Effects of fremanezumab in patients with chronic migraine and comorbid depression: Subgroup analysis of the randomized HALO CM study

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Abstract
Objective: To evaluate the efficacy of fremanezumab in patients with chronic migraine (CM) and moderate to severe depression.

Background: Fremanezumab, a fully humanized monoclonal antibody that selectively targets calcitonin gene–related peptide, has been approved for the preventive treatment of migraine in adults. CM and depression are highly comorbid.

Methods: The 12-week, Phase 3 HALO trial randomized patients with CM to fremanezumab quarterly (675 mg/placebo/placebo), fremanezumab monthly (675/225/225 mg), or placebo. Post hoc analyses evaluated the effects of fremanezumab in patients with moderate to severe depression (baseline 9-item Patient Health Questionnaire sum score ≥10) on monthly number of headache days of at least moderate severity; monthly migraine days; Patient Global Impression of Change (PGIC); 6-item Headache Impact Test (HIT-6) scores; and depression.

Results: For the 219/1121 (19.5%) patients with moderate to severe depression at baseline, fremanezumab was associated with a significant reduction in monthly number of headache days of at least moderate severity for active treatment versus placebo (least-squares mean change ± standard error for quarterly dosing: −5.3 ± 0.77; for monthly dosing: −5.5 ± 0.72; and for placebo: −2.2 ± 0.81; both p < 0.001). More patients achieved a ≥50% reduction in headache days of at least moderate severity with active treatment versus placebo (quarterly: 31/78 [39.7%]; monthly: 39/96 [40.6%]) than placebo (9/67 [13.4%]; both p < 0.001). Compared with placebo, fremanezumab improved PGIC and HIT-6 scores.

Conclusions: Fremanezumab demonstrated efficacy in the preventive treatment of CM and reduced headache impact in patients with comorbid depression.

Abbreviations: CBT, cognitive behavioral therapy; CI, confidence interval; CM, chronic migraine; EF, emotional function; EM, episodic migraine; FAS, full analysis set; HIT-6, 6-item Headache Impact Test; HRQoL, health-related quality of life; ICHD-3 beta, International Classification of Headache Disorders, third edition, beta version; IRB, institutional review board; LSM, least-squares mean; MSQv2, Migraine-specific Quality of Life Questionnaire, version 2.1; PGIC, Patient Global Impression of Change; PHQ-9, 9-item Patient Health Questionnaire; RFP, role function–preventive; RFR, role function–restrictive; SD, standard deviation; SE, standard error.

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INTRODUCTION

In population studies, comorbid depression is common in people with episodic migraine (EM) and even more common in chronic migraine (CM). In a clinic-based study, 86% of the CM population experienced some degree of depression and 59% experienced moderate to severe depression. Furthermore, in people with migraine, depressive symptoms predict increases in headache-related disability and decrements in health-related quality of life (HRQoL).

Antidepressants and behavioral treatments play a prominent role in the treatment of both migraine and depression but have rarely been studied in the treatment of patients with coexisting migraine and depression. Open-label studies suggest that onabotulinumtoxinA is effective in the treatment of patients with CM and depression. Additional studies are needed to assess the benefits of preventive treatment in people with CM and depression.

Fremanezumab, a fully humanized monoclonal antibody (IgG2Δα) that selectively targets calcitonin gene–related peptide, is approved in the United States and European Union for migraine prevention in adults. In the Phase 3 HALO CM trial, fremanezumab significantly reduced both the number of headache days of at least moderate severity and the number of migraine days in patients with CM. This post hoc analysis of HALO CM data evaluated the effect of fremanezumab in the subgroup of patients with CM and comorbid moderate to severe depression based on the reduction of headache and migraine days, as well as changes in depression and other patient-reported outcomes. We hypothesized that fremanezumab would be effective as a preventive treatment for migraine in patients with CM and comorbid moderate to severe depression.

METHODS

Standard protocol approvals, registrations, and patient consent

This trial was conducted in accordance with the study protocol (ClinicalTrials.gov Identifier: NCT02621931, https://clinicaltrials.gov/ct2/show/NCT02621931), the International Conference for Harmonisation guidelines for Good Clinical Practice, the Declaration of Helsinki, and relevant national and local regulations. The protocol was approved by relevant ethics committees and institutional review boards (IRBs). The central US IRB was the Quorum Review IRB (1501 Fourth Avenue, Suite 800, Seattle, WA, 98101), which approved the study protocol, investigator’s brochure, and informed consent documents. Written informed consent was obtained from each patient before any study procedures or assessments were performed.

Patient and public involvement

Patients and the public were not involved in the co-production of this clinical trial.

Study design and patients

The study design and patient selection criteria for HALO CM have been described previously. In brief, this was a randomized, double-blind, placebo-controlled, parallel-group, Phase 3 trial comprising a screening visit, a 28-day pretreatment period, and a 12-week treatment period, with final evaluation at Week 12 (Figure 1). The study protocol allowed for a subset of patients (≤30% of total) using a stable dosage of 1 migraine preventive medication for ≥2 months before the pretreatment period to continue this medication during the trial. Please see the previously published manuscript (and supplementary appendix) reporting the primary study outcomes for additional details regarding trial design and randomization.

Adults (18–70 years old) with prospectively confirmed CM (i.e., headache on ≥15 days and ≥8 days meeting the International Classification of Headache Disorders, Third Edition, Beta Version [ICHD-3 beta] criteria for migraine) during the 28-day pretreatment period and a history of migraine (according to ICHD-3 beta criteria) for ≥12 months were eligible to participate in the study. Patients were excluded from study participation if they had used onabotulinumtoxinA during the 4 months prior to screening, had received treatment with migraine interventions or devices such as nerve blocks or transcranial magnetic stimulation at any time during the 2 months before screening, used an opioid or barbiturate on >4 days during the 28-day pretreatment period, had a history of clinically significant psychiatric issues (including suicide attempt in the past or suicidal ideation in the past 2 years), or had previously not responded to two out of four groups of traditional migraine-preventive agents, as described in the study protocol.

While there was no cutoff for eligibility based on the baseline 9-item Patient Health Questionnaire (PHQ-9) score (described below), the post hoc analyses described here were conducted based on these baseline scores: in a subgroup of patients with moderate to severe depression (PHQ-9 scores ≥10, described in detail below), as well as in a subgroup of patients with no, minimal, or mild depression (PHQ-9 scores <10).
Treatment and evaluation

Following the pretreatment period, patients were randomized 1:1:1 to subcutaneous fremanezumab quarterly or monthly, or placebo.\textsuperscript{19} Patients in the fremanezumab quarterly group received fremanezumab 675 mg at baseline and placebo at Weeks 4 and 8; those in the fremanezumab monthly group received fremanezumab 675 mg at baseline and fremanezumab 225 mg at Weeks 4 and 8; patients in the placebo group received volume-matched placebo injections at baseline and at Weeks 4 and 8.\textsuperscript{19} Headache/migraine data, including occurrence, duration, peak headache pain severity, and migraine symptoms, were captured using an electronic diary device.\textsuperscript{19}

Outcomes

Post hoc analyses of data collected in the clinical trial as primary and secondary outcomes were conducted in patient subgroups based on PHQ-9 scores. Mean changes from baseline (i.e., the 28-day pretreatment period) in the monthly average number of headache days of at least moderate severity (described below), monthly average number of migraine days, and monthly average number of days of acute headache medication use during the 12-week treatment period were evaluated.\textsuperscript{29} Other outcomes evaluated included the proportion of patients achieving \( \geq 50\% \) reduction in the monthly average number of headache days of at least moderate severity and mean change from baseline (Day 0) in the 6-item Headache Impact Test (HIT-6) at 4 weeks after the last dose of study drug.\textsuperscript{19,20} A headache day of at least moderate severity was defined as a calendar day with \( \geq 4 \) consecutive hours of headache pain and peak severity of at least a moderate level or a day when acute migraine-specific medication (triptans or ergots) was used to treat a headache of any severity or duration.\textsuperscript{19}

Depression was evaluated with the PHQ-9, a validated screening and diagnostic tool designed to detect major depressive disorder based on the Diagnostic and Statistical Manual for Mental Disorders, fourth edition criteria.\textsuperscript{21–23} For the PHQ-9, each of the items is scored on a scale of 0 (“not at all”), 1 (“several days”), 2 (“more than half the days”), and 3 (“nearly every day”) based on the frequency of symptoms during the past 2 weeks. If the score of the first 2 questions of the PHQ-9 was \( \geq 3 \), patients completed questions 3 through 9. Scores were assessed at baseline (Day 0) and at the end of the study providing a depression severity total score from 0 to 27 (categorized into: 0–4 for no or minimal depression, 5–9 for mild depression, 10–14 for moderate depression, 15–19 for moderately severe depression, and 20–27 for severe depression).\textsuperscript{23} PHQ-9 scores were recorded at baseline and 12 weeks.

HRQoL was assessed using the Migraine-Specific Quality of Life Questionnaire, version 2.1 (MSQv.2), a 14-item tool that measures the impact of migraine across three domains over the previous 4 weeks.\textsuperscript{24,25} The three MSQoL domains are role function–restrictive (RFR; seven questions about limitations on daily activities), role function–preventive (RFP; four questions about prevention of daily activities), and emotional function (EF; three questions on emotions associated with migraine). Each domain is scored from 0 to 100, with higher scores indicating better HRQoL. Mean changes from baseline in scores for all three MSQv.2 domains were analyzed at all visits (Weeks 4, 8, and end of the study) comparing fremanezumab quarterly, fremanezumab monthly, and placebo in the moderate to severe depression subgroup of patients with CM.

Patient-reported change in overall health status since the beginning of treatment was also analyzed categorically based on the Patient Global Impression of Change (PGIC) scale. The PGIC is a 7-point single-item scale with scores ranging from 1 (no change) to 7 (a great deal better).

Statistical analyses

A total of 1020 participants were planned for randomization to allow for a discontinuation rate of 15\%. On the basis of a previous Phase 2b trial of fremanezumab in CM,\textsuperscript{26} 867 evaluable patients were required to detect with 90\% power a mean (standard deviation [SD]) difference of 1.7 \( \pm 6.3 \) in the monthly average number of headache days.
days between the fremanezumab monthly and placebo groups at a two-sided alpha level of 0.05. Post hoc analyses of these efficacy outcomes were conducted in a subgroup of patients in the full analysis set (FAS), which included all randomized patients who had received ≥1 dose of study drug and had ≥10 days of post-baseline efficacy assessments on the primary endpoint. The mean change from baseline in PHQ-9 scores during the 12-week treatment period was analyzed in the subgroup comprised patients who had moderate to severe depression (i.e., a score ≥10 on the PHQ-9) at baseline. Additional post hoc analyses were performed to evaluate outcomes in patients with no, minimal, or mild depression (i.e., a score <10 on the PHQ-9).

Continuous variables were summarized using descriptive statistics (mean, SD, and standard error [SE]) and categorical variables were summarized as counts and percentages. Analysis of covariance was performed for continuous data, with treatment, sex, country, and baseline preventive medication use as fixed effects, and baseline value and years since migraine onset as covariates. Ninety-five percent confidence intervals (95% CIs) were calculated for the least-squares mean (LSM) differences among the fremanezumab quarterly, fremanezumab monthly, and placebo groups. In the HALO CM study, the normality assumption was checked using visual inspections of QQ plots and histograms, as well as the Shapiro–Wilk test for all efficacy endpoints based on the assumption. Where the validity of the assumption was suspected, a nonparametric method was used as a sensitivity analysis. As expected from the large-sample normal approximation theory, the results from the sensitivity analyses and the primary analyses were consistent, demonstrating the robustness of study results using the normality assumption or normal approximation theory. Therefore, for these post hoc analyses, we only conducted analyses and reported study results based on the normality assumption. All data points were analyzed as the primary analyses and statistical significance was defined as \( p < 0.05 \).

Treatment–subgroup interactions were assessed using an analysis of covariance model for the main outcome of interest (headache days of at least moderate severity). In this analysis, region, sex, baseline preventive medication use, treatment, baseline PHQ-9 score category (<10 and ≥10), and treatment by baseline PHQ-9 score category were factors and baseline headache days of at least moderate severity and time from migraine onset were covariates.

Statistical analyses were generated using SAS software version 9.4 (SAS Institute Inc.).

## RESULTS

### Patients

In total, 1130 patients with CM were randomized to receive fremanezumab quarterly (\( n = 376 \)), fremanezumab monthly (\( n = 379 \)), or placebo (\( n = 375 \)). Baseline demographics and clinical characteristics in the intention-to-treat population were similar among all treatment groups stratified by PHQ-9 scores (Tables 1 and 2). The FAS comprised 1121 patients: fremanezumab quarterly and fremanezumab monthly, 375 each; placebo, 371. In the fremanezumab quarterly group, 275/375 (73.3%) patients had PHQ-9 scores of 0–4, 19/375 (5.1%) had scores of 5–9, 47/375 (12.5%) had scores of 10–14, 27/375 (7.2%) had scores of 15–19, and 4/375 (1.1%) had scores >19. In the fremanezumab monthly group, 259/375 (69.1%) patients had PHQ-9 scores in the 0–4 range, 18/375 (4.8%) had scores of 5–9, 50/375 (13.3%) had scores of 10–14, 38/375 (10.1%) had scores of 15–19, and 8/375 (2.1%) had scores >19. In the placebo group, 294/371 (79.2%) patients had scores in the 0–4 range, 9/371 (2.4%) had scores of 5–9, 33/371 (8.9%) had scores of 10–14, 24/371 (6.5%) had scores of 15–19, and 10/371 (2.7%) had scores >19. Post hoc analyses in patients with moderate to severe depression at baseline were performed in a subgroup of 241 patients (fremanezumab quarterly, \( n = 78 \); fremanezumab monthly, \( n = 96 \); placebo, \( n = 67 \)). Additional post hoc analyses were performed in a subgroup of 874 patients with no, minimal, or mild depression at baseline (fremanezumab quarterly, \( n = 294 \); fremanezumab monthly, \( n = 277 \); placebo, \( n = 303 \)). Six patients (fremanezumab quarterly, \( n = 3 \)); fremanezumab quarterly, \( n = 2 \); placebo, \( n = 1 \) did not have PHQ-9 scores and were excluded from these post hoc analyses. There were no significant differences between treatment arms in baseline demographics and clinical characteristics for patients with no, minimal, or mild depression and those with moderate to severe depression (Tables 1 and 2).

### Post hoc analyses in the moderate to severe depression (PHQ-9 score ≥10) subgroup

During the 12-week treatment period, patients in the moderate to severe depression subgroup experienced significant reductions from baseline in the monthly average number of headache days of at least moderate severity in both the fremanezumab quarterly group (LSM ± SE, −5.3 ± 0.77 days) and fremanezumab monthly group (−5.5 ± 0.72 days) compared with those receiving placebo (−2.2 ± 0.81 days; both comparisons \( p < 0.001 \); Figure 2A). Significant treatment effects were observed as early as Week 4: all patients treated with fremanezumab (both groups only having received the first dose of 675 mg) experienced a reduction from baseline of 5.3 ± 0.68 days compared with 1.0 ± 0.87 days in the placebo group (\( p = 0.001 \)). Significantly greater proportions of patients achieved ≥50% reduction in monthly headache days of at least moderate severity with fremanezumab quarterly (31/78 [39.7%]) and fremanezumab monthly (39/96 [40.6%]) as compared with placebo (9/67 [13.4%]; both comparisons, \( p < 0.001 \)) over the 12-week treatment period (Figure 2B).

Similarly, patients in both fremanezumab groups experienced a significant reduction from baseline in monthly average migraine days (quarterly: −5.4 ± 0.86 days, \( p = 0.002 \) vs. placebo; monthly: −5.5 ± 0.81 days, \( p < 0.001 \)) compared with those in the placebo group (−2.4 ± 0.90 days; Figure 2C). Again, significant changes were observed within the first 4 weeks of treatment (\( p < 0.001 \)).
The proportion of patients who achieved ≥50% reduction in monthly migraine days was higher with fremanezumab quarterly (22/78 [28.2%]; \( p = 0.031 \) vs. placebo) and monthly (32/96 [33.3%]; \( p = 0.004 \) vs. placebo) treatment than with placebo (9/67 [13.4%]) during the 12-week treatment period (Figure 2D). However, the moderate to severe depression subgroup demonstrated reductions in mean PHQ-9 scores from baseline to Week 12 with fremanezumab quarterly (–10.9 ± 1.01 points; reduction of 77.3%) or monthly (–9.8 ± 0.93 points; reduction of 66.4%), though differences were not significant compared with placebo (–9.2 ± 1.03 points).

### Table 1: Baseline demographics and disease history of patients with no, minimal, or mild depression (PHQ-9 score <10) and moderate to severe depression (PHQ-9 score ≥10) at baseline, according to treatment group (N = 1115)

| Characteristic                  | Fremanezumab |            | Monthly | Placebo |            |
|--------------------------------|--------------|------------|---------|---------|------------|
|                                | PHQ-9 <10    | PHQ-9 ≥10  | PHQ-9 <10 | PHQ-9 ≥10 | PHQ-9 <10 | PHQ-9 ≥10 |
|                                | (n = 294)    | (n = 78)   | (n = 277) | (n = 96) | (n = 303) | (n = 67)  |
| Age, mean ± SD, years          | 42.0 ± 12.5  | 41.7 ± 11.2 | 39.7 ± 11.9 | 43.4 ± 11.9 | 41.1 ± 12.0 | 42.9 ± 12.1 |
| BMI, mean ± SD, kg/m²           | 26.5 ± 5.1   | 26.9 ± 6.4  | 26.4 ± 5.2  | 26.9 ± 5.0  | 26.3 ± 5.0  | 27.0 ± 5.5  |
| Female sex, n (%)               | 256 (87)     | 71 (91)     | 238 (86)   | 87 (91)    | 265 (87)    | 60 (90)    |

### Disease history

| Characteristic                  | Fremanezumab |            | Monthly | Placebo |            |
|                                | PHQ-9 <10    | PHQ-9 ≥10  | PHQ-9 <10 | PHQ-9 ≥10 | PHQ-9 <10 | PHQ-9 ≥10 |
|                                | (n = 294)    | (n = 78)   | (n = 277) | (n = 96) | (n = 303) | (n = 67)  |
| Years since initial migraine diagnosis, mean ± SD | 19.9 ± 12.7  | 18.7 ± 12.9 | 19.7 ± 11.9 | 21.2 ± 12.3 | 20.0 ± 13.0 | 20.4 ± 12.6 |
| Current preventive medication use, n (%) | 59 (20)      | 18 (23)     | 58 (21)    | 26 (27)     | 66 (22)     | 11 (16)    |
| Current acute headache medication use, n (%) | 282 (96)     | 73 (94)     | 260 (94)   | 94 (98)     | 291 (96)    | 62 (93)    |
| Prior topiramate use, n (%)      | 86 (29)      | 17 (22)     | 83 (30)    | 30 (31)     | 93 (31)     | 23 (34)    |
| Prior onabotulinumtoxinA use, n (%) | 50 (17)      | 15 (19)     | 35 (13)    | 15 (16)     | 36 (12)     | 12 (18)    |

### Table 2: Disease characteristics of patients with no, minimal, or mild depression (PHQ-9 score <10) and moderate to severe depression (PHQ-9 score ≥10) at baseline, according to treatment group (N = 1115)

| Characteristic                  | Fremanezumab |            | Monthly | Placebo |            |
|                                | PHQ-9 <10    | PHQ-9 ≥10  | PHQ-9 <10 | PHQ-9 ≥10 | PHQ-9 <10 | PHQ-9 ≥10 |
|                                | (n = 294)    | (n = 78)   | (n = 277) | (n = 96) | (n = 303) | (n = 67)  |
| Headache days of at least moderate severity, mean ± SD | 12.9 ± 5.5  | 14.0 ± 5.4  | 12.4 ± 5.7  | 14.2 ± 5.8  | 12.8 ± 5.5  | 15.2 ± 6.9  |
| Migraine days, mean ± SD        | 15.9 ± 4.8  | 17.2 ± 4.9  | 15.4 ± 5.0  | 17.8 ± 5.3  | 15.9 ± 4.9  | 18.4 ± 5.7  |
| PHQ-9 score, mean ± SD, points  | 1.6 ± 1.8   | 14.1 ± 3.3  | 1.6 ± 1.9  | 14.8 ± 3.4  | 1.4 ± 1.4  | 15.0 ± 3.8  |
| HIT-6 score, mean ± SD, points  | 63.5 ± 4.6  | 67.3 ± 4.2  | 63.5 ± 4.1  | 67.8 ± 3.6  | 63.2 ± 4.6  | 67.8 ± 3.5  |
| MSQv.2 domain score, mean ± SD, points | RFR 52.1 ± 17.3 | 35.6 ± 18.0 | 53.7 ± 17.3 | 32.3 ± 15.8 | 53.1 ± 18.8 | 31.9 ± 14.4 |
|                                 | RFP 71.3 ± 18.2 | 52.1 ± 22.9 | 72.0 ± 18.8 | 48.0 ± 22.3 | 71.8 ± 20.1 | 47.8 ± 21.0 |
|                                 | EF 61.2 ± 25.2 | 41.5 ± 25.9 | 63.9 ± 23.5 | 37.6 ± 24.0 | 62.5 ± 24.6 | 36.9 ± 24.5 |

### Abbreviations:
- BMI, body mass index
- PHQ-9, 9-item Patient Health Questionnaire
- SD, standard deviation

### Notes:
- Plus–minus values are means ± SD.
- The intent-to-treat population included all individuals who underwent randomization. There were no significant between-group differences at baseline for any characteristics.

- A headache day of at least moderate severity was defined as a calendar day in which the patient reported either a day with headache pain that lasted ≥4 h consecutively with a peak severity of at least moderate severity, or a day when acute migraine-specific medications (triptans or ergots) were used to treat a headache of any severity or duration.

- A migraine day was defined as a calendar day in which the patient reported either a day with headache pain that lasted ≥4 h consecutively and meeting criteria for migraine, probable migraine, or a day when a headache of any duration was treated with migraine-specific medication (triptans or ergots).
FIGURE 2 Efficacy of fremanezumab in patients with CM and moderate to severe depression at baseline during the 12-week treatment period. (A) Change from baseline in monthly average number of headache days of at least moderate severity; (B) change from baseline in monthly average number of migraine days, and (C) the ≥50% response rates from baseline in monthly average number of headache days of at least moderate severity, and (D) the ≥50% response rates for migraine days. Direct comparisons between subgroup treatment arms are represented as LSM difference versus placebo (95% CI). CM, chronic migraine; LSM, least-squares mean; SE, standard error [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 3 Mean change from baseline in PHQ-9 scores during the 12-week treatment period in patients with CM and moderate to severe depression at baseline. Direct comparisons between subgroup treatment arms are represented as LSM difference versus placebo (95% CI). CM, chronic migraine; LSM, least-squares mean; PHQ-9, 9-item Patient Health Questionnaire; SE, standard error [Color figure can be viewed at wileyonlinelibrary.com]

reduction of 61.3%; \( p = 0.113 \) for fremanezumab quarterly vs. placebo and \( p = 0.558 \) for fremanezumab monthly vs. placebo; Figure 3).

Headache impact, as assessed by HIT-6, was also improved in patients treated with fremanezumab between baseline and end of the study with larger reductions in scores from baseline for the quarterly group (−8.6 ± 1.1 points) and monthly group (−9.4 ± 1.1 points) compared with placebo (−5.9 ± 1.2 points); the difference versus placebo was significant for both the monthly (\( p = 0.004 \)) and quarterly (\( p = 0.035 \)) groups (Table 3). For both the fremanezumab quarterly and monthly groups, the differences versus placebo were considered clinically meaningful based on the established criteria of minimally important difference between groups in HIT-6 score of 1.5 points.27

HRQoL improved in patients with moderate to severe depression receiving fremanezumab. Fremanezumab monthly, but not fremanezumab quarterly, yielded significantly larger changes in MSQv.2 RFR and RFP domain scores compared with placebo (\( p = 0.019 \) and \( p = 0.034 \), respectively; Figure 4). However, in both groups, these differences are regarded as clinically meaningful based on established criteria of minimally important differences for this instrument (i.e., 8.6 and 8.5 for the RFR and RFP domains, respectively).28 The RFR score increased by 28.9 ± 3.89 points (\( p = 0.066 \) vs. placebo) in the fremanezumab quarterly group and 30.8 ± 3.58 points (\( p = 0.019 \)) in the fremanezumab monthly group compared with an increase of 21.3 ± 3.99 points in the placebo group (Table 3). Similarly, changes in the RFP score were 28.4 ± 3.82 points (\( p = 0.058 \) vs. placebo) for fremanezumab quarterly and 29.1 ± 3.52 points (\( p = 0.034 \) vs. placebo) for fremanezumab monthly compared with 20.7 ± 3.93 points for placebo. Increases in the EF scores for fremanezumab quarterly and fremanezumab monthly (31.4 ± 4.37 [\( p = 0.706 \) vs. placebo] and 32.8 ± 4.02 points [\( p = 0.483 \) vs. placebo], respectively) were not significantly different compared with placebo (29.7 ± 4.49 points), potentially due to the small sample size (Table 3). At the end of the study, the proportion of patients with an improved perception of their overall health status (PGIC score ≥5 [at least moderately better]) was significantly larger in fremanezumab quarterly (43/78 [55.1%]; \( p = 0.007 \) vs. placebo) and monthly (51/96 [53.1%]; \( p = 0.016 \)) compared with placebo (22/68 [32.4%]; Table 3).
Post hoc analyses in no, minimal, or mild (PHQ-9 score <10) subgroup

In the no, minimal, or mild depression subgroup, patients in the fremanezumab dosing groups experienced significant reductions compared with placebo-treated patients during the 12-week treatment period in monthly headache days of at least moderate severity (both comparisons, p < 0.001; Figure 5A,B) and monthly migraine days (both comparisons, p < 0.001; Figure 6A,B). Reductions in monthly headache days of at least moderate severity were consistent across subgroups with no treatment-by-subgroup interaction (p = 0.069).

In the no, minimal, or mild depression subgroup, changes in the RFR domain of the MSQv.2 were significantly larger for patients treated with fremanezumab than for the placebo group (quarterly: 18.5 ± 1.35; monthly: 18.9 ± 1.35, both comparisons p < 0.001).
Patients treated with fremanezumab also experienced significantly greater improvements in the RFP domain than patients who received placebo (quarterly: $13.8 \pm 1.12 \ [p = 0.002 \text{ vs. placebo}]$; monthly: $13.0 \pm 1.12 \ [p = 0.013 \text{ vs. placebo}]$; placebo: $9.9 \pm 1.11$). In the EF domain, significant improvements compared with placebo were achieved in patients with no, minimal, or mild depression who were treated with fremanezumab quarterly or monthly (quarterly: $18.4 \pm 1.44, p = 0.004 \text{ vs. placebo}$; monthly: $17.6 \pm 1.45, p = 0.016 \text{ vs. placebo}$; placebo: $13.8 \pm 1.44$).

**FIGURE 5** Mean change from baseline in monthly headache days of at least moderate severity during the 12-week treatment period in patients with CM in the no, minimal, or mild depression subgroup. *Direct comparisons between subgroup treatment arms are represented as LSM difference versus placebo (95% CI). CI, confidence interval; CM, chronic migraine; LSM, least-squares mean; PHQ-9, 9-item Patient Health Questionnaire; SE, standard error [Color figure can be viewed at wileyonlinelibrary.com]

**FIGURE 6** Mean change from baseline in monthly migraine days during the 12-week treatment period in patients with CM in the no, minimal, or mild depression subgroup. *Direct comparisons between subgroup treatment arms are represented as LSM difference versus placebo (95% CI). CI, confidence interval; CM, chronic migraine; LSM, least-squares mean; PHQ-9, 9-item Patient Health Questionnaire; SE, standard error [Color figure can be viewed at wileyonlinelibrary.com]

**DISCUSSION**

Results from post hoc analyses of a subgroup of patients in the HALO CM trial showed that fremanezumab was efficacious in patients with CM and comorbid depression; these findings extend the previous observations in the overall study population.\(^\text{19}\)

Benefits of fremanezumab in persons with moderate to severe depression were demonstrated across several outcomes. While the magnitude of improvement in these outcomes may be partially explained by differences in baseline values, as the moderate to severe...
depression cohort had higher headache frequency, higher headache impact, and lower MSQv.2 scores at baseline, the observed improvement following treatment with fremanezumab offers hope to patients with CM and comorbid moderate to severe depression. A prior longitudinal observational study has shown that patients with migraine and depression are more likely to progress to CM, suggesting that this group has a poor prognosis.

Patients with moderate to severe depression who were treated with fremanezumab experienced significant reductions in monthly migraine days and monthly headache days of at least moderate severity, as well as significantly higher ≥50% responder rates compared with those who received placebo. Reductions in PHQ-9 scores were not statistically significant, potentially due to the modest sample size. However, patients who received fremanezumab quarterly and fremanezumab monthly experienced respective reductions of 77.3% and 66.4% (vs. 61.3% for placebo) in mean PHQ-9 scores, suggesting that the observed improvement in depression in these patients may be clinically meaningful. Treatment with fremanezumab significantly improved the RFR and RFP domains of MSQv.2 compared with placebo for monthly dosing only. Both fremanezumab dosing regimens reduced disability (i.e., headache impact), as measured by HIT-6, and improved patient perception of overall health status, as measured by the PGIC. With a few exceptions, the improvements from baseline for the fremanezumab groups versus placebo in the moderate to severe depression subgroup were larger than those observed in the overall patient population. Taken together, these outcomes suggest a particular benefit of fremanezumab treatment in this population with potentially difficult-to-treat patient migraine and high unmet need.

This study has some limitations, most notably the use of a post hoc analytic approach in a patient subgroup. Because this is a post hoc analysis, all p values must be regarded as nominal. However, these results are generally consistent with the effects observed in the overall study population, and all individual outcome measures were assessed according to the prespecified statistical analysis plan. Limitations associated with the design of the HALO CM trial also apply. Although the ICHD-3 beta criteria were used to confirm CM in patients enrolled in this study, the frequency of headache days was determined over a 28-day pretreatment period; a longer pretreatment period might have provided more stable estimates and improved detection of change. A further limitation is that this study excluded patients with a medical history of clinically significant psychiatric issues. The inclusion of only a small number of patients with severe depression at baseline (2%) may limit generalizability. The restricted range of depression severity might have reduced the magnitude of observed changes in PHQ-9 scores. We assessed depression using the PHQ-9 and not a semi-structured interview performed by a clinician applying Diagnostic and Statistical Manual of Mental Disorders, fifth edition criteria. Though the PHQ-9 is a validated instrument, the sum score was determined using algorithmic scoring. The algorithm required a score of being ≥3 on the first questions to determine if the rest of the questionnaire should be completed.

Prior work has suggested that migraine and depression independently contribute to decrements in HRQoL. Depression and migraine are bidirectionally associated, with each condition increasing the risk of the other. However, bidirectionality does not apply to other severe headache types. Depression is nearly three times more common in people with migraine than in those without, and depression and migraine are each independent risk factors for impaired HRQoL, with depression being the larger risk factor of the two. In people with CM, comorbid depression has a statistically significant, clinically negative impact on HRQoL. Furthermore, depression is associated with significantly greater impairment of HRQoL in CM than in EM, and severity of depression in CM predicts HRQoL impairment in CM but not in EM. In this study, effective treatment of migraine was associated with numerical reductions in depression-associated scores and improvements in migraine-specific HRQoL. From these analyses, we cannot determine whether the reduction in depression occurred as a direct or indirect effect of migraine improvement with fremanezumab or whether this represents a regression to the mean or other nonspecific artifacts of clinical trial conduct. A similar phenomenon was previously observed in two studies involving the treatment of CM with onabotulinumtoxin A; in both studies, reductions in monthly headache days were associated with reductions in depression severity. Data from meta-analyses and evidence-based guidelines demonstrate that biobehavioral therapies for migraine, such as cognitive behavioral therapy (CBT), are effective for the preventive treatment of migraine and that outcomes are most highly optimized when appropriate pharmacotherapy and behavioral treatments are combined. CBT is also a highly effective treatment for depression. Outcomes might even be greater for both migraine and depression if fremanezumab was combined with CBT. Although the precise nature of the bidirectional link between migraine and depression (including common genetic and environmental risk factors and the possibility of a shared mechanism) remains to be further elucidated, there is clear evidence that migraine and major affective disorders share genetic links. It is increasingly apparent that psychiatric comorbidities should be considered when selecting a migraine preventive medication. A larger study, with a serial assessment of migraine and depression, would be required to better understand their separate and combined contributions to HRQoL, including the amount of time needed for these improvements to take place and the order in which they occur.

CONCLUSIONS

In this post hoc analysis, fremanezumab demonstrated a significant treatment benefit over placebo in reducing the monthly average number of headache days of at least moderate severity and migraine days in patients with CM and comorbid moderate to severe depression. Greater improvements in HRQoL, headache impact, and patient-reported overall health status were also seen with fremanezumab than with placebo. Fremanezumab may benefit patients with migraine and comorbid depression by reducing the frequency of migraine and headache days, decreasing disability, and improving HRQoL.
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**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the Supporting Information section.