Effect of fremanezumab on quality of life and productivity in patients with chronic migraine

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Abstract

Objective
To evaluate fremanezumab quarterly or monthly vs placebo on health-related quality of life, health status, patients’ global impression of change, and productivity in patients with chronic migraine (CM).

Methods
HALO CM was a double-blind, placebo-controlled trial in patients with CM. Patients were randomized 1:1:1 to treatment with fremanezumab quarterly (675 mg at baseline, placebo at weeks 4 and 8), fremanezumab monthly (225 mg at baseline, weeks 4 and 8), or placebo. This article assessed the effect of treatment with fremanezumab on health-related quality of life and productivity using the following prespecified assessments: the Migraine-Specific Quality of Life (MSQoL) questionnaire at baseline and weeks 4, 8, and 12; Patient Global Impression of Change (PGIC) questionnaire at weeks 4, 8, and 12; and EuroQoL 5-dimension, 5-response level (EQ-5D-5L) questionnaire and Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire at baseline and week 12.

Results
The full analysis set included 1,121 patients: 375 patients with quarterly dosing, 375 with monthly dosing, and 371 with placebo. Fremanezumab quarterly and monthly was associated with significant improvements over placebo in change from baseline mean scores in MSQoL domains (all, \( p < 0.05 \)) to week 12. At week 12, fremanezumab also showed significant improvements in EQ-5D-5L visual analog scale (\( p < 0.05 \)) and PGIC scores (\( p < 0.0001 \)) as well as significant reductions from baseline in WPAI:GH scores (\( p < 0.01 \)) and presenteeism (impairment while working; \( p < 0.05 \)) vs placebo.

Conclusions
Fremanezumab quarterly or monthly was associated with improvement over placebo in migraine-specific quality of life, overall health status, patients’ global impression of change with treatment, and productivity in patients with CM.

ClinicalTrials.gov identifier
NCT02621931.

Classification of evidence
This study provides Class II evidence that in patients with CM, treatment with fremanezumab quarterly or monthly is associated with improvements in health-related quality of life and productivity.
Migraine is ranked globally as the second-leading cause of years lived with disability and the leading cause in adults under the age of 50.1–5 People with migraine experience substantially impaired daily functioning, associated disability, and reduced health-related quality of life (HRQoL).6,7 Those with chronic migraine (CM) have more comorbidities, including depression, anxiety, and cardiovascular disorders; have increased impairment of occupational, academic, financial, social, and family life; and contribute to a financial burden on health care systems and society through direct and indirect costs of the disease.8–12

Over the past decade, a few trials13,14 have targeted preventive treatment to individuals with CM. These studies typically assess reduction in monthly migraine or headache days as their primary endpoint; however, they may not fully capture the benefits of preventive treatments, including improvements in quality of life and productivity.16 Validated and clinically relevant patient-reported outcome measures16–18 provide a patient-centric approach that more fully captures the effects of migraine on quality of life and supports better-informed treatment decisions.

Fremanezumab (AJOVY [North Wales, PA]), a fully humanized monoclonal antibody (immunoglobulin G2a), selectively targets calcitonin gene-related peptide and is indicated for the preventive treatment of migraine in adults in the United States and European Union.19–21 The efficacy and safety of fremanezumab quarterly and monthly in CM were demonstrated in the placebo-controlled phase 3 HALO CM study; this study met its primary outcome of a reduction in the monthly average number of headache days of at least moderate severity, as well as all prespecified secondary endpoints.22 Here we report the outcomes of prespecified exploratory endpoints, including HRQoL, general health status, patients’ global impression of change, productivity, and activity impairment in patients with CM.

**Methods**

**Classification of evidence**

This interventional study provides Class II evidence that fremanezumab quarterly and monthly is associated with improvements in patient-reported outcomes of HRQoL, general health status, productivity, and activity impairment in patients with CM.

**Standard protocol approvals, registrations, and patient consents**

The HALO CM phase 3 study was conducted in full accordance with International Council on Harmonisation Good Clinical Practice Consolidated Guidelines, the principles of the Declaration of Helsinki, and all applicable national and local laws and regulations. It was registered at ClinicalTrials.gov as NCT02621931. All patients provided written informed consent before screening, and all protocols were approved by institutional review committees for each site. The studies were conducted from March 2016 through January 2017 at headache centers, neurology clinics, and primary care facilities at 132 sites in Canada, the Czech Republic, Finland, Israel, Japan, Poland, Russia, Spain, and the United States. Results from exploratory analyses of the HALO CM study are reported here.

**Study design**

The HALO CM methodology has been reported previously. Brieﬂy, it was a 16-week, randomized, double-blind, placebo-controlled, parallel-group study. The trial consisted of a screening visit, a 28-day pretreatment period, a 12-week treatment period, and a final evaluation at week 12. Based on information from screening and an electronic daily headache diary captured during the pretreatment period, individuals were assigned to the current study for CM (ClinicalTrials.gov NCT02621931) or a concurrent study for episodic migraine (EM) (ClinicalTrials.gov NCT02629861); alternatively, they were excluded if they did not meet eligibility criteria for either study.

Patients with CM were randomly assigned in a 1:1:1 ratio to receive fremanezumab quarterly, fremanezumab monthly, or placebo, administered as a subcutaneous injection. Fremanezumab quarterly dosing consisted of 675 mg at baseline (three 225 mg/1.5 mL injections) and placebo (one 1.5 mL injection) at weeks 4 and 8. Fremanezumab monthly dosing consisted of 675 mg at baseline (three 225 mg/1.5 mL injections) and 225 mg fremanezumab at weeks 4 and 8 (one 225 mg/1.5 mL injection). Placebo dosing consisted of placebo injections at baseline (three 1.5 mL injections) and at weeks 4 and 8 (one 1.5 mL injection). Randomization was performed with electronic interactive-response technology and patients were stratified according to sex, country, and baseline use of preventive medication (yes or no). Patients, investigators, the sponsor, and trial staff (except for those involved in bioanalytical analyses) were blinded to study group assignments.
**Study participants**

Key inclusion criteria were an age of 18–70 years, a history of migraine (International Classification of Headache Disorders, third edition, beta version criteria) for at least 12 months, and the fulfillment of criteria for CM during the 28-day pretreatment period (headache of any duration or severity on ≥15 days and headache for ≥8 days meeting specific migraine criteria). Key exclusion criteria were the use of onabotulinumtoxinA in the 4 months before screening, the use of barbiturates on ≥4 days during the pretreatment period, and a lack of efficacy of ≥2 of 4 specific clusters of migraine preventive treatments. The protocol permitted entry of a limited subset of patients who had been using a maximum of one preventive migraine medication, which had shown at least moderate evidence of efficacy, at a stable dosage for at least 2 consecutive months prior to screening.

**Study assessments**

All the endpoints assessed here were part of a prespecified exploratory analysis. The Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQoL), assessed at baseline and at weeks 4, 8, and 12, is a reliable and valid measure of migraine-specific HRQoL. The MSQoL assesses the effect of migraine on daily functioning in 3 domains: role function–restrictive, 7 items on how migraine limits daily activities; role function–preventive, 4 items on how migraine prevents these activities; and emotional function, 3 items on emotions associated with migraine. Raw domain scores are computed as a sum of item responses and rescaled from 0 to 100, with higher scores indicating better HRQoL. The thresholds for minimally clinically important differences have been established as 3.2 for role function–restrictive, 4.6 for role function–preventive, and 7.5 for emotional function.

The EuroQol-5 (EQ-5D-5L) standardized questionnaire, assessed at baseline and week 12, is a quantitative assessment of overall state of health. Patients are asked to rate their current general health state on a scale from 0 to 100 using a 20-cm visual analog scale (VAS), with higher scores indicating better health.

The Patient Global Impression of Change (PGIC) scale, assessed at weeks 4, 8, and 12, is a validated tool to evaluate patients’ impression of change in overall status after treatment. Patients are asked to self-evaluate their overall response to treatment by rating the effect that their migraine/headache have had on their general quality of life and health status since beginning the treatment. The assessment is based on a 7-point scale (1, no change; 2, almost the same; 3, a little better; 4, somewhat better; 5, moderately better; 6, better; 7, a great deal better).

The Work Productivity and Activity Impairment: General Health (WPAI-GH) questionnaire, assessed at baseline and week 12, is a 6-item validated instrument that reflects the effect of an individual’s general health on the ability to work and perform regular activities as measured by absenteeism (work time missed), presenteeism (impairment while working), overall work productivity loss (composite of absenteeism and presenteeism), and activity impairment. Participants who self-identified as employed were eligible to complete all questionnaire items, whereas those not employed were eligible to complete only the activity impairment item. Outcomes are reported as impairment percentages, with higher values indicating greater impairment.

**Statistical analysis**

Statistical analyses were performed in the full analysis set (FAS), which included all randomized patients who received ≥1 dose of study drug and had ≥10 days of postbaseline efficacy assessment on the primary endpoint. A sample size of 867 patients (289 patients per treatment group) provided at least 90% power for the study to succeed on the primary outcome at an α level of 0.05. Assuming a 15% discontinuation rate, 340 patients per treatment group were randomized. Sample size calculations were not performed for this subgroup analysis.

MSQoL, EQ-5D-5L, and WPAI:GH scores were analyzed using an analysis of covariance approach, with years since onset of migraine and baseline measurements for the corresponding questionnaire as covariates. A mixed-effects repeated-measures analysis model (MMRM) was also used on MSQoL scores as a supportive analysis. For the PGIC, responses were divided into 2 categories: patients reporting a score of ≥5 (moderately better to a great deal better) and those reporting a score of ≤4 (no change to somewhat better). The percentages of patients reporting a score of ≥5 and patients reporting a score of ≤4 were analyzed using the Cochran-Mantel-Haenszel test stratified by baseline preventive migraine medication use.

**Results**

**Patients**

The study was conducted from March 2016 through January 2017. In total, 1,130 patients were randomized to fremanezumab quarterly (n = 376), fremanezumab monthly (n = 379), or placebo (n = 375). Of these, 1,034 patients completed the trial: fremanezumab quarterly (n = 349 [93%]), fremanezumab monthly (n = 343 [91%]), and placebo (n = 342 [91%]) (figure 1). The FAS population included 1,121 patients: 375 patients with quarterly dosing, 375 with monthly dosing, and 371 with placebo.

Baseline patient demographics and clinical characteristics were similar among all treatment arms. On average, patients
were approximately 41 years of age, had a migraine diagnosis for approximately the last 20 years, and reported severe headache-related disability (6-item Headache Impact Test [HIT-6] scores > 60) (table).

**Improvement in HRQoL**

Fremanezumab was associated with clinically meaningful and statistically significant increases in the mean scores for each MSQoL domain (role function–restrictive [figure 2A], role function–preventive [figure 2B], and emotional function [figure 2C]) from baseline (day 0) to the end of treatment (4 weeks after administration of the last dose) compared with placebo. At 4 weeks, the role function–restrictive least-squares mean (LSM) score changes were 19.1 and 19.4 for fremanezumab quarterly and monthly, respectively, vs 12.0 for placebo ($p < 0.0001$ for both fremanezumab dosing regimens). At 12 weeks, the role function–restrictive LSM score changes were 20.3 and 21.0 for fremanezumab quarterly and monthly, respectively, vs 14.7 for placebo ($p < 0.0001$ for both). For the role function–preventive score at 4 weeks, LSM changes were 15.3 and 15.8 for quarterly and monthly administration vs 9.4 for placebo ($p < 0.0001$ for both fremanezumab dosing regimens). At 12 weeks, the role function–preventive score at 4 weeks, LSM score changes were 19.1 and 19.5 for quarterly and monthly administration, respectively, vs 12.1 for placebo ($p < 0.0001$ for both fremanezumab dosing regimens). At 12 weeks, the emotional function LSM score changes were 20.9 and 20.3 for quarterly and monthly administration vs 17.0 for placebo (fremanezumab quarterly, $p = 0.0126$; fremanezumab monthly, $p = 0.0348$).

The above differences in the role function–restrictive and role function–preventive scores exceeded the threshold for minimally clinically important differences at 4 weeks for fremanezumab quarterly and monthly. The improvements in the role function–restrictive score for both dosing arms exceeded the minimally clinically important difference at 12 weeks.24

**Improvement in general health state**

Fremanezumab was associated with significantly improved overall health state, as measured by the EQ-5D-5L VAS score, from baseline (day 0) to 4 weeks after administration of the last dose of study drug, compared with placebo (figure 3). The LSM score changes were 4.6 and 4.8 for fremanezumab quarterly and monthly vs 2.2 for placebo (quarterly, $p = 0.0402$; monthly, $p = 0.0291$).

**Patient global impression of change**

Fremanezumab was associated with significantly greater proportions of patients who reported PGIC scores ≥5 from the start of the study drug treatment, compared with placebo (figure 4). At 4 weeks, the percentage of patients reporting PGIC scores ≥5 was 53% and 54% for quarterly and monthly fremanezumab administration vs 31% for placebo (fremanezumab quarterly, $p < 0.0001$; fremanezumab monthly, $p < 0.0001$); at 12 weeks, similar percentages of patients reporting...
PGIC scores ≥5 were observed (55% and 54% for fremanezumab quarterly and monthly vs 37% for placebo; p < 0.0001 for both).

**Improvement in productivity**

Significant improvements in productivity, from baseline (day 0) to 4 weeks after administration of the last dose, were seen with fremanezumab treatment compared with placebo across the 4 dimensions of the WPAI:GH scale (figure 5). Patients who received fremanezumab also reported significant reductions from baseline in overall work productivity loss than those who received placebo (quarterly: −16.6%, p = 0.0009; monthly: −15.9%, p = 0.0026; placebo: −9.1%). Similarly, patients treated with fremanezumab quarterly or monthly reported significant reductions from baseline in presenteeism than those who received placebo (fremanezumab quarterly: −15.7%, p = 0.0049; fremanezumab monthly: −14.9%, p = 0.0169; placebo: −10.0%). There were no significant differences in absenteeism for either treatment group compared with placebo, despite a nonsignificant trend in the monthly fremanezumab administration group (quarterly: −0.1%, p = 0.5918; monthly: −2.1%, p = 0.0873; placebo: 0.8%). Nevertheless, fremanezumab significantly reduced impairment of activity outside of work in patients who received fremanezumab quarterly compared with placebo (fremanezumab quarterly: −15.0%, p = 0.0311; monthly: −12.9%, p = 0.3230; placebo: −11.0%).

**Discussion**

The results presented here demonstrate that fremanezumab quarterly or monthly improved migraine-specific quality of life, overall health status, patients’ global impression of change, and productivity in patients with CM. Taken in combination with the reduction in number of headache days
demonstrated in the HALO CM trial and an increase in number of headache-free days with normal functional performance observed in an analysis of a preceding phase 2 trial, these results demonstrate that fremanezumab quarterly or monthly is an effective and well-tolerated treatment for patients with CM. Convergence of evidence from both

Figure 2 Effect of fremanezumab on health-related quality of life as measured with the Migraine-Specific Quality of Life

(A) Role function-restrictive. (B) Role function-preventive. (C) Emotional function. LSM = least-squares mean.
Fremanezumab was associated with statistically significant improvements in all MSQoL domains (i.e., role function–restrictive, role function–preventive, and emotional function),24 with these improvements seen as early as week 4 and maintained through week 12. Clinically meaningful improvements were observed for role function–restrictive at weeks 4 and 12. The role function–restrictive domain measures the restriction in daily life activities due to migraine, including the effect on relationships with family and friends, interference in leisure time activities, and the ability to concentrate on work or activities, indicating these factors were improved with fremanezumab. Similarly, clinically meaningful improvements were observed in the role function–preventive domain (the magnitude of change exceeded the established minimally important difference at week 4). Improvement in the role function–preventive domain indicates that patients were able to undertake more daily life activities that had been previously prevented by migraine (e.g., a reduced need to cancel or stop work or activities, ask for help in handling routine tasks, or avoid social activities).32 Emotional function improved after treatment with fremanezumab, indicating that patients felt less of an emotional effect of migraine, including feeling less frustration, feeling less burdensome to others, and feeling less afraid of letting others down.32 The MSQoL has been used in many studies, and improvement in scores has been shown to be an effective measure of treatment outcomes for migraine and CM.32 The significant improvement in MSQoL after fremanezumab treatment is also consistent with previously reported score improvements with fremanezumab on the HIT-6 questionnaire, a tool that reliably assesses headache-related disability and headache-specific impact.22,33 Taken together, these results show that patients with CM...
treated with fremanezumab experience significant and meaningful improvements in quality of life, and find more opportunities to engage in their everyday activities.

Overall patient health state was measured using the EQ-5D-5L questionnaire. The EQ-5D-5L questionnaire has often been used in health technology assessments and population health surveys. Fremanezumab quarterly or monthly led to significant improvements in the EQ-5D-5L score, compared with placebo. Given that CM is associated with a high prevalence of comorbidities,34 improvement in overall health status may have particular relevance in this patient population. Further study may be useful to elucidate whether part of the improvement in overall health status is associated with improvement in those comorbidities.

Global rating of change scales are often used in clinical research, and clinicians often ask their patients to rate the change in their condition with treatment.35 Here, the PGIC scale was used to measure the patients’ global assessment of this change after fremanezumab treatment. A significantly greater proportion of patients treated with either dose of fremanezumab reported that they felt “moderately better,” “better,” or “a great deal better,” compared with patients treated with placebo. These results were observed at the first assessment after the first dose (week 4) and were maintained till the end-of-treatment visit (week 12), indicating that patients assessed their condition as improved over the course of treatment. The patient’s perception of change and treatment effect may be particularly important for medication adherence. Adherence to oral migraine preventive medications is low, even among patients with CM, with rates between 26%–29% at 6 months and 17%–20% at 12 months.37 Treatment efficacy and patients’ perception of treatment efficacy have been associated with treatment adherence.38,39

Fremanezumab quarterly or monthly also resulted in improved scores in the overall work impairment and presenteeism measures of the WPAI:GH questionnaire, compared with placebo, at final visit/end of treatment (4 weeks after the final dose). These are consistent with the other patient-reported outcomes in this study, including improved HRQoL and overall health status in patients being treated with fremanezumab. Presenteeism is a risk factor for future work absence and poor self-rated health over time.40,41 Therefore, reducing work impairment and presenteeism may have meaningful effects not just for companies, but for patients themselves. From a societal perspective, improved work productivity and reduced presenteeism may indirectly

![Figure 5](image-url)
decrease the economic burden of CM. Estimates for the total annual cost of migraine are $78 billion in the United States and €111 billion in the European Union.\textsuperscript{42,43} Indirect costs such as loss of productivity account for up to 70% of total CM-related annual costs in the United States and over 90% of total migraine-related annual costs in Europe.\textsuperscript{42,44} Taken together, the results of this study suggest that fremanezumab has the potential to reduce the significant economic burden of CM on both patients and society.

It is not clear why fremanezumab had no improvements in regards to absenteeism, although fremanezumab quarterly in employed patients led to increased activity outside of work, as compared with placebo. Previous research has shown that the majority of lost productivity in patients with migraine is due to reduced performance while at work, also known as presenteeism.\textsuperscript{45}

It is possible that patients with CM have developed other means to reduce absenteeism, leading to lower baseline absenteeism and thus presenting a challenge in noting changes from baseline, while these patients still have high levels of presenteeism.\textsuperscript{45} Therefore, measurements of presenteeism might be better indicators of the effect of a treatment than the measure of absenteeism, which may have a floor effect.

The 2018 Guidelines of the International Headache Society continue to recommend headache frequency as the primary endpoint for controlled trials of preventive treatment of CM\textsuperscript{15}; however, this does not fully capture the benefits of treatment. Fremanezumab did indeed show positive outcomes for such a recommended primary endpoint of reduction in monthly headache days,\textsuperscript{22} and this is aligned with the positive patient-reported outcome measures reported here during the same time course. Similar associations between reduction in headache day frequency and improvements in patient-reported outcome measures have been shown for other treatments, including onabotulinumtoxinA for CM\textsuperscript{46,47} topiramate for CM,\textsuperscript{48} and erenumab for EM.\textsuperscript{49} Although it is expected that the reduction in headache days produces these improved patient-reported outcomes, it is also possible that an indirect association exists and that certain aspects of patient-reported outcome measures capture treatment effects that are at least partially independent of headache frequency. Comorbidities, subclinical depression/anxiety symptoms, personality, and psychological or behavioral coping skills of patients with migraine are all likely to be relevant to the quality of life measures reported here, and it is possible that improvements in these elements may partially explain the improvements in the patient-reported outcomes independently of attack frequency.

This study has limitations. There was a substantial placebo effect both on change in monthly migraine and headache days and on patient-reported outcomes. The patient-reported outcome measures, which were part of the prespecified exploratory objectives of the HALO CM study, only measured the outcomes up to 4 weeks after last study drug administration. Longer-term data and data from future real-world studies on the effects of fremanezumab on patient functioning will provide further evidence on the value of this treatment in improving patient outcomes. The results presented here are from multiple comparisons without adjustment in the threshold for significance; these comparisons were all prespecified.

This study reports significant improvements in established patient-reported outcome measures with both fremanezumab quarterly and monthly dosing, allowing clinicians and patients flexibility in the dosing schedule. Fremanezumab, which has an established efficacy and safety profile in treating CM, also improves migraine-specific quality of life, overall health status, patient’s global impression of change in overall status with treatment, and productivity and activity impairment in patients with CM. These improvements highlight the importance of assessing the patient wholly, including both headache days and quality of life, in order to guide treatment. Further, they give hope to both patient and society that the burden of CM can be substantially reduced and quality of life improved.

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**References**

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