Efficacy of Fremanezumab in Patients With Chronic Migraine and Comorbid Moderate to Moderately Severe Depression

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CONCLUSIONS

- Patients with moderate to moderately severe depression who were treated with fremanezumab experienced significant reductions in the monthly average number of headache days of at least moderate severity and migraine days, with effects observed by Week 4
  - A significantly larger proportion of patients treated with fremanezumab achieved at least a 50% reduction in monthly headache days of at least moderate severity, compared with patients receiving placebo
- Patients with moderate to moderately severe depression who were treated with fremanezumab also showed improved patient-reported outcomes of level of depressive symptomology, health-related quality of life (QoL), headache impact, and perception of change compared with patients receiving placebo
- A limitation of the present study is that it is a *post hoc* analysis
  - However, all measures and assessments evaluated were prespecified
- Overall, fremanezumab demonstrated efficacy in preventive treatment of chronic migraine (CM) in patients with moderate to moderately severe depression

INTRODUCTION

- Depression is a common comorbidity of CM, with up to 80% of CM patients being reported to meet criteria for depression[1]
  - Patients with CM are twice as likely to meet criteria for depression than those with episodic migraine (EM)[2]
- Depression as a comorbidity with migraine has been associated with higher migraine-related disability, poor treatment response, and challenges with adherence, as well as significantly impaired quality of life, further compounding the already substantial burden of migraine[2-8]
- Fremanezumab is a fully humanized monoclonal antibody (IgG2Δa) that selectively targets calcitonin gene-related peptide (CGRP)[9,10]
- Fremanezumab has been studied in two subcutaneous dose regimens, quarterly and monthly, to offer flexible administration for the preventive treatment of migraine
  - In clinical trials, fremanezumab significantly reduced the frequency of migraine and headache, without serious treatment-related adverse events (AEs)[11,12]
- The Phase 3 HALO CM trial (ClinicalTrials.gov number, NCT02621931) evaluated fremanezumab for the preventive treatment of CM[13]
- This study is a *post hoc* analysis of the HALO CM trial to evaluate the effect of fremanezumab in the subgroup of patients with CM and comorbid moderate to moderately severe depression

OBJECTIVE

- To evaluate the efficacy of fremanezumab in patients with CM and comorbid moderate to moderately severe depression

METHODS

Study Design

- HALO CM was a randomized, double-blind, placebo-controlled, parallel-group study consisting of a screening visit, a 28-day pre-treatment period, and a 12-week treatment period, with a final evaluation at Week 12 (**Figure 1**)

Patient Population

Key inclusion criteria

- 18–70 years of age
- History of migraine (International Classification of Headache Disorders [ICHD]-3 beta criteria) for ≥12 months prior to screening
- Prospectively confirmed CM during the 28-day pre-treatment baseline period:
  - Headache on ≥15 days
  - ≥8 days fulfilling ICHD3-beta criteria for migraine or probable migraine; or use of triptan or ergot medications

Key exclusion criteria

- Use of onabotulinumtoxinA in the 4 months before screening
- Use of opioids or barbiturates on >4 days per month during the pre-treatment period
- Use of interventions or devices for migraine in the 2 months before screening
- Medical history of clinically significant psychiatric issues, including suicide attempts or ideation in the past 2 years
- Previous failure in ≥2 of four of the following medication clusters after ≥3 months of treatment for EM or CM:
  - Divalproex sodium and sodium valproate
  - Flunarizine and pizotifen
  - Amitriptyline, nortriptyline, venlafaxine, and duloxetine
  - Atenolol, nadolol, metoprolol, propranolol, and timolol
- A subset of patients was allowed use of one preventive migraine medication if the dosing was stable ≥2 months before the pre-treatment period

Study Treatment

- Eligible patients were randomized 1:1:1 to receive subcutaneous injections of one of the following treatments approximately every 28 days for a total of 3 doses (**Figure 1**):
  - Fremanezumab quarterly (675 mg at baseline and placebo at Weeks 4 and 8)
  - Fremanezumab monthly (675 mg at baseline and 225 mg at Weeks 4 and 8)
  - Placebo at each time point over a 12-week treatment period

Outcomes

- All endpoints compared baseline (28-day pre-treatment period) and the 12-week period after the first dose of study drug, unless otherwise stated

Primary endpoint

- Mean change in the monthly average number of headache days of at least moderate severity

Key secondary endpoints

- Mean change in the monthly average number of migraine days
- Proportion of patients with ≥50% reduction in the monthly average number of headache days of at least moderate severity
- Mean change in the monthly average number of days of acute headache medication use
- Mean change in the monthly average number of headache days of at least moderate severity during the 4-week period after the first dose of study drug
- Mean change in six-item Headache Impact Test (HIT-6) score from baseline (Day 0) to 4 weeks after administration of the last dose of study drug

Additional pre-specified patient-reported assessments

- Patient depression status, using the nine-item Patient Health Questionnaire (PHQ-9): higher scores indicate higher frequency of symptoms
  - Each PHQ-9 question corresponds to a criterion for diagnosis of major depressive disorder on the Statistical Manual for Mental Disorders, 4th edition
  - Responses are scored based on the frequency of symptoms during the previous 2 weeks, providing a depression severity score from 0 to 27 (0–4: none; 5–9: mild; 10–14: moderate; 15–19: moderately severe; 20–27: severe)[14]
- QoL assessments, using version 2.1 of the Migraine-Specific Quality of Life (MSQoL) questionnaire
  - Role Function-Restrictive (RFR) domain: seven questions on how migraines limit daily activities; higher scores indicate better QoL
  - Role Function-Preventive (RFP) domain: four questions on how migraines prevent these activities; higher scores indicate better QoL
- Patient Global Impression of Change (PGIC): seven-point single-item scale on how migraines affect overall health status and QoL since beginning of treatment; higher score indicates more improvement

Statistical Analysis

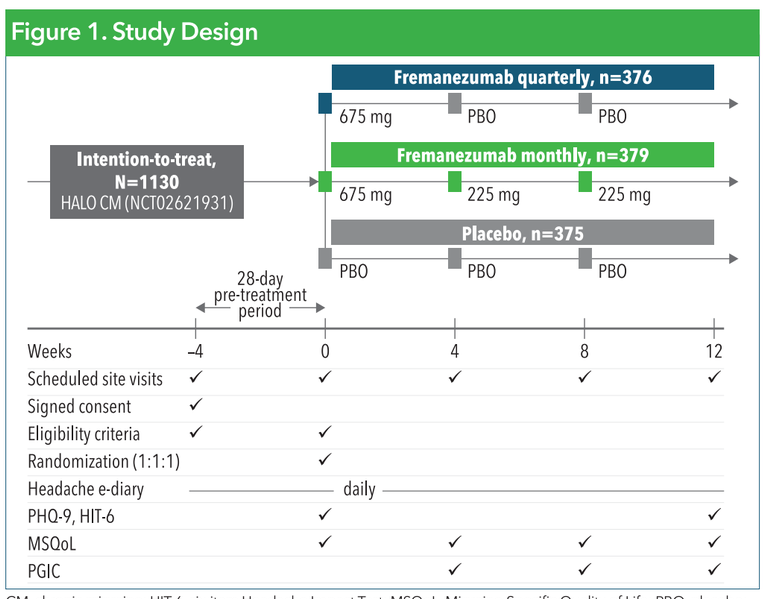
- Efficacy analyses were conducted in the full analysis set (FAS): randomized patients who received ≥1 dose of study drug and had ≥10 days of post-baseline efficacy assessments on the primary endpoint
- *Post hoc* analyses reported here were performed on a subgroup of patients in the FAS population who had moderate to moderately severe depression (a score of 10–19 on the PHQ-9) at baseline

RESULTS

Patient Demographics and Baseline Characteristics

- A total of 1130 patients were randomized 1:1:1 to receive fremanezumab quarterly (n=376), fremanezumab monthly (n=379), or placebo (n=375) (**Figure 1**)
  - More than 90% in each study arm completed the trial

Figure 1. Study Design



CM, chronic migraine; HIT-6, six-item Headache Impact Test; MSQoL, Migraine-Specific Quality of Life; PBO, placebo; PGIC, Patient Global Impression of Change; PHQ-9, nine-item Patient Health Questionnaire.

- Baseline demographics and clinical characteristics were similar between all three groups, regardless of baseline PHQ-9 scores (**Table 1**)
- Almost 20% (219/1130) of randomized patients included in this *post hoc* analysis had moderate to moderately severe depression at baseline (quarterly, n=74; monthly, n=88; placebo, n=57)

Table 1. Baseline Patient Demographics and Clinical Characteristics

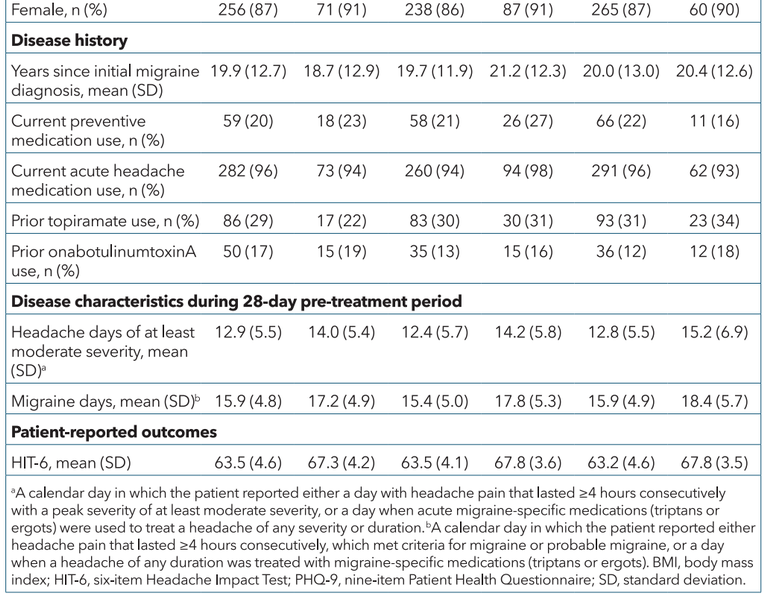
Characteristic	Fremanezumab Quarterly PHQ-9 <10 (n=294)	Fremanezumab Quarterly PHQ-9 ≥10 (n=78)	Fremanezumab Monthly PHQ-9 <10 (n=277)	Fremanezumab Monthly PHQ-9 ≥10 (n=96)	Placebo PHQ-9 <10 (n=303)	Placebo PHQ-9 ≥10 (n=67)
Age, mean (SD)	42.0 (12.5)	41.7 (11.2)	39.7 (11.9)	43.4 (11.9)	41.1 (12.0)	42.9 (12.1)
BMI, kg/m^2, mean (SD)	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, n (%)	256 (87)	71 (91)	238 (86)	87 (91)	265 (87)	60 (90)
Disease history						
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)
Disease characteristics during 28-day pre-treatment period						
Headache days of at least moderate severity, mean (SD)[a]	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)[b]	15.9 (4.8)	17.2 (4.9)	15.4 (5.0)	17.8 (5.3)	15.9 (4.9)	18.4 (5.7)
Patient-reported outcomes						
HIT-6, mean (SD)	63.5 (4.6)	67.3 (4.2)	63.5 (4.1)	67.8 (3.6)	63.2 (4.6)	67.8 (3.5)

[a]A calendar day in which the patient reported either a day with headache pain that lasted ≥4 hours 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. [b]A calendar day in which the patient reported either headache pain that lasted ≥4 hours consecutively, which met criteria for migraine or probable migraine, or a day when a headache of any duration was treated with migraine-specific medications (triptans or ergots). BMI, body mass index; HIT-6, six-item Headache Impact Test; PHQ-9, nine-item Patient Health Questionnaire; SD, standard deviation.

Change in the Monthly Average Number of Headache Days of At Least Moderate Severity

- Patients with moderate to moderately severe depression at baseline who were treated with fremanezumab experienced significant reductions in the mean number of monthly headache days of at least moderate severity from baseline to Week 12 compared with those who received placebo (**Figure 2A**). Significant effects were observed as early as Week 4 after the first dose of fremanezumab (**Figure 2B**)
- Among these patients, the proportion who achieved at least a 50% reduction in monthly headache days of at least moderate severity was significantly greater with fremanezumab quarterly (41%) and monthly (40%) treatment groups compared with the placebo group (12%) during the 12-week treatment period (P<0.001) (data not shown)

Figure 2. Change in the Monthly Average Number of Headache Days of At Least Moderate Severity in Patients With Moderate to Moderately Severe Depression

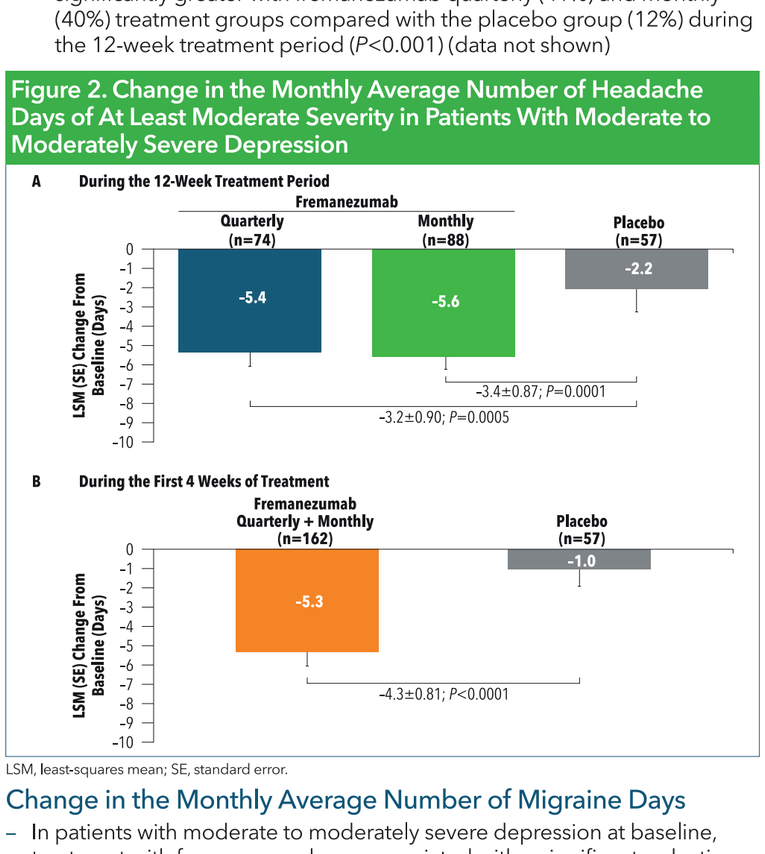


LSM, least-squares mean; SE, standard error.

Change in the Monthly Average Number of Migraine Days

- In patients with moderate to moderately severe depression at baseline, treatment with fremanezumab was associated with a significant reduction from baseline in monthly average migraine days in both the quarterly and monthly treatment groups compared with those in the placebo group (**Figure 3A**). Significant effects were observed as early as Week 4 after the first dose of fremanezumab (**Figure 3B**)

Figure 3. Change in the Monthly Average Number of Migraine Days in Patients With Moderate to Moderately Severe Depression

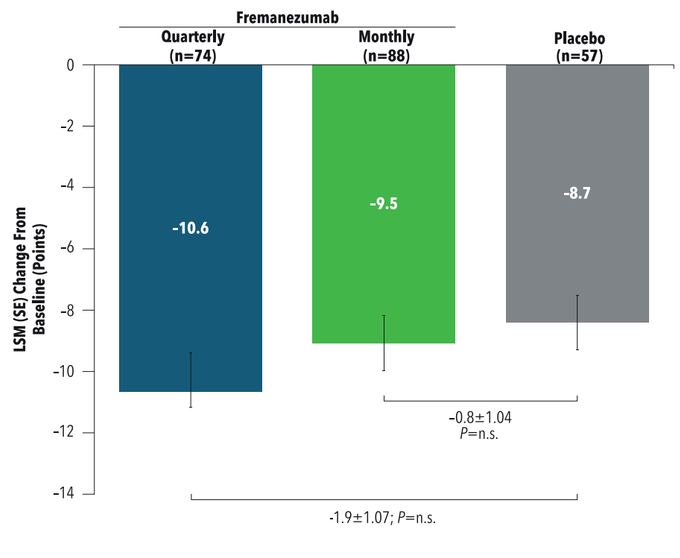


LSM, least-squares mean; SE, standard error.

Change in Depression

- Patients with depression at baseline receiving fremanezumab showed larger reductions in mean PHQ-9 scores from baseline to Week 12 in both treatment groups compared with placebo (**Figure 4**)

Figure 4. Change in PHQ-9 Scores for Patients With Moderate to Moderately Severe Depression at Baseline

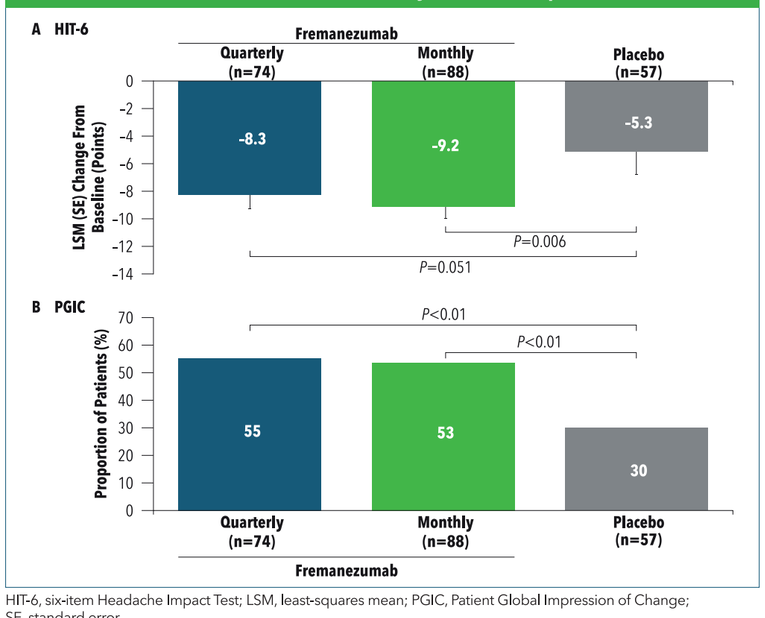


BL, baseline; LSM, least-squares mean; n.s., not significant; PHQ-9, nine-item Patient Health Questionnaire; SE, standard error.

Change in Headache Impact and Perception of Overall Health Status

- Disability was improved in patients with moderate to moderately severe depression at baseline who were treated with fremanezumab during the 12-week treatment period; treatment was associated with larger reductions in HIT-6 scores from baseline compared with placebo (**Figure 5A**)
  - The difference was significant for the monthly group but not in the quarterly group, although both differences are considered clinically relevant
- The proportion of patients with an improved perception of their overall health status (PGIC score ≥5 [at least moderately better]) was significantly larger in both the fremanezumab quarterly and monthly groups compared with placebo at the end of the study (**Figure 5B**)

Figure 5. Change in (A) HIT-6 Scores and (B) PGIC Responders in Patients With Moderate to Moderately Severe Depression

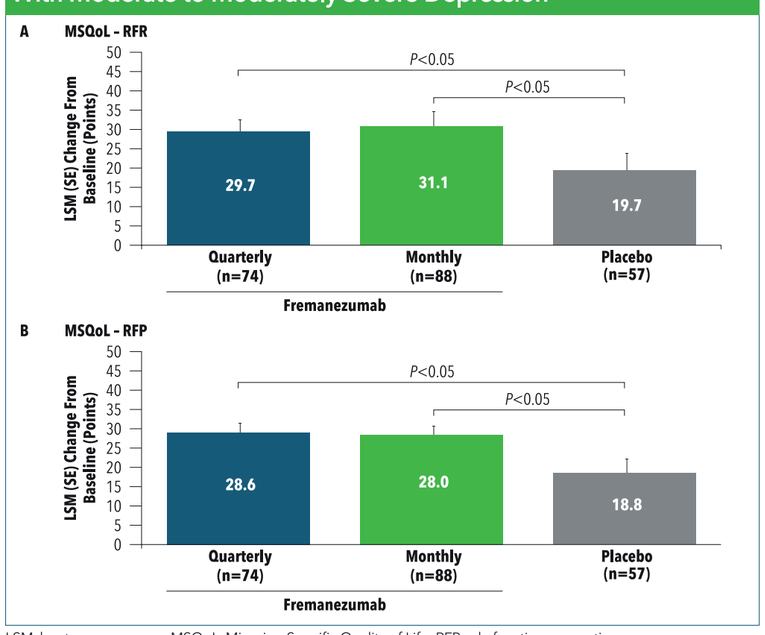


HIT-6, six-item Headache Impact Test; LSM, least-squares mean; PGIC, Patient Global Impression of Change; SE, standard error.

Change in QoL

- QoL was improved in patients with moderate to moderately severe depression at baseline who were treated with fremanezumab, with both the quarterly and monthly groups showing significantly larger changes in MSQoL RFR and RFP domain scores compared with placebo (**Figure 6**)

Figure 6. Change in (A) RFR and (B) RFP MSQoL Scores in Patients With Moderate to Moderately Severe Depression



LSM, least-squares mean; MSQoL, Migraine-Specific Quality of Life; RFP, role function-preventive; RFR, role function-restrictive; SE, standard error.

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Michael J. Seminerio: Employee of Teva Pharmaceuticals.
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