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Long-term Impact of Fremanezumab on Response Rate, Acute Headache Medication Use, and Disability in Episodic Migraine Patients With Acute Medication Overuse at Baseline: Results of a 1-Year Study

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CONCLUSIONS

- Long-term treatment with fremanezumab reduced the number of headache days of at least moderate severity, the number of migraine days, acute headache medication use, and headache-related disability in patients with episodic migraine (EM) who had acute medication overuse (AMO) at baseline
- Results from this *post hoc* analysis may help to inform clinical decision-making for physicians treating patients with EM who had AMO at baseline

INTRODUCTION

- Patients with EM may overuse acute headache medication, including triptans, ergot derivatives, opioids, and combination analgesics[1]
- Overuse of acute headache medications can cause medication overuse headache and may increase the risk of developing chronic migraine (CM)[2]
- 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 impact of fremanezumab on response rate, the use of acute headache medication, and disability in patients with EM who had AMO (defined as non-specific 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) at baseline

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 prior Phase 3 trials, as well as an additional subset of new patients 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 on 6–14 days (rollover patients) or on 4–14 days (new patients)
  - ≥4 days fulfilling ICHD-3 beta criteria for migraine, 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 rolling over from 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 active treatment in the prior placebo-controlled trial continued the same treatment, while patients who previously received placebo and new patients 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 number of migraine days and in the number of headache days of at least moderate severity
- Mean change from baseline (28-day pre-treatment period) in the monthly average number of days of any acute headache medication use
- Mean change from baseline (Day 0) in Migraine Disability Assessment (MIDAS) scores

Safety and tolerability

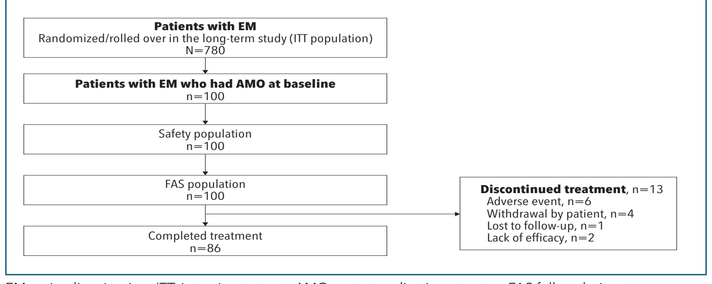
- Adverse events (AEs) and systematic local injection-site assessments (immediately and at 1 hour post-injection)

RESULTS

Patient Demographics and Baseline Characteristics

- Of the 780 patients with EM enrolled in this study, 100 (12.8%) had AMO at baseline (**Figure 1**)

Figure 1. Patient Disposition[a]



EM, episodic migraine; ITT, intention to treat; AMO, acute medication overuse; FAS full analysis set.
[a]Patient flow was based on an interim analysis with some patients' complete status unknown (missing or ongoing); group numbers may not sum to total.

- Baseline patient demographics and clinical characteristics of patients with EM who had AMO at baseline were similar between both treatment arms (**Table 1**)

Table 1. Baseline Demographics and Clinical Characteristics for Patients With EM Who Had AMO at Baseline

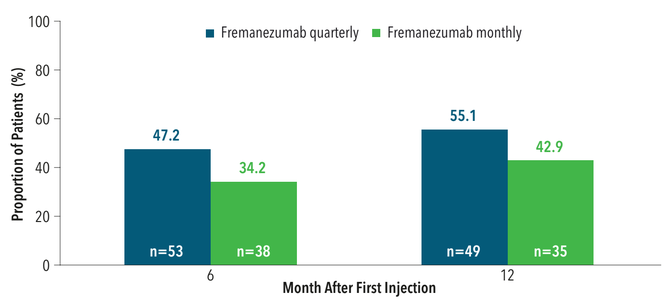
	Fremanezumab quarterly (n=58)	Fremanezumab monthly (n=42)
Patient demographics		
Age, mean (SD), y	47.5 (11.8)	50.1 (9.8)
Sex, female, n (%)	49 (84)	38 (90)
BMI, mean (SD), kg/m^2	24.9 (4.2)	26.0 (4.6)
Disease history		
Years since initial migraine diagnosis, mean (SD)	28.0 (13.9)	27.9 (14.1)
Current preventive medication use, n (%)	15 (26)	11 (26)
Current acute headache medication use, n (%)	58 (100)	42 (100)
Prior topiramate use, n (%)	25 (43)	17 (40)
Prior onabotulinumtoxinA use, n (%)	8 (14)	7 (17)
Disease characteristics		
Headache days of any severity and duration, mean (SD)	13.0 (1.7)	12.7 (1.7)
Headache days of at least moderate severity, mean (SD)[a]	11.8 (1.8)	11.5 (2.0)
Migraine days, mean (SD)[b]	12.2 (1.8)	12.3 (1.8)
Days with any acute headache medication use, mean (SD)	12.1 (1.9)	12.2 (1.5)
MIDAS score, mean (SD)	36.1 (26.3)	46.0 (40.7)

EM, episodic migraine; AMO, acute medication overuse; 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 patient 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).

≥50% Response Rates in Patients With EM Who Had AMO at Baseline

- The proportion of patients with a ≥50% reduction in the monthly average number of migraine days with fremanezumab quarterly and monthly was maintained from Month 6 to Month 12 (**Figure 2**)

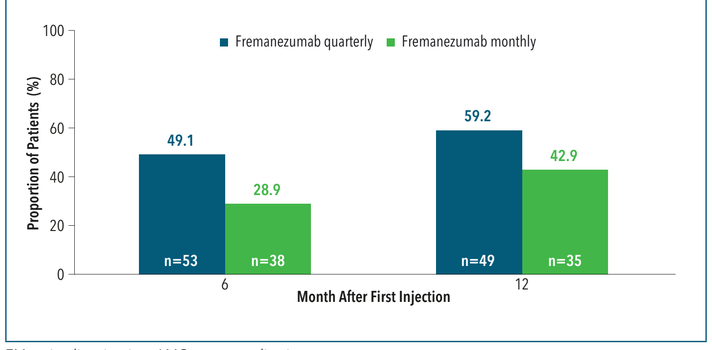
Figure 2. ≥50% Reduction in the Monthly Average Number of Migraine Days in Patients With EM Who Had AMO at Baseline



EM, episodic migraine; AMO, acute medication overuse.

- The proportion of patients with a ≥50% reduction in the monthly average number of headache days of at least moderate severity with fremanezumab quarterly and monthly was maintained from Month 6 to Month 12 (**Figure 3**)

Figure 3. ≥50% Reduction in the Monthly Average Number of Headache Days of at Least Moderate Severity in Patients With EM Who Had AMO at Baseline

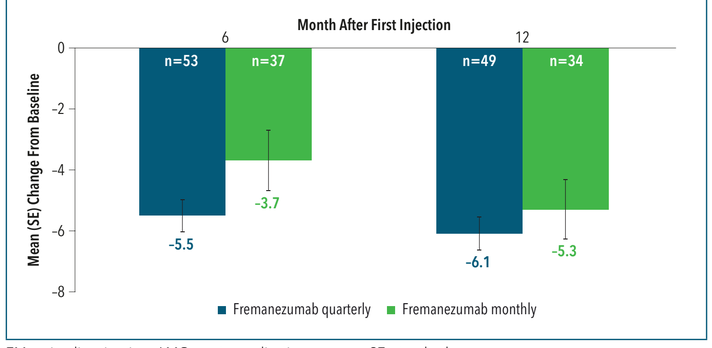


EM, episodic migraine; AMO, acute medication overuse.

Change in Any Acute Headache Medication Use

- Fremanezumab quarterly and monthly reduced monthly average number of days of any acute medication use by EM patients with AMO at Month 6 and Month 12 (**Figure 4**)
- Following treatment with fremanezumab, more than 60% of patients with EM and AMO at baseline had reverted to no AMO at Month 6 (quarterly: 85% [n=45/53]; monthly: 61% [n=23/38]), and reversion was maintained through Month 12 (quarterly: 86% [n=42/49]; monthly: 77% [n=27/35])

Figure 4. Change in the Monthly Average Number of Days of Any Acute Headache Medication Use in Patients With EM Who Had AMO at Baseline

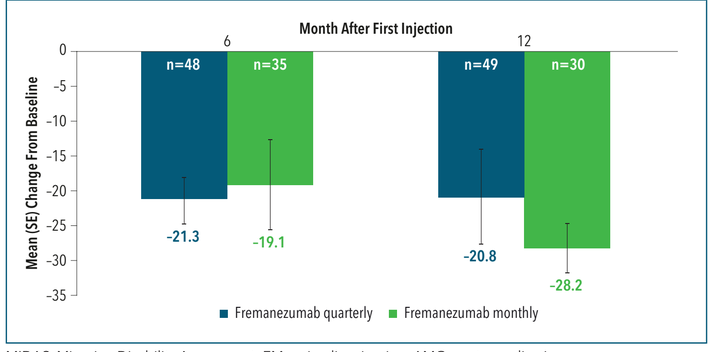


EM, episodic migraine; AMO, acute medication overuse; SE, standard error.

Headache-Related Disability

- Fremanezumab quarterly and monthly reduced headache-related disability in patients with EM who had AMO at baseline, as demonstrated by a decrease from baseline in MIDAS score at Month 6 and Month 12 (**Figure 5**)

Figure 5. Change in MIDAS Scores in Patients With EM Who Had AMO at Baseline



MIDAS, Migraine Disability Assessment; EM, episodic migraine; AMO, acute medication overuse; SE, standard error.

Safety and Tolerability in Patients With EM Who Had AMO at Baseline

- Similar proportions of patients with EM in each fremanezumab treatment arm reported at least one AE (**Table 2**)
- The most commonly reported AEs were injection-site reactions, with proportions of patients being slightly higher in the fremanezumab monthly group (**Table 2**)
- Serious AEs and AEs leading to discontinuation were infrequent, with similar proportions of patients between treatment groups (**Table 2**)

Table 2. AEs in Patients With EM Who Had AMO at Baseline

	Fremanezumab quarterly (n=58)	Fremanezumab monthly (n=42)
Patients with AEs, n (%)		
At least one AE	48 (83)	35 (83)
At least one treatment-related AE	29 (50)	26 (62)
At least one serious AE	3 (5)	2 (5)
Any AE leading to discontinuation of the study	2 (3)	4 (10)
Injection-site reactions (occurring in >6% of patients in any treatment group), n (%)[a]		
Injection-site induration	15 (26)	15 (36)
Injection-site pain	17 (29)	18 (43)
Injection-site erythema	13 (22)	15 (36)
Injection-site hemorrhage	2 (3)	4 (10)
Other common AEs (occurring in >6% of patients in any treatment group), n (%)		
Upper respiratory tract infection	6 (10)	4 (10)
Nasopharyngitis	10 (17)	7 (17)
Vertigo	2 (3)	3 (7)
Urinary tract infection	3 (5)	4 (10)
Ligament sprain	2 (3)	3 (7)
Anxiety	2 (3)	3 (7)

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

References

1. Saper JR, Da Silva AN. *CNS Drugs* 2013;27:867–877.
2. Katsarava Z et al. *Curr Pain Headache Rep* 2012;6:86–92.
3. Hoy SM. *Drugs* 2018;78:1829–1834.
4. AJOVY® (fremanezumab) [prescribing information]. Teva Pharmaceuticals USA, Inc.; 2018.
5. AJOVY (fremanezumab) [Summary of Product Characteristics]. Teva Pharmaceuticals GmbH; 2019.

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