 clinical trial program**

The efficacy of fremanezumab for the preventive treatment of migraine was evaluated in phase 3 trials in patient populations with different types of migraine and clinical challenges (Figure 2). All studies were performed in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. Study protocols were reviewed and approved by local independent ethics committees or institutional review boards [22–25]. Two pivotal phase 3 studies of fremanezumab enrolled participants with CM (HALO CM; ClinicalTrials.gov Identifier: NCT02621931) [25] or participants with EM (HALO EM; NCT02629861) [26]. Both were randomized, double-blind, placebo-controlled, parallel-group studies that included a screening visit, a 28-day pretreatment period, a 12-week double-blind treatment period, and a final assessment at Week 12. The enrollment process occurred simultaneously for both trials. Based on the information regarding headache frequency and symptoms collected in daily headache diary entries during the pretreatment period, participants were classified as having either CM or EM and randomized into the appropriate study. CM was defined as headache of any duration or severity on ≥15 days and headache meeting *International Classification of Headache Disorders, 3rd edition* (beta version; ICHD-3 beta) criteria [6] for migraine on ≥8 days. EM was defined as headache occurring on 6–14 days, with ≥4 days fulfilling ICHD-3 beta criteria for migraine. In both HALO studies, participants were randomized in a 1:1:1 ratio to receive subcutaneous injections of one of the following treatments, administered as 3 separate injections at baseline and 1 injection at Weeks 4 and 8 to maintain the blind: quarterly fremanezumab (675 mg at baseline and placebo at Weeks 4 and 8); monthly fremanezumab (HALO CM: 675 mg at baseline and 225 mg at Weeks 4 and 8; HALO EM: 225 mg at baseline and at Weeks 4 and 8); or placebo at baseline and at Weeks 4 and 8. A total of 1130 participants were enrolled in HALO CM and 875 in HALO EM [25,26].

**Figure 2. Fremanezumab phase 3 clinical trial program for migraine [25–28].**

DB, double-blind; CM, chronic migraine; EM, episodic migraine; HIT-6, 6-item Headache Impact Test; LTS, long-term study; MIDAS, Migraine Disability Assessment. *For HALO LTS, subgroups of participants with comorbid depression, acute medication overuse, and concomitant preventive medication use were also evaluated. †675-mg starting dose for CM. ‡Evaluated using scales specific to migraine- or headache-related disability: MIDAS and HIT-6.
On completion of the HALO CM and HALO EM studies, participants had the option to continue into a randomized, double-blind, parallel-group, phase 3 long-term study (HALO LTS; ClinicalTrials.gov Identifier: NCT02638103) [27]. New participants were also directly enrolled into the LTS. The HALO LTS included a screening visit and 28-day run-in period (new participants only) and a 12-month double-blind treatment period. A total of 1890 participants were enrolled in the LTS. Participants randomized to fremanezumab in HALO CM or HALO EM continued their same dosing, while those randomized to placebo and new participants were randomized (1:1 ratio) to the quarterly or monthly fremanezumab regimen for 12 months.

The efficacy of fremanezumab was further explored in individuals with difficult-to-treat EM or CM in the 12-week, phase 3 FOCUS study (ClinicalTrials.gov Identifier: NCT03308968) [28]. Eligible participants for this randomized, double-blind, placebo-controlled, parallel-group study had documented inadequate response to 2–4 of the following pharmacological classes of migraine preventive medications: beta-blockers, anticonvulsants, tricyclic antidepressants, calcium channel blockers, angiotensin II receptor antagonists, or onabotulinumtoxinA. Inadequate response was defined based on a lack of efficacy, per the physician’s clinical judgement, after 3 months of stably dosed treatment; poor tolerability leading to discontinuation; or contraindication or unsuitability. The 3-month period did not apply for drugs that were intolerable, contraindicated, or unsuitable. If onabotulinumtoxinA was one of the prior migraine preventive medications, ≥2 sets of injections and 3 months must have passed since the last set of injections prior to the screening visit. These inadequate responses were typically documented in the participant’s medical record. Participants were randomized in a 1 : 1 : 1 ratio to receive subcutaneous injections of quarterly or monthly fremanezumab or matched placebo, with the same dosing schedules for CM and EM as used in the HALO CM and HALO EM studies. The study enrolled a total of 838 participants [28].

Measures of efficacy across these studies included changes from pretreatment in the monthly average number of migraine days and headache days of at least moderate severity; proportions of participants achieving ≥50% reduction and ≥75% reduction from baseline (28-day run-in period) in the monthly average number of migraine days or headache days of at least moderate severity during the 12-week double-blind treatment period of the HALO EM, HALO CM, and FOCUS studies and during the 1-month period at Months 3, 6, and 12 during the HALO LTS; and changes in disability, as assessed using scales specific to migraine- or headache-associated disability (Migraine Disability Assessment [MIDAS] questionnaire and 6-item Headache Impact Test [HIT-6]) [25–28]. For the HALO LTS, subgroup analyses evaluated the long-term efficacy of fremanezumab, based on these and other relevant outcomes, in participants with difficult-to-treat migraine, including those with comorbid depression, medication overuse, and concomitant preventive medication use [29–32].

**Fremanezumab for preventive treatment of CM and EM: HALO CM and HALO EM**

For participants with CM or EM, treatment with quarterly or monthly fremanezumab provided a significant reduction in the average number of migraine days that participants experienced per month compared with placebo over the 12-week study period (Figure 3) [25,26]. Participants with CM reported an average of approximately 16 migraine days at baseline across treatment groups and experienced average reductions of 4.9 and 5.0 monthly migraine days with quarterly or monthly fremanezumab treatment, respectively, compared with 3.2 fewer days with placebo [25]. Participants with EM, who reported an average of approximately 9 migraine days at baseline across treatment groups, experienced 3.4 and 3.7 fewer monthly migraine days on average with quarterly or monthly fremanezumab treatment, respectively, compared with 2.2 fewer days with placebo [26]. In both studies, the significant difference in reductions in monthly migraine days with both fremanezumab dosing regimens compared with placebo was evident by Week 4 (P < 0.001 for all comparisons vs. placebo). Similarly, treatment with quarterly or monthly fremanezumab provided significant reductions in average monthly headache days of at least moderate severity compared with placebo in both the CM and EM studies (Figure 3) [25,33].

Significantly more participants who received fremanezumab also experienced clinically meaningful reductions of ≥50% in the monthly average number of headache days of at least moderate severity and migraine days during 12 weeks of double-blind treatment than did participants who received placebo in the HALO CM and HALO EM studies, respectively (P < 0.001 for all comparisons vs. placebo; Figure 3) [25,26]. With quarterly and monthly fremanezumab, 38% and 41% of participants, respectively, with CM experienced a ≥50% reduction in monthly headache days of at least moderate severity compared with 18% receiving placebo, while 44% and 48%, respectively, with EM experienced a ≥50% reduction in monthly migraine days compared with
Figure 3. Placebo-subtracted efficacy outcomes and response rates in the phase 3, double-blind, placebo-controlled studies.

(A) Placebo-subtracted efficacy outcomes for fremanezumab across populations during 12-week, double-blind, placebo-controlled, phase 3 studies [25,26,28]. (B) Percentage of participants with ≥50% reductions in headache days of moderate severity (HALO CM) or ≥50% reductions in migraine days (HALO EM and FOCUS). CM, chronic migraine; EM, episodic migraine; HIT-6, 6-item Headache Impact Test; MIDAS, Migraine Disability Assessment. *For migraine days and headache days of at least moderate severity, reductions are in monthly average days from baseline (28-day pretreatment period) during 12 weeks of double-blind treatment. For disability, reductions are in average scores from baseline during the 4-week period after the last dose. †Participants with CM or EM and inadequate response to 2–4 prior migraine preventive treatment classes.
28% receiving placebo. Likewise, the proportion of participants who experienced a reduction of ≥75% in monthly headache days of at least moderate severity was significantly greater with both fremanezumab dosing regimens compared with placebo in the HALO CM study (quarterly fremanezumab, 15%; monthly fremanezumab, 15%; placebo, 7%), as was the proportion of participants who experienced a reduction of ≥75% in monthly migraine days in the HALO EM study (quarterly fremanezumab, 18%; monthly fremanezumab, 19%; placebo, 10%; \( P < 0.01 \) for all comparisons vs. placebo) [33,34].

Improvements in headache- or migraine-related disability were seen with both quarterly and monthly fremanezumab dosing compared with placebo (Figure 3) [25,26]. In HALO CM, the degree of headache-related disability, as measured by HIT-6, decreased between baseline and the 4-week period after the final dose, with significantly greater reductions in HIT-6 scores with quarterly and monthly fremanezumab with placebo (\( P < 0.001 \) for both comparisons with placebo) [25]. Similarly, in HALO EM, the degree of migraine-related disability, as measured by MIDAS, showed significantly greater reductions with quarterly and monthly fremanezumab than with placebo (\( P = 0.002 \) and \( P < 0.001 \), respectively, vs. placebo) [26].

**Fremanezumab for the preventive treatment of difficult-to-treat CM and EM: FOCUS**

For individuals with CM or EM who had previously experienced an inadequate response to 2–4 classes of preventive migraine medications due to lack of efficacy, poor tolerability, or contraindication, quarterly or monthly fremanezumab provided a significant reduction in monthly migraine days compared with placebo (\( P < 0.0001 \) for all comparisons vs. placebo; Figure 3) [28]. During 12 weeks of treatment in the overall study population, which had a reported average of 14 migraine days per month at baseline, participants experienced 3.7 and 4.1 fewer migraine days on average per month with quarterly and monthly fremanezumab, respectively, compared with 0.6 fewer days on average per month with placebo. Significantly greater reductions in monthly migraine days were seen with both fremanezumab dosing regimens compared with placebo as early as 4 weeks after starting treatment (both \( P < 0.0001 \) vs. placebo). Similarly, during 12 weeks of treatment, average reductions in monthly headache days of at least moderate severity were greater with quarterly fremanezumab (3.9 days) and monthly fremanezumab (4.2 days) compared with placebo (–0.6 days, both \( P < 0.0001 \); Figure 3).

The proportions of participants with a ≥50% reduction in monthly migraine days over 12 weeks were higher with quarterly fremanezumab (34%) and monthly fremanezumab (34%) compared with placebo (9%, both \( P < 0.0001 \)). The proportions of participants with a ≥75% reduction in monthly migraine days over 12 weeks were also higher with quarterly fremanezumab (8%) and monthly fremanezumab (12%) compared with placebo (2%, \( P = 0.0021 \) and \( P < 0.0001 \), respectively) [28].

Improvements in both headache- and migraine-related disability were seen with both fremanezumab dosing regimens compared with placebo (Figure 3) [27]. Reductions from baseline at 4 weeks after administration of the third dose of the study drug in both HIT-6 and MIDAS scores were greater with both quarterly and monthly fremanezumab dosing versus placebo (\( P = 0.0002 \) and \( P < 0.0001 \), respectively).

**Fremanezumab for the long-term preventive treatment of CM and EM: HALO LTS**

Over 12 months of treatment, quarterly or monthly fremanezumab dosing provided sustained reductions in monthly migraine days and monthly headache days of at least moderate severity for participants with CM or EM [27]. A total of 21% of enrollees discontinued treatment during the 12-month period, most commonly due to participant withdrawal (8%), lack of efficacy (4%), side effects (4%), or lost to follow-up (3%). At Month 12, mean monthly migraine days were reduced by 7.2–8.0 days for participants with CM and 5.1–5.2 days for those with EM, compared with the study baseline (Figure 4). Mean monthly headache days of at least moderate severity were also reduced by 6.4–6.8 days in the CM group and 4.2–4.4 days in the EM group.

More than half of the group with CM and approximately two-thirds of those with EM had a ≥50% reduction in the monthly average number of migraine days from baseline to Month 12 [27]. By the end of the LTS, more than one-quarter of those with CM had a ≥75% reduction, and approximately 1 in 10 had complete alleviation of migraine days; in the EM group, more than one-third of participants had a ≥75% reduction, and approximately one-fifth achieved 100% reduction (Figure 5) [35]. Notably, responder rates at each threshold demonstrated gradual improvements over time, showing that greater percentages of participants were able to achieve significant reductions in migraine and headache days with longer treatment duration.
Figure 4. Mean change from baseline in monthly average migraine days over 12 months in participants with CM or EM in the overall HALO LTS population and subgroups with difficult-to-treat migraine [27,29–32].

CM, chronic migraine; EM, episodic migraine; LTS, long-term study.

| Participants (study) | Overall population | Comorbid depression | Acute medication overuse | Concomitant preventive medication use |
|----------------------|--------------------|---------------------|--------------------------|---------------------------------------|
| CM (HALO LTS)        | Quarterly: -7.2, Monthly: -8.0 | Quarterly: -7.2, Monthly: -8.6 | Quarterly: -7.5, Monthly: -7.0 | Quarterly: -6.8, Monthly: -6.8 |
|                      | n = 549, n = 554   | n = 82, n = 83      | n = 367, n = 292         | n = 100, n = 105                      |
| EM (HALO LTS)        | Quarterly: -5.2, Monthly: -5.1 |                      | Quarterly: -5.9, Monthly: -5.1 | Quarterly: -4.2, Monthly: -4.8 |
|                      | n = 393, n = 392   |                      | n = 58, n = 42           | n = 71, n = 75                       |

Figure 5. Percentage of participants experiencing ≥50%, ≥75%, and 100% (complete) reductions in mean monthly migraine days during 12 months of fremanezumab treatment in the HALO long-term study.

(A) CM (B) EM [27,35].

CM, chronic migraine; EM, episodic migraine; LTS, long-term study.
Over 12 months of treatment, the degree of headache- and migraine-related disability decreased for participants with CM and those with EM [27]. At baseline, participants with CM had mean HIT-6 scores reflective of ‘severe’ impairment from their headaches (64–65 points), which reduced to mean scores indicating ‘substantial’ impairment (approximately 56 points) at Month 12 [36,37]. Likewise, participants with EM had mean MIDAS scores at baseline that indicated ‘severe’ disability (38–39 points), which reduced to mean scores indicative of ‘moderate’ disability (approximately 11–12 points) at Month 12 [2,38].

## Efficacy in difficult-to-treat migraine in the LTS: comorbid depression, acute medication overuse, and concomitant preventive medication use

### CM and comorbid depression

At study baseline in the LTS, 21% (229/1103) of participants with CM were identified as having comorbid moderate to severe depression, based on a score of ≥10 [29] on the 9-item Patient Health Questionnaire (PHQ-9), which evaluates patient-reported severity of depressive symptoms [39]. Of these participants with comorbid depression, 51% and 55% in the quarterly and monthly fremanezumab dosing groups, respectively, had moderate depression; 36% and 35%, respectively, had moderately severe depression; and 12% and 10%, respectively, had severe depression. Compared with study baseline, 12 months of fremanezumab treatment reduced the monthly average number of migraine days by 7.2–8.6 days in these participants with comorbid depression (Figure 4). In addition, decreases from baseline of approximately 10 points in PHQ-9 score were observed over 12 months of fremanezumab treatment with both dosing regimens, indicating a substantial improvement in depressive symptoms for these participants with comorbid depression [29].

### Acute medication overuse

At study baseline, 54% (602/1110) of participants with CM and 13% (100/780) of those with EM had medication overuse, defined as nonspecific acute headache medication use on ≥15 days, migraine-specific acute medication use on ≥10 days, or use of combination medications for headache on ≥10 days over the 28-day pretreatment period [30]. At Month 12, reductions from baseline that were comparable to those observed in the overall population were seen in the monthly average number of migraine days in participants with CM or EM with acute medication overuse at baseline (Figure 4). Reductions in monthly migraine days were greater than or equal to reductions in participants without acute medication overuse at baseline [30]. Following quarterly and monthly fremanezumab treatment, respectively, approximately 60% or more of patients who were overusing acute medications at baseline reverted to no acute medication overuse at Month 6 (CM: 59% and 65%; EM: 85% and 61%), with reversion maintained through Month 12 (CM: 66% and 68%; EM: 86% and 77%) [30].

### Concomitant preventive medication use

At study baseline, 24% (270/1110) of participants with CM and 23% (181/780) of those with EM were using concomitant preventive medication. The most commonly used concomitant preventive medications were topiramate (37% in CM group and 24% in EM group), followed by amitriptyline (22% and 17% in CM and EM groups, respectively). At Month 12, sustained reductions from baseline were seen in the monthly average number of migraine days with both fremanezumab dosing regimens in participants with CM or EM and concomitant preventive medication use at baseline (Figure 4) [31,32].

## Ongoing studies

Three ongoing studies are investigating the efficacy of fremanezumab in difficult-to-treat pain and headache disorders. A phase 2, randomized, placebo-controlled study is evaluating the efficacy and safety of monthly dosing with fremanezumab in participants diagnosed with posttraumatic headache (i.e. headache resulting from traumatic injury to the head) (ClinicalTrials.gov Identifier: NCT03347188). Efficacy outcome measures include the number of monthly headache days of at least moderate severity and headache-related disability. This 12-week study is expected to complete in January 2021. Another phase 2, randomized, placebo-controlled study is investigating the effect of monthly dosing of fremanezumab in reducing pain for individuals with fibromyalgia (ClinicalTrials.gov Identifier: NCT03965091). Outcome measures include pain ratings, quality of life, sleep, fatigue, physical functioning, and mood. This 35-week study aims to enroll 240 individuals and is
expected to complete in August 2021. Following the positive results of the comorbid depression subgroup analysis of the HALO LTS, a 28-week, phase 4, randomized, placebo-controlled study is evaluating the efficacy of monthly fremanezumab in individuals with migraine and major depressive disorder (ClinicalTrials.gov Identifier: NCT04041284). The study comprises a 12-week double-blind phase followed by an open-label extension phase. Outcome measures include monthly migraine days, depression rating score, and migraine-specific quality of life. The study aims to enroll 340 individuals and is expected to complete in August 2021.

**Conclusion**

Across phase 3 studies involving participants with CM and EM, including those with types of difficult-to-treat migraine, fremanezumab dosed quarterly or monthly has demonstrated efficacy in reducing the frequency of migraine and headache days and reducing associated disability. Importantly, fremanezumab has proven efficacy in individuals with treatment-resistant migraine who had previously not responded to up to 4 pharmacological classes of migraine preventive medications. Increasing responder rates during long-term therapy suggest that individuals with migraine may expect to see an increased likelihood of greater treatment benefits with prolonged therapy. Results from subgroup analyses provide evidence that may help to inform clinical decision-making. For example, the efficacy shown in individuals with acute medication overuse suggests that it may not be necessary to discontinue overused medications prior to initiation of fremanezumab in order to achieve a significant improvement in migraine. In addition, the subgroup analysis involving participants using concomitant preventive medications demonstrated that fremanezumab can be added to an existing oral migraine preventive medication regimen and provide additional efficacy. The improvement in migraine days observed with fremanezumab treatment in participants with migraine and comorbid moderate to severe depression may translate into a reduced overall disease burden for these individuals. Although the efficacy and tolerability of fremanezumab has been demonstrated in different patient groups and over different durations of therapy in the phase 3 clinical trial program, additional research is needed to better understand the benefit in these individuals. For fremanezumab and the other approved CGRP pathway–targeted mAbs, there is currently a lack of direct comparative effectiveness data for these treatments relative to oral migraine preventive medications. Although subgroup analyses demonstrated the benefits of fremanezumab for patients with comorbid depression, the benefits of fremanezumab in patients with other common migraine comorbidities have not been evaluated. The subgroup analyses in patients with concomitant preventive medication use at baseline demonstrated the efficacy of fremanezumab in this population but did not examine the relative benefits in patients who continued using these preventive medications or stopped preventive medication use during fremanezumab treatment. It is hoped that forthcoming results from ongoing studies will further expand the understanding of the role of fremanezumab in the treatment of migraine and pain disorders.

**Summary**

- Migraine is a prevalent neurologic disease, and experts recommend preventive treatment in patients with frequent or disabling headache; while several classes of preventive drugs have been commonly used, prior to 2018, no agent targeted the underlying pathophysiology of migraine.

- Fremanezumab is a fully humanized monoclonal antibody (IgG2Δa) against calcitonin gene-related peptide (CGRP), a key neuropeptide involved in the pathogenesis of migraine; it is the only approved antibody against CGRP that can be administered by quarterly or monthly subcutaneous injection.

- In phase 3 studies, fremanezumab provided significant reduction in the frequency of migraine days, headache days of at least moderate severity, and migraine- and headache-related disability versus placebo in participants with chronic or episodic migraine; efficacy was sustained during long-term treatment.
Fremanezumab demonstrated efficacy in participants with migraine who had not responded to up to 4 previous classes of preventive medication and efficacy in subgroups of participants with migraine and comorbid depression, overuse of acute headache medications, and concomitant use of other preventive treatments that was sustained over long-term treatment.

Ongoing studies are further exploring the potential benefits of fremanezumab in difficult-to-treat migraine and other headache and pain disorders.

Competing Interests
D.I.F. serves as a consultant/advisory board member for Allergan, Amgen, Biohaven Pharmaceuticals, electroCore, Eli Lilly, Impel, Lundbeck (formerly Alder Biopharmaceuticals), Revance, Supernus, Teva Pharmaceuticals, Theranica, and Zosano. She receives grant support from Allergan, Autonomic Technologies, Inc., Eli Lilly, Merck, and Zosano. She has received compensation from MedLink Neurology and Medscape as a contributing author and from Neurology Reviews for service on the editorial board. J.M.C. is an employee of Teva Pharmaceuticals.

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Abbreviations
CGRP, calcitonin gene-related peptide; CM, chronic migraine; DB, double-blind; EM, episodic migraine; HIT-6, 6-item Headache Impact Test; ICHD-3 beta, International Classification of Headache Disorders, 3rd edition (beta version); LTS, long-term study; mAb, monoclonal antibody; MIDAS, Migraine Disability Assessment; PHQ-9, 9-item Patient Health Questionnaire.

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