Reversion of Patients With Chronic Migraine to an Episodic Migraine Classification With Fremanezumab Treatment

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CONCLUSIONS

- Fremanezumab demonstrated efficacy as a preventive therapy for chronic migraine (CM), based on the decrease in monthly average number of headache days over the treatment period
- Fremanezumab treatment also demonstrated the potential benefit for reversion from CM to episodic migraine (EM)
  - One potential limitation of these findings concerns the fluctuations in headache day frequency observed in people with EM and CM[1]
- While the placebo reversion rate in this study (23%) is similar to that reported in epidemiologic studies (15-26%), fremanezumab treated patients experienced a significantly higher rate of reversion (32-35%)
- Patients who reverted from CM to EM had an average 62% reduction in headache days over the 3-month treatment period
- Fremanezumab treatment did not result in any safety signals

INTRODUCTION

- CM and EM are clinically, functionally, and anatomically differentiated, with evidence suggesting that they may be separate conditions[4,5]
- Patients with CM usually have more comorbid conditions and more-frequent medication overuse than patients with EM, which complicates the clinical management of CM[2,5]
  - The estimated rate of reversion from CM to EM is relatively low, with studies reporting remission rates of around 15–26%[2,3]
- Fremanezumab is a fully humanized monoclonal antibody (IgG2Δa) that selectively targets calcitonin gene-related peptide (CGRP)[6,7]
- Fremanezumab has been studied using two subcutaneous dose regimens, quarterly and monthly, to offer flexible administration for the preventive treatment of migraine[8–10]
  - In clinical trials, fremanezumab significantly reduced the frequency of migraine and headache, without serious treatment-related adverse events (AEs)[8–10]
- The Phase 3 HALO CM trial evaluated fremanezumab for the preventive treatment of CM[10]

OBJECTIVE

- To evaluate the effect of fremanezumab on reversion from CM to EM

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 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 pre-treatment 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) ≥12 months prior to screening
- Prospectively confirmed CM during the 28-day pre-treatment baseline period:
  - Headache on ≥15 days
  - ≥8 days fulfilling ICHD3-beta criteria for migraine or 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 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 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 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 endpoints

- Mean change in the monthly average number of migraine days
- Proportion of patients with ≥50% reduction in the monthly average number of headache days of at least moderate severity
- Mean change in the monthly average number of days of acute headache medication use
- Mean change in the monthly average number of headache days of at least moderate severity during the 4-week period after the first dose of study drug
- Mean change in six-item Headache Impact Test (HIT-6) score from baseline (Day 0) to 4 weeks after administration of the last dose of study drug

Other

- Safety and tolerability: AEs, vital signs, clinical lab tests, systematic local injection-site assessments (immediately and at 1 hour post-injection)
- Serum anti-drug antibodies were assessed from blood samples

Post hoc

- Proportion of patients who reverted from CM to EM, defined as patients who had ≥15 headache days per month at baseline and <15 headache days per month in all 3 months of the treatment period

Statistical Analysis

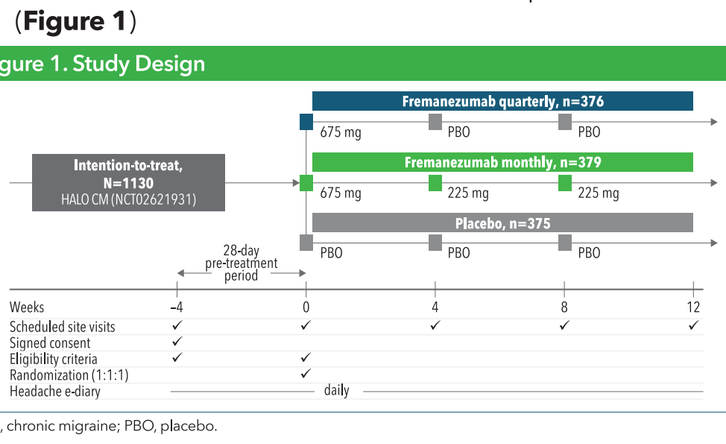
- Efficacy analyses were conducted in the full analysis set (FAS): randomized patients who received ≥1 dose of study drug and had ≥10 days of post-baseline assessments
- Safety population: randomized patients who received ≥1 dose of study drug

RESULTS

Study Population

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

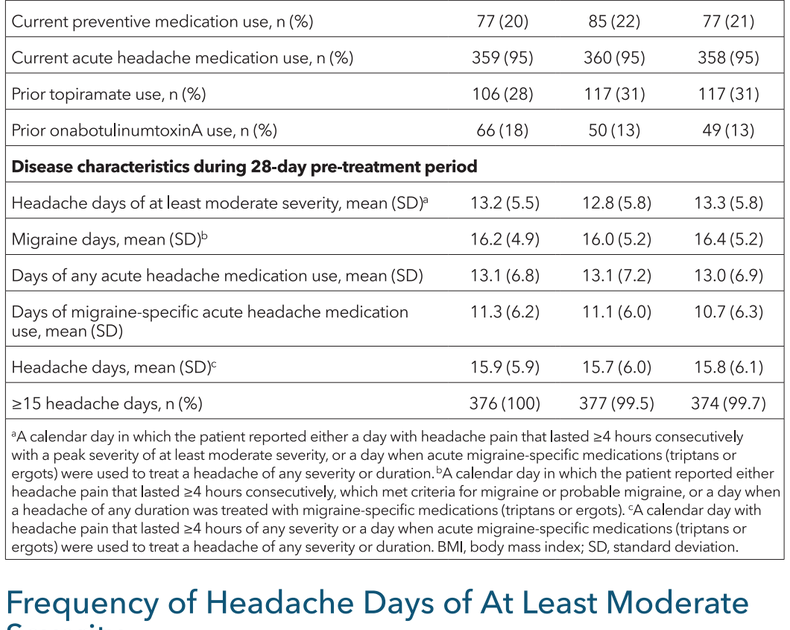
Characteristic	Fremanezumab		Placebo
	Quarterly (n=376)	Monthly (n=379)	(n=375)
Age, mean (SD)	42.0 (12.4)	40.6 (12.0)	41.4 (12.0)
BMI, kg/m^2, mean (SD)	26.6 (5.4)	26.5 (5.1)	26.5 (5.0)
Female, n (%)	331 (88)	330 (87)	330 (88)
Disease history			
Years since initial migraine diagnosis, mean (SD)	19.7 (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)
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)
Headache days, mean (SD)[c]	15.9 (5.9)	15.7 (6.0)	15.8 (6.1)
≥15 headache days, n (%)	376 (100)	377 (99.5)	374 (99.7)

[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) were 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 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). [c]A calendar day with headache pain that lasted ≥4 hours of any severity or a day when acute migraine-specific medications (triptans or ergots) were used to treat a headache of any severity or duration. BMI, body mass index; SD, standard deviation.

Frequency of Headache Days of At Least Moderate Severity

- During the 12-week treatment period, the mean number of monthly headache days of at least moderate severity was significantly reduced from baseline with both fremanezumab regimens compared with placebo (**Figure 2A**)
  - Significant treatment effects with fremanezumab were observed within 4 weeks of the initial dose and maintained at subsequent monthly intervals (**Figure 2B**)

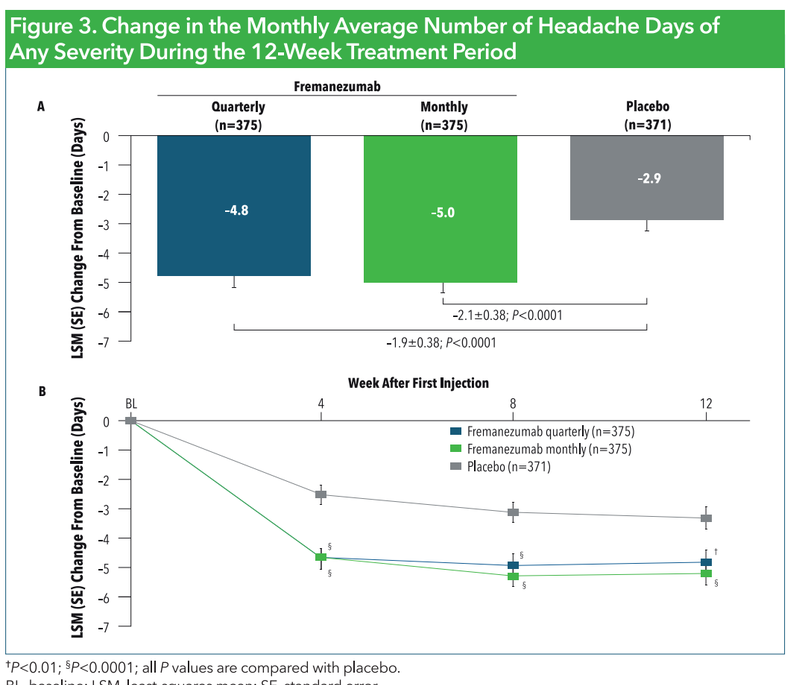
Figure 2. Change in the Monthly Average Number of Headache Days of At Least Moderate Severity During the 12-Week Treatment Period



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

- During the 12-week treatment period, the mean number of monthly headache days of any severity was significantly reduced from baseline with both fremanezumab regimens compared with placebo (**Figure 3A**)
  - Significant treatment effects with fremanezumab were observed within 4 weeks of the initial dose and maintained at subsequent monthly intervals (**Figure 3B**)

Figure 3. Change in the Monthly Average Number of Headache Days of Any Severity During the 12-Week Treatment Period

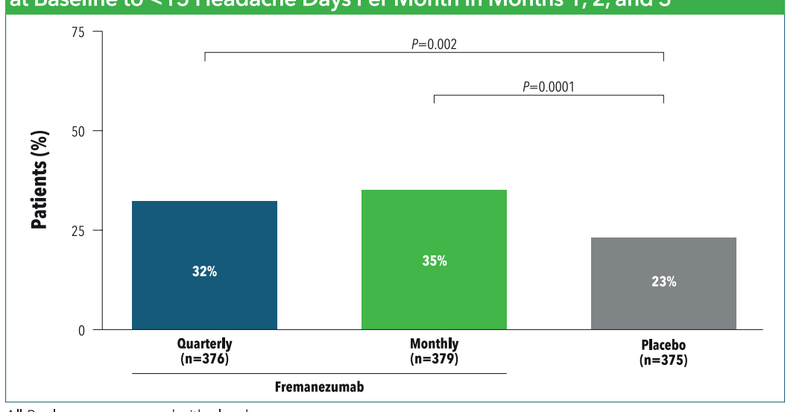


†P<0.01; §P<0.0001; all P values are compared with placebo.
BL, baseline; LSM, least-squares mean; SE, standard error.

Reversion from CM to EM

- A significantly greater proportion of fremanezumab-treated patients reverted from having ≥15 headache days of any severity per month at baseline to <15 headache days of any severity per month in Months 1, 2, and 3 than those who received placebo (**Figure 4**)

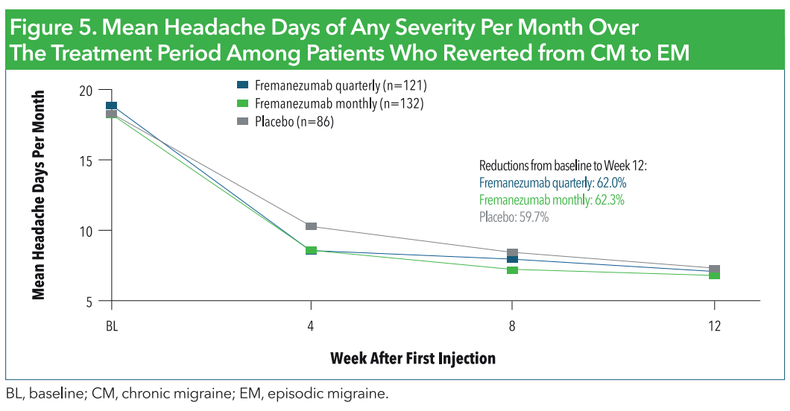
Figure 4. Reversion from ≥15 Headache Days of Any Severity Per Month at Baseline to <15 Headache Days Per Month in Months 1, 2, and 3



All P values are compared with placebo.

- On average, fremanezumab-treated patients who reverted from CM to EM had 18–19 headache days of any severity per month at baseline and showed reductions to about 7 headache days of any severity during any month in the treatment period (**Figure 5**)

Figure 5. Mean Headache Days of Any Severity Per Month Over The Treatment Period Among Patients Who Reverted from CM to EM



BL, baseline; CM, chronic migraine; EM, episodic migraine.

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**)
- Two patients who received the fremanezumab quarterly regimen developed anti-drug antibodies

Table 2. Adverse Events in the Safety Population

Characteristic	Fremanezumab		Placebo
	Quarterly (n=376)	Monthly (n=379)	(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(<1)[a]	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 chronic obstructive pulmonary disease 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.

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Disclosures

Zaza Katsarava: Provides consultation to Allergan, Novartis, Eli Lilly, and Teva Pharmaceuticals.
Stephen D. Silberstein: Provides consultation to Alder, Allergan, Amgen, Autonomic Technologies, Avanir, Curefaster Inc., Deponed, Dr. Reddy's Laboratories, Ensured Inc., ElectroCore Medical LLC, eNeura Therapeutics, INSYS Therapeutics, Lilly USA LLC, Supernus Pharmaceuticals Inc., Teva Pharmaceuticals, Theranica, and Trigemina Inc.
Sait Ashina: Provides consultation to Allergan, Eli Lilly, Amgen, Novartis, and Promius and is a speaker for Teva Pharmaceuticals.
Jessica Ailani: Received honoraria from Allergan (speaking/consulting), Avanir (speaking), Eli Lilly (speaking/advisory board), Teva Pharmaceuticals (advisory board), Promius (speaking), *Current Pain and Headache Reports* (section editor), Theranica (clinical trials).
Rashmi B. Halker Singh: Received honoraria from *Current Neurology and Neuroscience Reports*, MedLink, and Amgen.
Michael J. Seminerio: Employee of Teva Pharmaceuticals.
Joshua M. Cohen: Employee of Teva Pharmaceuticals.
Verena Ramirez Campos: Employee of Teva Pharmaceuticals.
Ronghua Yang: Employee of Teva Pharmaceuticals.

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