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Long-Term Efficacy of Fremanezumab in Chronic and Episodic Migraine Patients Who Failed at Least One Prior Migraine Preventive Medication: Results of a 1-Year Study

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CONCLUSIONS

- In patients with chronic migraine (CM) or episodic migraine (EM) who had failed at least one prior migraine preventive medication, long-term fremanezumab treatment showed sustained efficacy, as demonstrated by reductions in the number of headache days of at least moderate severity and the number of migraine days for up to 12 months
  - These data suggest that migraine patients with prior migraine preventive treatment failure, who may represent a patient population with more difficult-to-treat migraine, can achieve long-term benefit with fremanezumab treatment
- These results support the findings of the 12-week, placebo-controlled HALO CM and HALO EM studies and demonstrate that the efficacy and safety of fremanezumab are maintained over long-term treatment in this population with more-complex disease
- Results from this *post hoc* analysis will help to inform clinical decision-making for physicians treating patients with CM or EM who have failed at least one prior migraine preventive medication

INTRODUCTION

- Many of the currently available medications used for the prevention of CM or EM were not designed for the treatment of migraine and have limited-to-moderate 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 efficacy and safety of fremanezumab in patients with CM or 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 prior Phase 3 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 CM during the 28-day pre-treatment baseline period:
  - Headache on ≥15 days
  - ≥8 days fulfilling ICHD-3 beta criteria for migraine, probable migraine, or use of triptan or ergot medications
- 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, probable migraine, or use of triptan or ergot medications

Key exclusion criteria

- For patients at screening from prior phase 3 (HALO EM and HALO CM) 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 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 CM and HALO 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 trial, patients who received fremanezumab quarterly or monthly in the prior placebo-controlled trials continued on the same treatment, while patients who previously received placebo and new patients were randomized 1:1 to fremanezumab either quarterly or monthly
- All patients remained blinded as to which dosing regimen they received during the long-term study

Outcomes

Efficacy

- Mean change 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

Safety and tolerability

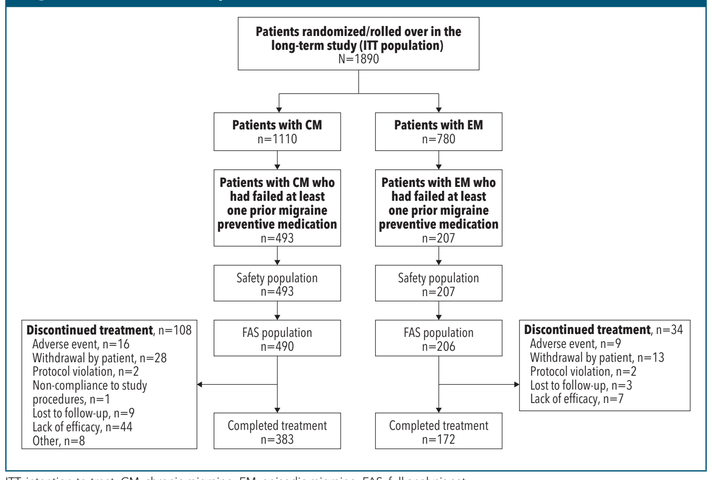
- Adverse events (AEs) and systematic local injection-site assessments (immediately and at 1 hour post-injection)

RESULTS

Study Population

- Of the 1890 patients with CM or EM enrolled in this study, 700 (37.0%) had failed at least one prior migraine preventive medication (**Figure 1**)

Figure 1. Patient Disposition[a]



ITT, intention-to-treat; CM, chronic migraine; EM, episodic migraine; 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 demographics and disease characteristics were similar between fremanezumab treatment arms within diagnosis (**Table 1**)

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

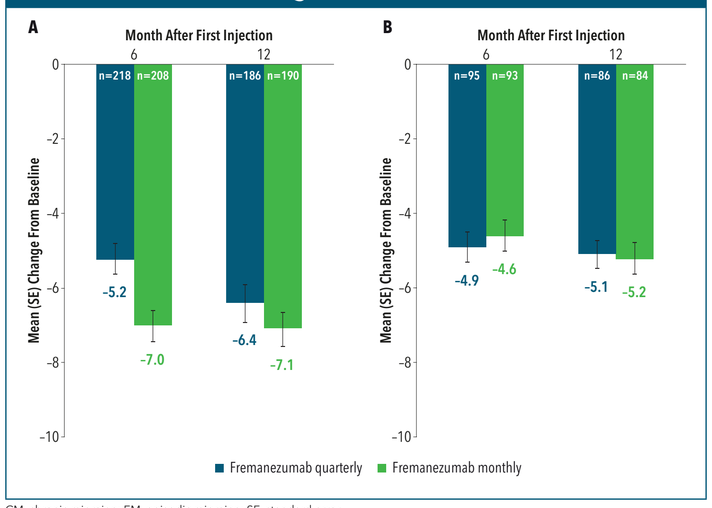
	CM		EM	
	Fremanezumab quarterly (n=247)	Fremanezumab monthly (n=246)	Fremanezumab quarterly (n=105)	Fremanezumab monthly (n=102)
Patient demographics				
Age, mean (SD), y	45.6 (11.8)	45.1 (11.8)	47.2 (11.7)	47.2 (11.7)
Sex, female, n (%)	218 (88)	217 (88)	91 (87)	93 (91)
BMI, mean (SD), kg/m^2	25.9 (4.9)	26.0 (5.2)	26.8 (5.0)	25.9 (4.4)
Disease history				
Years since initial migraine diagnosis, mean (SD)	23.6 (13.3)	24.2 (12.2)	26.4 (14.0)	24.5 (13.3)
Current preventive medication use, n (%)	68 (28)	69 (28)	30 (29)	28 (27)
Current acute headache medication use, n (%)	242 (98)	240 (98)	103 (98)	100 (98)
Prior topiramate use, n (%)	194 (79)	192 (78)	81 (77)	92 (90)
Prior onabotulinumtoxinA use, n (%)	109 (44)	112 (46)	24 (23)	23 (23)
Disease characteristics during the 28-day pre-treatment period				
Headache days of any severity and duration, mean (SD)	20.6 (4.3)	21.1 (4.3)	11.6 (2.2)	11.4 (2.4)
Headache days of at least moderate severity, mean (SD)[a]	15.1 (5.6)	15.1 (5.9)	8.4 (3.2)	8.3 (2.8)
Migraine days, mean (SD)[b]	17.1 (5.2)	17.0 (5.5)	9.8 (2.6)	9.7 (2.7)
Days with any acute headache medication use, mean (SD)	14.7 (6.6)	14.7 (6.7)	9.3 (3.3)	9.0 (3.2)

CM, chronic migraine; EM, episodic migraine; SD, standard deviation; BMI, body mass index.
[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 ≥4 (for CM) or ≥2 (for EM) 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).

Change in Migraine Days in Patients With CM or EM Who Had Failed at Least One Prior Migraine Preventive Medication

- At Month 12, the monthly average number of migraine days reported by patients with CM who had failed at least one prior migraine preventive medication decreased by 39% with fremanezumab quarterly and by 44% with fremanezumab monthly (**Figure 2A**)
- In patients with EM who had failed at least one prior migraine preventive medication, fremanezumab quarterly and monthly reduced the monthly average number of migraine days by 53% and 52%, respectively, at Month 12 (**Figure 2B**)

Figure 2. Change in the Monthly Average Number of Migraine Days in (A) Patients With CM or (B) Patients With EM Who Had Failed at Least One Prior Migraine Preventive Medication

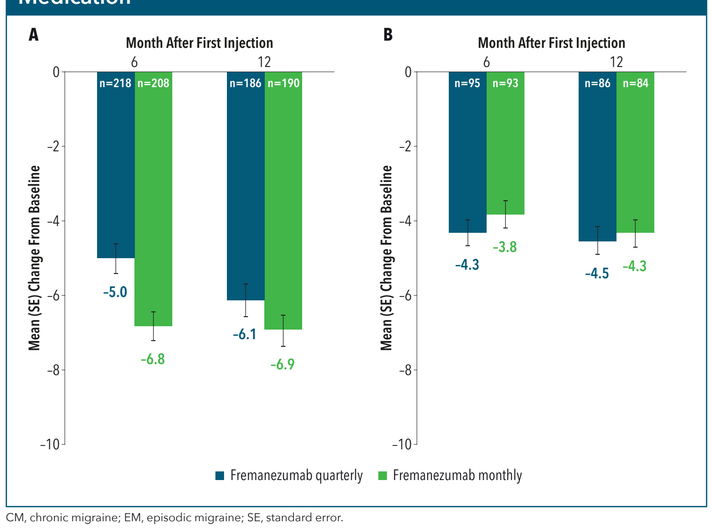


CM, chronic migraine; EM, episodic migraine; SE, standard error.

Change in Headache Days of at Least Moderate Severity in Patients With CM or EM Who Had Failed at Least One Prior Migraine Preventive Medication

- At Month 12, the monthly average number of headache days of at least moderate severity reported by CM patients who had failed at least one prior migraine preventive medication decreased by 43% with fremanezumab quarterly and by 48% with fremanezumab monthly (**Figure 3A**)
- In EM patients who had failed at least one prior migraine preventive medication, fremanezumab quarterly and monthly reduced the monthly average number of migraine days by 54% and 49%, respectively, at Month 12 (**Figure 3B**)

Figure 3. Change in the Monthly Average Number of Headache Days of at Least Moderate Severity in Patients With (A) CM and (B) EM Who Had Failed at Least One Prior Migraine Preventive Medication



CM, chronic migraine; EM, episodic migraine; SE, standard error.

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

- Similar proportions of CM and EM patients in each fremanezumab treatment arm 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 Patients With CM or EM Who Had Failed at Least One Prior Migraine Preventive Medication

	CM		EM	
	Fremanezumab quarterly (n=247)	Fremanezumab monthly (n=246)	Fremanezumab quarterly (n=105)	Fremanezumab monthly (n=102)
Patients with AEs, n (%)				
At least one AE	212 (86)	226 (92)	92 (88)	81 (79)
At least one treatment-related AE	141 (57)	162 (66)	61 (58)	57 (56)
At least one serious AE	17 (7)	16 (7)	6 (6)	8 (8)
Any AE leading to discontinuation of the study	10 (4)	7 (3)	5 (5)	4 (4)
Injection-site reactions (occurring in >6% of patients in any treatment group), n (%)[a]				
Injection-site induration	76 (31)	100 (41)	30 (29)	35 (34)
Injection-site pain	70 (28)	92 (37)	30 (29)	29 (28)
Injection-site erythema	72 (29)	84 (34)	26 (25)	30 (29)
Injection-site pruritus	15 (6)	22 (9)	7 (7)	11 (11)
Injection-site hemorrhage	22 (9)	27 (11)	5 (5)	5 (5)
Other common AEs (occurring in >6% of patients in any treatment group), n (%)				
Upper respiratory tract infection	33 (13)	28 (11)	11 (10)	13 (13)
Nasopharyngitis	28 (11)	27 (11)	9 (9)	10 (10)
Bronchitis	12 (5)	10 (4)	7 (7)	4 (4)
Gastroenteritis	4 (2)	1 (<1)	7 (7)	1 (<1)
Sinusitis	21 (9)	21 (9)	5 (5)	2 (2)
Urinary tract infection	15 (6)	12 (5)	6 (6)	8 (8)

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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Disclosures

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