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Long-Term Impact of Fremanezumab on Response Rates, Acute Headache Medication Use, and Disability in Patients With Episodic Migraine Who Have Failed at Least One Prior Preventive Migraine Medication: Results of a 1-Year Study

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CONCLUSIONS

- In patients with episodic migraine (EM) who had failed at least one prior migraine preventive medication, long-term fremanezumab treatment showed sustained efficacy, as demonstrated by increase in number of patients achieving meaningful reduction in the monthly number of headache days of at least moderate severity and migraine days; reduction in acute headache medication use; and improvement in headache-related disability for up to 12 months
  - These data suggest that EM patients with prior migraine preventive treatment failure, who may represent a more difficult-to-treat patient population, can achieve long-term benefit with fremanezumab treatment
- Results from this *post hoc* analysis may help to inform clinical decision-making for physicians treating patients with EM who have failed at least one prior migraine preventive medication

INTRODUCTION

- Many of the currently available medications used for the prevention of chronic migraine (CM) or EM were not designed for the treatment of migraine and have limited efficacy and poor tolerability[1,2]
- Few options exist for patients with migraine who do not respond to these preventive therapies
- Fremanezumab, a fully humanized monoclonal antibody (IgG2Δa) that selectively targets calcitonin gene-related peptide (CGRP), is approved in the United States and the European Union for the preventive treatment of migraine in adults[3-5]
- A 52-week extension study evaluated the long-term safety and efficacy of fremanezumab

OBJECTIVE

- To evaluate the long-term effect of fremanezumab on response rates, use of acute headache medication, and disability in patients with EM who had failed (lack of efficacy or intolerability) at least one prior migraine preventive medication

METHODS

Study Design

- This was a 12-month, multicenter, randomized, double-blind, parallel-group, Phase 3 study (NCT02638103) that included patients who rolled over from the pivotal 12-week, placebo-controlled, double-blind Phase 3 HALO clinical trials, as well as an additional subset of new patients who were not previously enrolled

Patient Population

Key inclusion criteria

- 18–70 years of age
- History of migraine (International Classification of Headache Disorders, third edition, beta version [ICHD-3 beta] criteria) for ≥12 months prior to screening
- Prospectively confirmed EM during the 28-day pre-treatment baseline period:
  - Headache of any severity and duration on 6–14 days (rollover patients) or on 4–14 days (new patients)
  - ≥4 days fulfilling ICHD-3 beta criteria or probable migraine, or use of triptan or ergot medications
- Patients could continue using a maximum of one (rollover patients) or two (new patients) concomitant migraine preventive medications for the duration of the study, provided that the medication was recognized as having at least moderate efficacy and dosage had been stable for ≥2 consecutive months prior to screening

Key exclusion criteria

- For patients at screening in a prior Phase 3 (HALO EM) trial:
  - 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
  - Previous failure in ≥2 of the following medication clusters after ≥3 months of treatment for CM or EM: divalproex sodium and sodium valproate; flunarizine and pizotifen; amitriptyline, nortriptyline, venlafaxine, and duloxetine; or atenolol, nadolol, metoprolol, propranolol, and timolol
- These exclusions were not applied to new patients

Study Treatment

- In the initial placebo-controlled HALO EM trial, 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 three doses:
  - Fremanezumab quarterly (675 mg at baseline and placebo at Weeks 4 and 8)
  - Fremanezumab monthly (225 mg at baseline and at Weeks 4 and 8)
  - Placebo at baseline and at Weeks 4 and 8
- In the long-term trial, patients who received fremanezumab quarterly or monthly in the prior placebo-controlled trials continued on the same treatment, and patients who previously received placebo were randomized 1:1 to either fremanezumab quarterly or monthly
- All patients remained blinded as to which dosing regimen they received during the long-term study

Outcomes

Efficacy

- Proportion of patients with a ≥50% reduction from baseline (28-day pre-treatment period) in the monthly average number of migraine days and in the monthly average number of headache days of at least moderate severity
- Mean change from baseline (28-day pre-treatment period) in the monthly number of days of acute headache medication use
- Mean change from baseline (Day 0) in headache-related disability, as measured by the Migraine Disability Assessment (MIDAS) questionnaire; higher scores indicate greater disability

Safety and tolerability

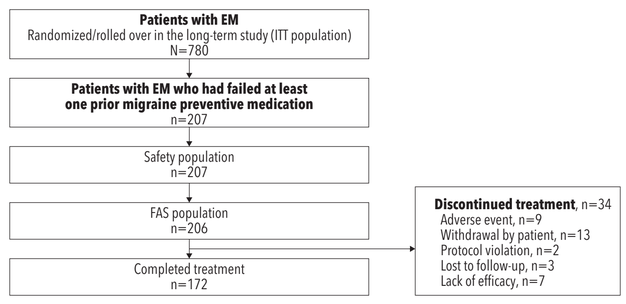
- Adverse events (AEs) and systematic local injection-site assessments (immediately and at 1 hour post-injection)

RESULTS

Study Population

- Of the 780 patients with EM enrolled in this study, 207 (26.5%) had failed at least one prior migraine preventive medication (**Figure 1**)

Figure 1. Patient Disposition



EM, episodic migraine; ITT, intention-to-treat; FAS, full analysis set.

- Baseline demographics and disease characteristics were similar between both fremanezumab treatment arms (**Table 1**)

Table 1. Baseline Demographics and Disease Characteristics of Patients With EM Who Had Failed at Least One Prior Migraine Preventive Medication

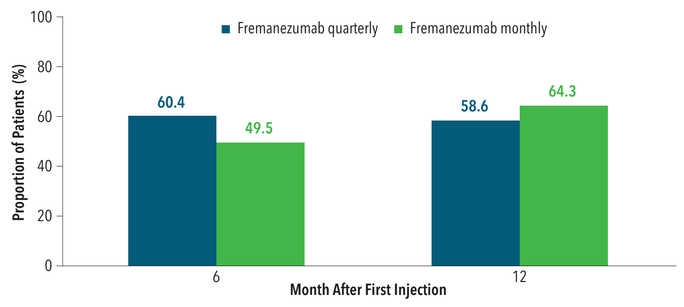
	Fremanezumab quarterly (n=105)	Fremanezumab monthly (n=102)
Patient demographics		
Age, mean (SD), y	47.2 (11.7)	47.2 (11.7)
Sex, female, n (%)	91 (87)	93 (91)
BMI, mean (SD), kg/m^2	26.8 (5.0)	25.9 (4.4)
Disease history		
Years since initial migraine diagnosis, mean (SD)	26.4 (14.0)	24.5 (13.3)
Current preventive medication use, n (%)	30 (29)	28 (27)
Current acute headache medication use, n (%)	103 (98)	100 (98)
Prior topiramate use, n (%)	81 (77)	92 (90)
Prior onabotulinumtoxinA use, n (%)	24 (23)	23 (23)
Disease characteristics during the 28-day pre-treatment period		
Headache days of any severity and duration, mean (SD)	11.6 (2.2)	11.4 (2.4)
Headache days of at least moderate severity, mean (SD)[a]	8.4 (3.2)	8.3 (2.8)
Migraine days, mean (SD)[b]	9.8 (2.6)	9.7 (2.7)
Days with any acute headache medication use, mean (SD)	9.3 (3.3)	9.0 (3.2)
MIDAS score, mean (SD)[c]	41.1 (31.1)	39.0 (30.0)

EM, episodic migraine; SD, standard deviation; BMI, body mass index; MIDAS, Migraine Disability Assessment. [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 medication (triptan or ergot) was used to treat a headache of any severity or duration. [b]A calendar day in which the patients reported either headache pain that lasted ≥2 hours consecutively, which met criteria for migraine or probable migraine, or a day when a headache of any duration was treated with migraine-specific medication (triptan or ergot). [c]Data reported for the full analysis set population (fremanezumab quarterly: n=105; fremanezumab monthly: n=101).

≥50% Response Rates in EM Patients Who Had Failed at Least One Prior Migraine Preventive Medication During the Long-Term Study

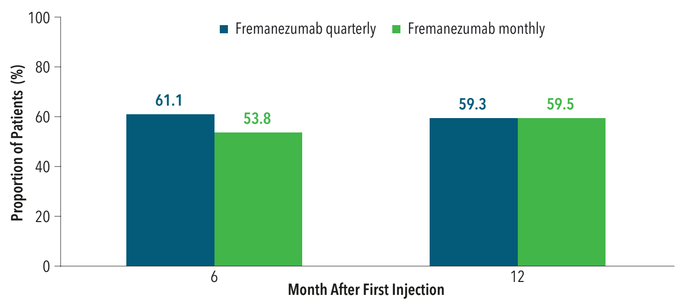
- After 12 months of treatment with fremanezumab, nearly 60% of EM patients who had failed at least one prior migraine preventive medication had a ≥50% reduction in the monthly average number of migraine days (**Figure 2**) and headache days of at least moderate severity (**Figure 3**)

Figure 2. ≥50% Reduction in the Monthly Average Number of Migraine Days in EM Patients Who Had Failed at Least One Prior Migraine Preventive Medication



EM, episodic migraine.

Figure 3. ≥50% Reduction in the Monthly Average Number of Headache Days of at Least Moderate Severity in EM Patients Who Had Failed at Least One Prior Migraine Preventive Medication

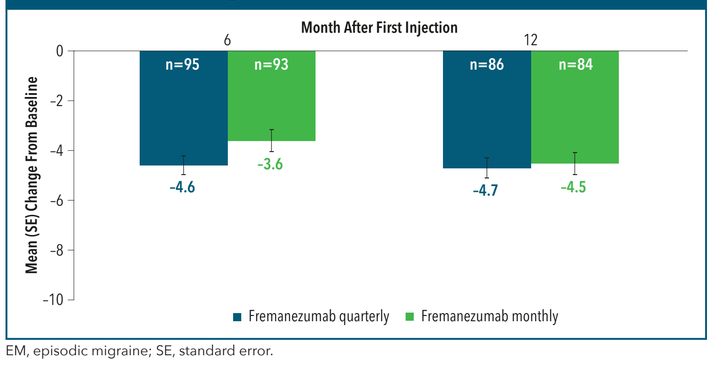


EM, episodic migraine.

Change in Days of Any Acute Headache Medication Use

- Fremanezumab quarterly and monthly demonstrated reductions of 51% and 47%, respectively, in the monthly average number of days of acute headache medication use by Month 12 (**Figure 4**)

Figure 4. Change in the Monthly Average Number of Days of Acute Headache Medication Use in EM Patients Who Had Failed at Least One Prior Migraine Preventive Medication

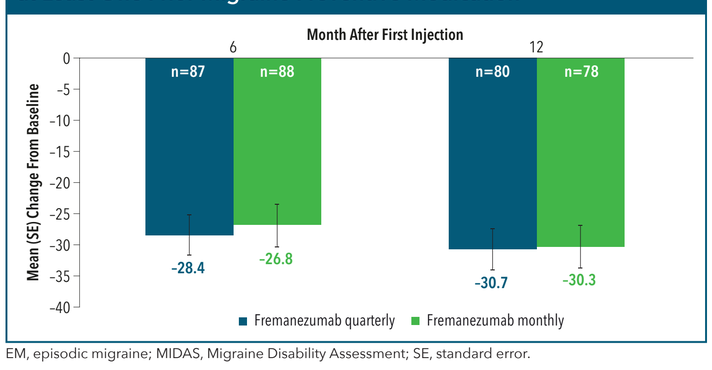


EM, episodic migraine; SE, standard error.

Headache-Related Disability

- Fremanezumab quarterly and monthly reduced headache-related disability, as demonstrated by the changes from baseline in MIDAS scores over the 12-month treatment period (**Figure 5**)

Figure 5. Change in MIDAS Score in EM Patients Who Had Failed at Least One Prior Migraine Preventive Medication



EM, episodic migraine; MIDAS, Migraine Disability Assessment; SE, standard error.

Safety and Tolerability in EM Patients Who Had Failed at Least One Prior Migraine Preventive Medication

- A total of 92 patients (88%) who received fremanezumab quarterly and 81 patients (79%) who received fremanezumab monthly reported at least one AE (**Table 2**)
- Injection-site reactions were the most commonly reported AEs (**Table 2**)
- Serious AEs and AEs leading to discontinuation were infrequent, with similar proportions of patients across treatment groups (**Table 2**)

Table 2. AEs in EM Patients Who Had Failed at Least One Prior Migraine Preventive Medication

	Fremanezumab quarterly (n=105)	Fremanezumab monthly (n=102)
Patients with AEs, n (%)		
At least one AE	92 (88)	81 (79)
At least one treatment-related AE	61 (58)	57 (56)
At least one serious AE	6 (6)	8 (8)
Any AE leading to discontinuation of the study	5 (5)	4 (4)
Injection-site reactions (occurring in >6% of patients in any treatment group), n (%)[a]		
Injection-site induration	30 (29)	35 (34)
Injection-site pain	30 (29)	29 (28)
Injection-site erythema	26 (25)	30 (29)
Injection-site pruritus	7 (7)	11 (11)
Other common AEs (occurring in >6% of patients in any treatment group), n (%)		
Upper respiratory tract infection	11 (10)	13 (13)
Nasopharyngitis	9 (9)	10 (10)
Bronchitis	7 (7)	4 (4)
Gastroenteritis	7 (7)	1 (<1)
Urinary tract infection	6 (6)	8 (8)

AE, adverse event; EM, episodic migraine.
[a]Local injection sites were systematically assessed for erythema, induration, ecchymosis, and pain both immediately and 1 hour after dosing.

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