Impact of Fremanezumab on the Number of Days With Use of Acute Headache Medications in Chronic Migraine

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CONCLUSIONS

- The HALO CM study of fremanezumab met the primary and all secondary endpoints (data not shown)[10]
- Fremanezumab resulted in significantly greater reductions in the need for use of acute headache medications, including migraine-specific medications, in patients with CM compared with placebo
- The sustained effect of fremanezumab in reducing the use of acute headache medication highlights its value as a preventive treatment for patients with CM

INTRODUCTION

- Chronic migraine (CM) is a debilitating neurological disease that afflicts 1.4–2.2% of the global population[1,2]
  - Patients with CM have ≥15 headache days per month for >3 months, with ≥8 days per month with the features of migraine headache[3]
- Overuse of acute headache medications is common in people with CM and can promote disease progression and the development of medication-overuse headache[3-5]
- Fremanezumab is a fully humanized monoclonal antibody (IgG2Δa) that selectively targets calcitonin gene-related peptide (CGRP)[6,7]
- Fremanezumab has demonstrated a significant treatment effect and a good tolerability/safety profile as a preventive treatment for migraine[8-10]
  - Fremanezumab has been studied in two subcutaneous dose regimens, quarterly and monthly, to offer flexible administration[8-10]
  - In clinical trials, fremanezumab significantly reduced the frequency of migraine headaches, without serious treatment-related adverse events (AEs)[8-10]
- The sustained effect of preventive migraine treatment on the reduction of acute migraine medication use may provide specific insight into the value of prophylaxis
- The Phase 3 HALO CM trial evaluated fremanezumab for the preventive treatment of CM[10]

OBJECTIVE

- To evaluate the efficacy of fremanezumab in patients with CM by assessing the change in use of acute headache medications

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 baseline period, a 12-week treatment period, and a final evaluation at Week 12 (**Figure 1**)
  - At screening, patients signed two consent forms, one for this study (NCT02621931) and one for the concurrent EM study (NCT02629861)
  - Based on screening and baseline daily diary information, patients were randomized into the appropriate trial or were excluded

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 per month
  - ≥8 days fulfilling ICHD3-beta criteria for migraine, 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 during the pre-treatment baseline period
- Use of interventions or devices for migraine in the 2 months before screening
- 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 baseline 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:
  - 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 endpoint

- Mean change in the monthly average number of days of use of any acute headache medications

Key exploratory endpoint

- Mean change in the monthly average number of days of use of migraine-specific acute headache medications (triptans and ergot compounds)

Safety endpoints

- AEs were monitored throughout the study
- Additional safety variables included vital signs, clinical lab tests, and injection-site assessments

Statistical Analysis

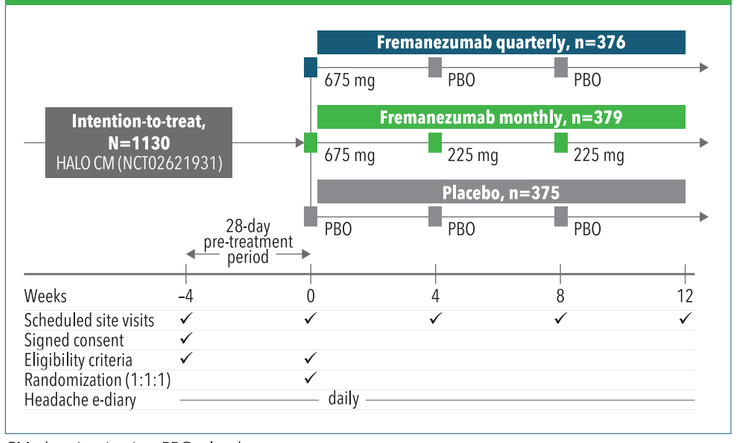
- Efficacy analyses were conducted in full analysis set (FAS): randomized patients who received ≥1 dose of study drug and had ≥10 days of post-baseline efficacy assessments on the primary endpoint
- Mean change from baseline for each endpoint during the 12-week period was analyzed via analysis of covariance (ANCOVA)
  - Fixed effects: treatment, sex, region (US vs non-US), and baseline preventive migraine medication
  - Covariates: baseline values and years since onset of migraines
- A mixed-effect repeated-measures (MMRM) analysis model was used to estimate the mean change from baseline for each endpoint
- Safety population: randomized patients who received ≥1 dose of study drug

RESULTS

Study Population

- A total of 1130 patients were randomized to this study, and more than 90% in each treatment arm completed the study (**Figure 1**)

Figure 1. Study Design



CM, chronic migraine; PBO, placebo.

- Baseline patient demographics and clinical characteristics were similar between all treatment arms (**Table 1**)

Table 1. Baseline Patient Demographics and Clinical Characteristics

Characteristic	Fremanezumab		
	Quarterly (n=376)	**Monthly** (n=379)	**Placebo** (n=375)
Age, mean (SD)	42.0 (12.4)	40.6 (12.0)	41.4 (12.0)
BMI, kg/m^2, mean (SD)	26.6 (5.4)	26.5 (5.1)	26.5 (5.0)
Female, n (%)	331 (88)	330 (87)	330 (88)
Disease history			
Years since initial migraine diagnosis, mean (SD)	19.7 (12.8)	20.1 (12.0)	19.9 (12.9)
Current preventive medication use, n (%)	77 (20)	85 (22)	77 (21)
Current acute headache medication use, n (%)	359 (95)	360 (95)	358 (95)
Prior topiramate use, n (%)	106 (28)	117 (31)	117 (31)
Prior onabotulinumtoxinA use, n (%)	66 (18)	50 (13)	49 (13)
Triptan/ergot use, n (%)	208 (55)	187 (49)	192 (51)
Disease characteristics during 28-day pre-treatment period			
Headache days of at least moderate severity, mean (SD)[a]	13.2 (5.5)	12.8 (5.8)	13.3 (5.8)
Migraine days, mean (SD)[b]	16.2 (4.9)	16.0 (5.2)	16.4 (5.2)
Days of any acute headache medication use, mean (SD)	13.1 (6.8)	13.1 (7.2)	13.0 (6.9)
Days of migraine-specific acute headache medication use, mean (SD)	11.3 (6.2)	11.1 (6.0)	10.7 (6.3)

[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) was used to treat a headache of any severity or duration. [b]A calendar day in which the patient reported either a day with 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; SD, standard deviation.

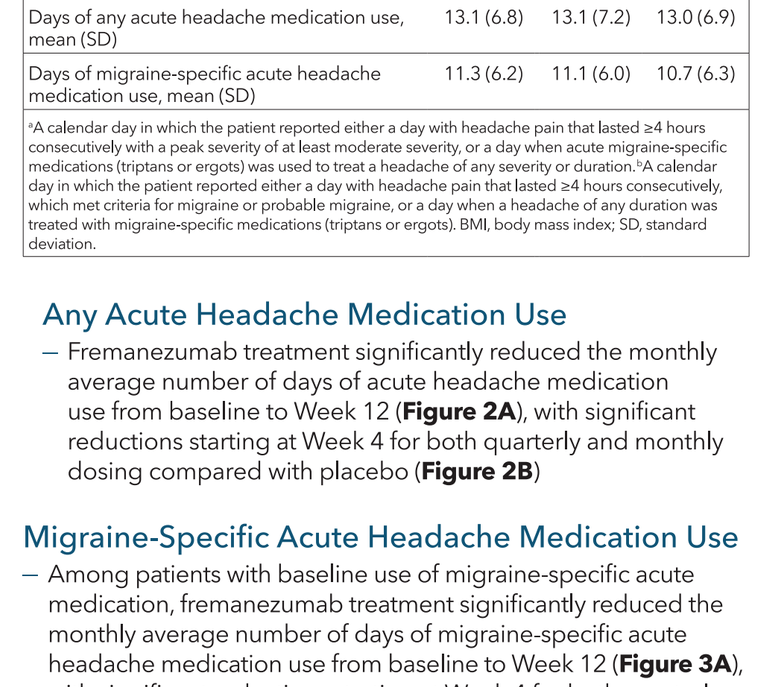
Any Acute Headache Medication Use

- Fremanezumab treatment significantly reduced the monthly average number of days of acute headache medication use from baseline to Week 12 (**Figure 2A**), with significant reductions starting at Week 4 for both quarterly and monthly dosing compared with placebo (**Figure 2B**)

Migraine-Specific Acute Headache Medication Use

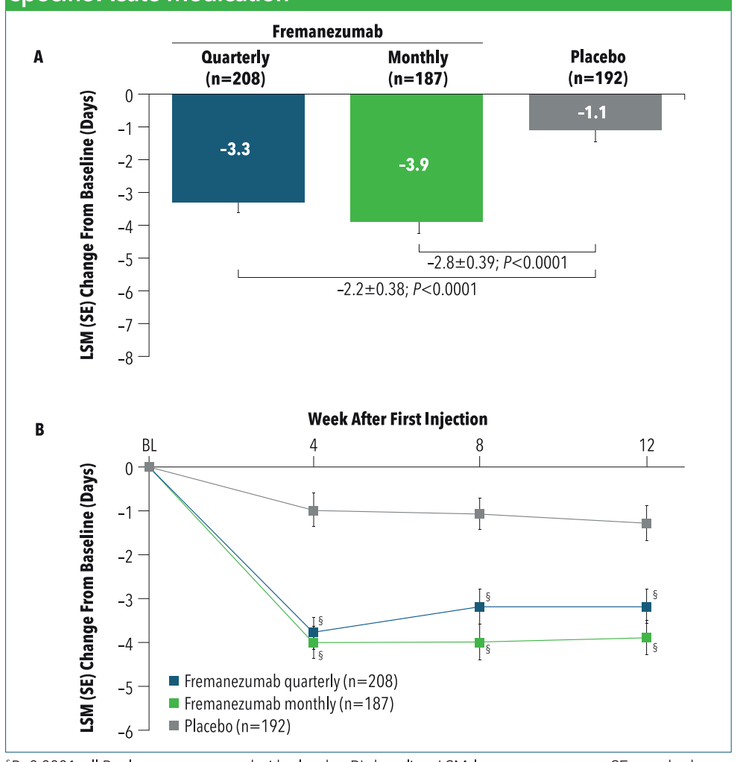
- Among patients with baseline use of migraine-specific acute medication, fremanezumab treatment significantly reduced the monthly average number of days of migraine-specific acute headache medication use from baseline to Week 12 (**Figure 3A**), with significant reductions starting at Week 4 for both quarterly and monthly dosing compared with placebo (**Figure 3B**)

Figure 2. Change in the Monthly Average Number of Days of Any Acute Headache Medication Use During the 12-Week Treatment Period



‡P<0.001; §P<0.0001; all P values are compared with placebo. BL, baseline; LSM, least-squares mean; SE, standard error.

Figure 3. Change in the Monthly Average Number of Days of Migraine-Specific Acute Headache Medication Use During the 12-Week Treatment Period: Patients With Baseline Use of Migraine-specific Acute Medication



§P<0.0001; all P values are compared with placebo. BL, baseline; LSM, least-squares mean; SE, standard error.

Safety and Tolerability

- Similar proportions of patients in each fremanezumab treatment arm reported at least one AE, compared with a lower proportion in the placebo arm (**Table 2**)
  - The most commonly reported AE was injection-site pain, with similar incidence rates between groups (**Table 2**)
- Serious AEs, and AEs leading to discontinuation were infrequent, with similar incidences across treatment groups (**Table 2**)
- One death occurred in the fremanezumab quarterly group and was due to chronic obstructive pulmonary disease (COPD) per autopsy, which was determined to be unrelated to treatment
- Two patients who received the fremanezumab quarterly regimen developed anti-drug antibodies

Table 2. Adverse Events in the Safety Population

Characteristic	Fremanezumab		
	Quarterly (n=376)	**Monthly** (n=379)	**Placebo** (n=375)
All events – number of patients (%)			
At least one AE	265 (70)	270 (71)	240 (64)
At least one treatment-related AE	186 (49)	194 (51)	159 (42)
At least one serious AE	3 (<1)	5 (1)	6 (2)
Any AE leading to discontinuation of the study	5 (1)	7 (2)	8 (2)
Death	1[a](<1)	0	0
Injection-site reactions – number of patients (%)[b]			
Injection-site pain	114 (30)	99 (26)	104 (28)
Injection-site induration	74 (20)	90 (24)	68 (18)
Injection-site erythema	80 (21)	75 (20)	60 (16)
Injection-site hemorrhage	7 (2)	8 (2)	10 (3)
Other AEs – number of patients (%)[c]			
Nasopharyngitis	19 (5)	15 (4)	20 (5)
Upper respiratory tract infection	18 (5)	16 (4)	15 (4)
Sinusitis	10 (3)	4 (1)	10 (3)
Dizziness	9 (2)	11 (3)	5 (1)
Nausea	4 (1)	6 (2)	11 (3)

[a]Patient died secondary to COPD per autopsy report. [b]Local injection sites were systematically assessed for erythema, induration, ecchymosis, and pain both immediately and 1 hour after dosing. Injection-site reactions shown include those reported in ≥2% of patients in any group. [c]Adverse events shown include those reported in ≥2% of patients in any group. AE, adverse event; COPD, chronic obstructive pulmonary disease.

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Disclosures

Patricia Pozo-Rosich: Has received honoraria as a consultant and speaker for Allergan, Amgen, Almirall, Chiesi, Eli Lilly, Medscape, Novartis, and Teva. Her research group has received research grants from Allergan and funding for clinical trials from Alder, electroCore, Eli Lilly, Novartis, and Teva.
Joshua Cohen: Employee of Teva Pharmaceuticals.
Melissa Grozinski-Wolff: Employee of Teva Pharmaceuticals.
Ronghua Yang: Employee of Teva Pharmaceuticals

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