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Long-Term Response Rates in Chronic and Episodic Migraine Patients With Concomitant Preventive Medication Use: Results of a 1-Year Study

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CONCLUSIONS

- Fremanezumab led to clinically meaningful reductions in the monthly number of headache days of at least moderate severity and migraine days in patients with CM or EM receiving concomitant migraine preventive medications
- Response rates generally increased over time, suggesting that greater percentages of patients had clinically meaningful reductions in headache and migraine days with longer treatment durations
- Fremanezumab had an acceptable safety profile in patients who used concomitant preventive medication
- This analysis demonstrated that adding fremanezumab to an existing oral migraine preventive medication regimen results in clinically meaningful response rates for up to 12 months with no safety signals

INTRODUCTION

- Response rates are important endpoints for assessing the efficacy of migraine preventive medications, and ≥50% response rates are considered clinically meaningful[1–3]
- 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[4–6]
- A 52-week extension study evaluated the long-term safety and efficacy of fremanezumab

OBJECTIVE

- To evaluate long-term response rates (≥50%, ≥75%, and 100% reductions in monthly average number of migraine days and headache days of at least moderate severity from baseline) in a subgroup of patients with concomitant preventive medication use

METHODS

Study Design

- This was a 12-month, multicenter, randomized, double-blind, parallel-group Phase 3 study (NCT02638103) (**Figure 1**)
  - Patients who completed the HALO CM (NCT02621931) and EM (NCT02629861) pivotal efficacy studies had the option to enroll in this long-term HALO study ("rollover patients"), and a subset of "new patients" could directly enroll

Patient Population

Key inclusion criteria

- 18–70 years of age
- History of migraine (according to International Classification of Headache Disorders, third edition, beta version [ICHD-3 beta] criteria) for ≥12 months prior to screening
- Patients with CM: prospectively confirmed CM during the 28-day pre-treatment baseline period
  - Headache of any severity and duration on ≥15 days
  - ≥8 days fulfilling ICHD-3 beta criteria for migraine or probable migraine or use of triptan or ergot medications
- Patients with EM: 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 for migraine 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
  - Patients using migraine preventive medications were encouraged to continue their preventive medication regimen without change for the duration of the study; however, if discontinuation was clinically indicated by the investigator, the medication could be stopped
  - Patients not using migraine preventive medications were asked not to initiate preventive medications during the study

Key exclusion criteria

- For rollover patients at screening in the previous HALO CM or EM trials:
  - 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 due to lack of efficacy in two or more of the following four 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
- The above exclusion criteria did not apply to new patients

Study Treatment

- In the initial placebo-controlled HALO CM and EM trials, 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 (CM: 675 mg at baseline and 225 mg at Weeks 4 and 8; EM: 225 mg at baseline and at Weeks 4 and 8)
  - Placebo at baseline and at Weeks 4 and 8
- In the long-term study, rollover patients who received fremanezumab quarterly or monthly in the placebo-controlled trials continued the same treatment, while rollover 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%, ≥75%, and 100% reduction from baseline in the monthly average number of headache days of at least moderate severity and in the monthly average number of migraine days

Safety and tolerability

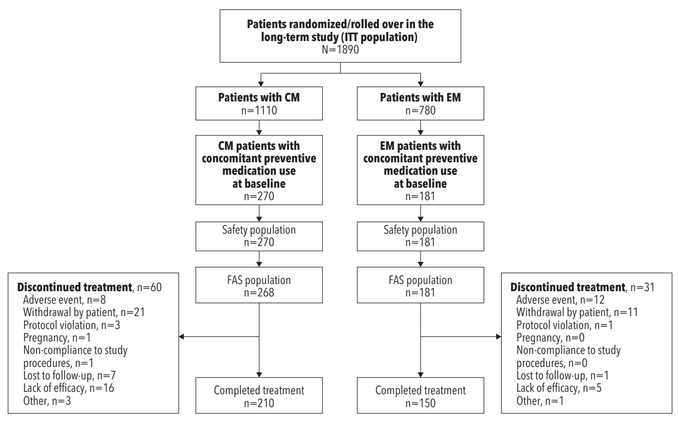
- Adverse events (AEs) and systematic local injection-site assessments (immediately and at 1 hour post-injection)

RESULTS

Study Population

- Of the 1890 patients enrolled in this study, 270 (24%) of 1110 patients with CM and 181 (23%) of 780 patients with EM were using concomitant preventive medication at baseline (**Figure 1**)

Figure 1. Patient Disposition



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

- Within each migraine diagnosis group, baseline demographics and disease characteristics were similar between treatment groups (**Table 1**)
- The most commonly used concomitant preventive medication for patients with CM and patients with EM was topiramate (CM, 37%; EM, 37%), followed by amitriptyline-containing compounds (CM, 22%; EM, 17%)

Table 1. Baseline Demographics and Disease Characteristics for Patients With CM and EM Using Concomitant Preventive Medication at Baseline[a]

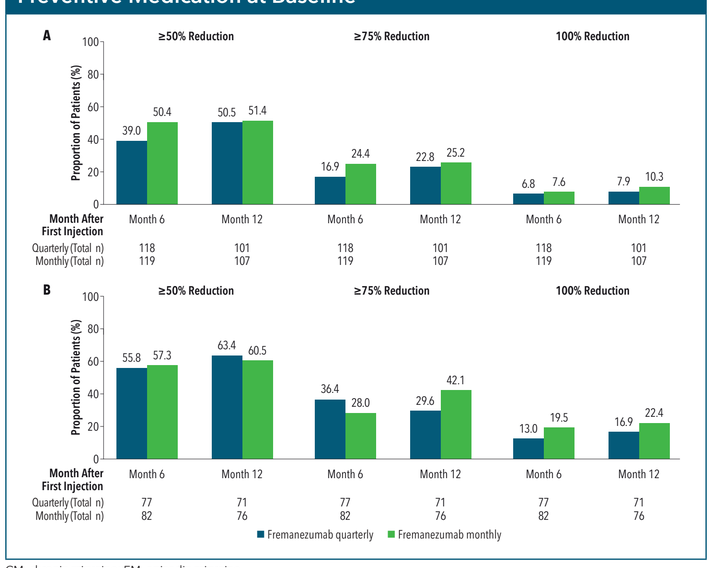
	CM		EM	
	Fremanezumab quarterly (n=128)	Fremanezumab monthly (n=142)	Fremanezumab quarterly (n=89)	Fremanezumab monthly (n=92)
Patient demographics				
Age, mean (SD), y	43.7 (11.3)	44.8 (11.5)	45.7 (12.3)	47.6 (12.3)
Sex, female, n (%)	115 (90)	128 (90)	79 (89)	82 (89)
BMI, mean (SD), kg/m^2	25.8 (5.1)	25.2 (4.9)	27.8 (5.2)	26.3 (5.2)
Disease history				
Years since initial migraine diagnosis, mean (SD)	20.1 (13.1)	23.0 (12.7)	23.0 (13.6)	22.7 (14.4)
Current preventive medication use, n (%)[b]	128 (100)	142 (100)	89 (100)	92 (100)
Antiepileptics	55 (43)	71 (50)	45 (51)	45 (49)
Antidepressants	58 (45)	70 (49)	34 (38)	31 (34)
Beta-blockers	38 (30)	30 (21)	17 (19)	25 (27)
Calcium channel blockers or benzocycloheptene	1 (1)	1 (1)	3 (3)	2 (2)
Current acute headache medication use, n (%)	127 (>99)	138 (97)	87 (98)	89 (97)
Prior topiramate use, n (%)	48 (38)	49 (35)	20 (22)	24 (26)
Prior onabotulinumtoxinA use, n (%)	39 (30)	45 (32)	10 (11)	9 (10)
Disease characteristics during the 28-day pre-treatment period				
Headache days of any severity and duration, mean (SD)	20.2 (4.3)	21.0 (4.4)	11.1 (2.4)	11.0 (2.5)
Headache days of at least moderate severity, mean (SD)[c]	14.2 (5.8)	14.7 (6.0)	7.5 (2.9)	7.8 (3.0)
Migraine days, mean (SD)[d]	16.6 (5.0)	17.1 (5.8)	9.1 (2.6)	9.3 (2.7)

CM, chronic migraine; EM, episodic migraine; SD, standard deviation; BMI, body mass index.
[a]In the intention-to-treat population. [b]Patients flagged for preventive medication use at baseline who did not have their medication recorded in the medication database were not included in the analysis of preventive medication by therapeutic class (CM: quarterly n=1, monthly n=4; EM: quarterly n=1, monthly n=2). [c]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 an acute migraine-specific medication (triptan or ergot) was used to treat a headache of any severity or duration. [d]A calendar day in which the patient reported either headache pain that lasted ≥4 hours (CM) or ≥2 hours (EM) 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).

Response Rates for Headache Days of at Least Moderate Severity

- Approximately half of all patients with CM had a ≥50% reduction in monthly average number of headache days of at least moderate severity at Month 12, while nearly one-quarter had a ≥75% reduction (**Figure 2A**)
- For patients with EM, a majority had a ≥50% reduction at Months 6 and 12, regardless of fremanezumab dosing regimen (**Figure 2B**)

Figure 2. ≥50%, ≥75%, and 100% Reductions in Monthly Average Number of Headache Days of at Least Moderate Severity in (A) Patients With CM and (B) Patients With EM Using Concomitant Preventive Medication at Baseline

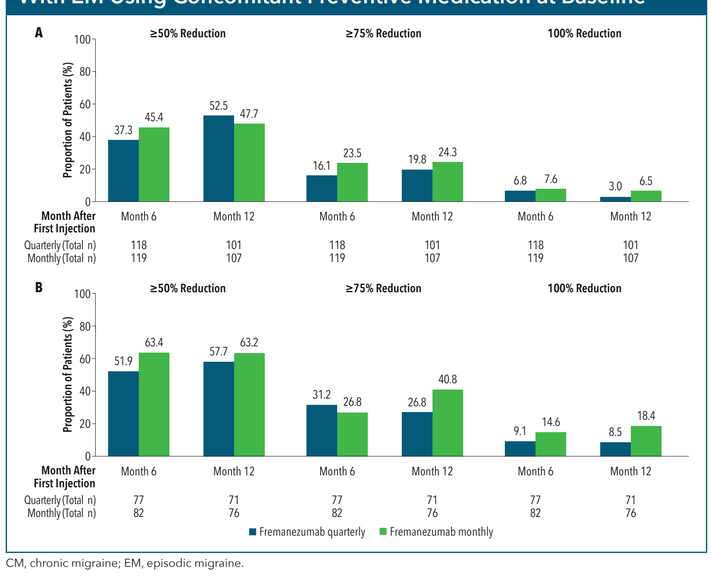


CM, chronic migraine; EM, episodic migraine.

Response Rates for Migraine Days

- Approximately half of patients with CM had a ≥50% reduction in average number of migraine days at Month 12 (**Figure 3A**)
- A majority of patients with EM who were treated with fremanezumab quarterly or monthly had a ≥50% reduction at Months 6 and 12 (**Figure 3B**)

Figure 3. ≥50%, ≥75%, and 100% Reductions in Monthly Average Number of Migraine Days in (A) Patients With CM and (B) Patients With EM Using Concomitant Preventive Medication at Baseline



CM, chronic migraine; EM, episodic migraine.

Safety and Tolerability

- AEs occurred with generally similar frequency across groups (**Table 2**)
- Treatment-related AEs were reported in 48–61% of patients (**Table 2**)
- Serious AEs and AEs leading to study discontinuation were infrequent, with similar proportions of patients within diagnosis groups (**Table 2**)
- Injection-site reactions (pain, induration, erythema) were the most frequently reported AEs across all groups (**Table 2**)

Table 2. Summary of AEs and AEs of Interest in the Safety Population for Patients With CM and EM Using Concomitant Oral Preventive Medication at Baseline

	CM		EM	
	Fremanezumab quarterly (n=128)	Fremanezumab monthly (n=142)	Fremanezumab quarterly (n=89)	Fremanezumab monthly (n=92)
Patients with AEs, n (%)				
At least one AE	104 (81)	125 (88)	75 (84)	77 (84)
At least one treatment-related AE	69 (54)	87 (61)	43 (48)	55 (60)
At least one serious AE	12 (9)	8 (6)	5 (6)	7 (8)
Any AE leading to discontinuation	4 (3)	4 (3)	6 (7)	6 (7)
Death	0	0	0	0
Injection-site reactions (occurring in >6% of patients in any treatment group), n (%)[a]				
Injection-site pain	38 (30)	50 (35)	23 (26)	31 (34)
Injection-site induration	30 (23)	51 (36)	18 (20)	32 (35)
Injection-site erythema	30 (23)	41 (29)	20 (22)	20 (22)
Injection-site pruritus	8 (6)	11 (8)	3 (3)	10 (11)
Injection-site hemorrhage	9 (7)	10 (7)	5 (6)	4 (4)
Other common AEs (occurring in >6% of patients in any treatment group), n (%)				
Nasopharyngitis	13 (10)	11 (8)	11 (12)	14 (15)
Upper respiratory tract infection	16 (13)	13 (9)	12 (13)	7 (8)
Sinusitis	15 (12)	9 (6)	7 (8)	5 (5)
Influenza	7 (5)	13 (9)	3 (3)	4 (4)
Urinary tract infection	9 (7)	6 (4)	5 (6)	4 (4)
Bronchitis	5 (4)	6 (4)	8 (9)	2 (2)
Diarrhea	7 (5)	10 (7)	1 (1)	3 (3)
Fatigue	1 (<1)	1 (<1)	2 (2)	6 (7)

AE, adverse event; CM, chronic migraine; 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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