The Impact of Fremanezumab on Medication Overuse in Patients With Chronic Migraine

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CONCLUSIONS

- The Phase 3 HALO CM trial shows the fremanezumab is efficacious in the preventive treatment of patients with chronic migrine (CM) with or without medication overuse
  - For the primary endpoint, a significant difference versus placebo was observed for both the fremanezumab quarterly and monthly dose regimens (both *P* <0.0001)
- Fremanezumab treatment was associated with reduction in overuse of acute headache medications and overall acute headache medication use
- Fremanezumab alone decreases medication overuse in patients with CM
  - Patients treated with fremanezumab may not need to be detoxified to achieve remission of medication overuse headache (MOH)

INTRODUCTION

- Overuse of acute headache medications (triptans, ergot derivatives, opioids, and combination analgesics) can cause MOH[1,2]
- CM is often accompanied by MOH, and elimination of MOH is important in the preventive treatment of migraine[1–3]
- Fremanezumab is a fully humanized monoclonal antibody (IgG2Δa) that selectively targets calcitonin gene-related peptide (CGRP)[4,5]
- Fremanezumab has been studied using two subcutaneous dose regimens, quarterly and monthly, to offer flexible administration for the preventive treatment of migraine[6–9]
- The Phase 3 HALO CM trial evaluated fremanezumab for the preventive treatment of CM[8]

OBJECTIVE

- To assess the effect of fremanezumab on medication overuse and acute headache medication use in patients with CM

METHODS

Study Design

- HALO CM was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 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 episodic migraine (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, third edition, beta version [ICHD3-beta]) for ≥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, probable migraine, or use of triptan or ergot medications
- A subset of patients was allowed use of one preventive migraine medication if the dosing was stable for ≥2 months before the pre-treatment period

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 (lack of efficacy after adequate therapeutic trial) in ≥2 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

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 three 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 baseline and Weeks 4 and 8

Outcomes

- All endpoints compared baseline (28-day pre-treatment period) and the 12-week treatment period after the first dose of study, unless otherwise stated

Primary endpoint

- Mean change in the monthly average number of headache days of at least moderate severity

Secondary endpoint

- Mean change from baseline in the monthly average number of days of acute headache medication use

Other endpoints

- Mean change from baseline in the monthly average number of headache days of at least moderate severity among patients who reverted from overusing medications at baseline to not overusing medications during the 12-week treatment period
- Proportion of patients who reverted from overusing medications at baseline to not overusing medications during the 12-week treatment period
- Mean change from baseline in the monthly average number of days of acute headache medication use among patients who reverted

Statistical Analysis

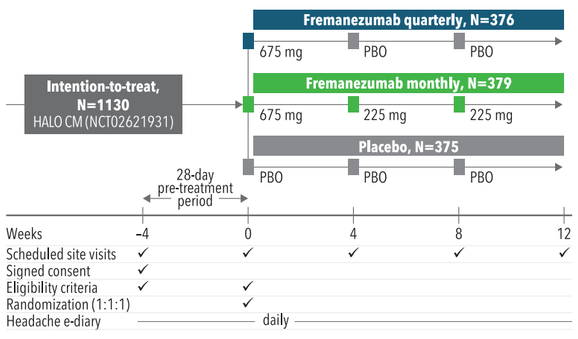
- Efficacy analyses were conducted in the full analysis set (FAS): randomized patients who received ≥1 dose of study drug and had ≥10 days of post-baseline efficacy assessments on the primary endpoint
- Mean change from baseline for each endpoint during the 12-week period was analyzed via analysis of covariance (ANCOVA)
  - Fixed effects: treatment, sex, region, and baseline preventive migraine medication use
  - Covariates: baseline values and years since onset of migraines
- The Cochran-Mantel-Haenszel test stratified by baseline preventive medication use was used to analyze proportions of patients
  - Early discontinued patients were considered as nonresponders for overall analysis

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.

- Among patients with medication overuse at baseline, patient demographics and clinical characteristics were similar between all treatment arms (**Table 1**)

Table 1. Demographics and Baseline Characteristics of Patients With Medication Overuse at Baseline[a]

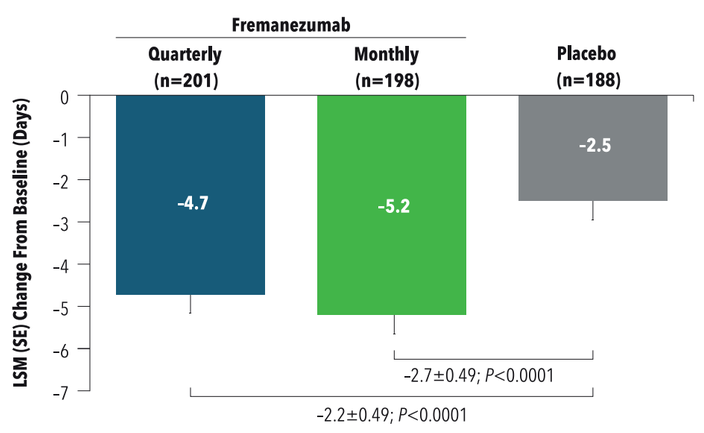
	Fremanezumab		Placebo
	Quarterly (n=201)	Monthly (n=198)	(n=188)
Age, years, mean (SD)	44.6 (11.6)	44.8 (10.9)	45.0 (10.8)
Sex, female, n (%)	183 (91)	173 (87)	168 (89)
BMI, kg/m^2, mean (SD)	26.4 (5.3)	26.4 (5.0)	26.0 (5.0)
Disease history			
Years since initial migraine diagnosis, mean (SD)	21.0 (12.7)	22.8 (12.3)	23.2 (13.8)
Current preventive medication use, n (%)	47 (23)	54 (27)	38 (20)
Current use of triptans or ergots, n (%)	141 (70)	138 (70)	128 (68)
Prior topiramate use, n (%)	65 (32)	72 (36)	77 (41)
Prior onabotulinumtoxinA use, n (%)	38 (19)	34 (17)	32 (17)

[a]Medication overuse was defined as either use of acute headache medication on ≥15 days, migraine-specific acute medication on ≥10 days, or combination medications for headache on ≥10 days during the 28-day pretreatment period. BMI, body mass index; SD, standard deviation.

Effect of Fremanzumab on Headache Days of at Least Moderate Severity in CM Patients With Medication Overuse at Baseline

- Quarterly and monthly fremanezumab treatment significantly decreased the monthly average number of headache days of at least moderate severity compared with placebo (**Figure 2**)

Figure 2. Change in Headache Days of At Least Moderate Severity in CM Patients With Medication Overuse at Baseline



CM, chronic migraine; LSM, least-squares mean; SE, standard error.

- Significantly more patients achieved ≥50% reduction in the monthly average number of headache days of at least moderate severity with quarterly or monthly fremanzumab treatment compared with placebo, regardless of medication overuse at baseline (**Figure 3**)

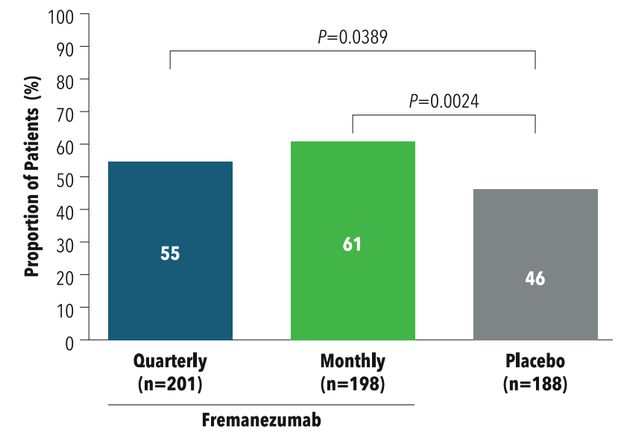
Figure 3. Proportion of CM Patients With ≥50% Reduction in Monthly Average Number of Headache Days of At Least Moderate Severity

CM, chronic migraine.

Effect of Fremanezumab on Medication Overuse in CM Patients

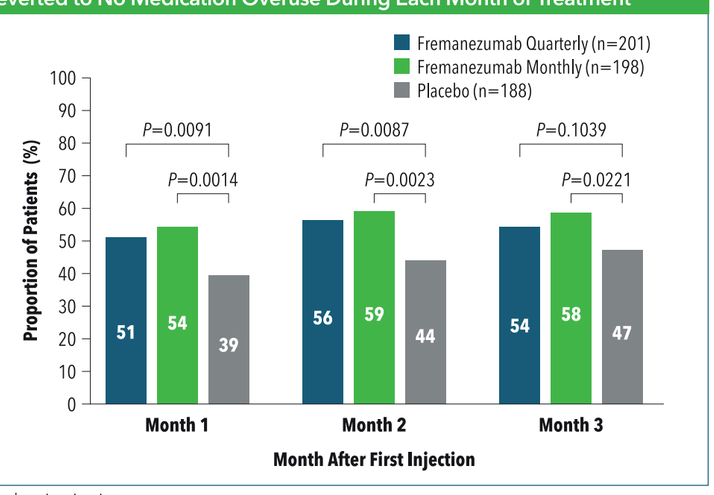
- Among CM patients with baseline medication overuse, significantly more patients treated with quarterly or monthly fremanezumab reported no medication overuse during the 12-week treatment period compared with placebo (**Figure 4**)
  - This effect was seen as early as Month 1 and sustained through Months 2 and 3 (**Figure 5**)

Figure 4. Proportion of CM Patients With Baseline Medication Overuse Who Reported No Medication Overuse During the 12-Week Treatment Period



CM, chronic migraine.

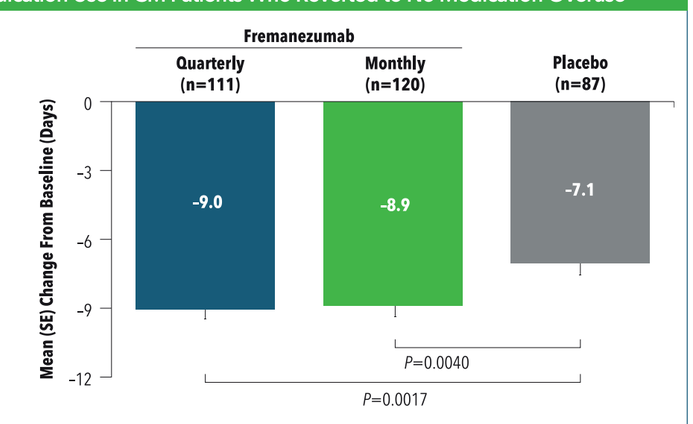
Figure 5. Proportion of CM Patients With Baseline Medication Overuse Who Reverted to No Medication Overuse During Each Month of Treatment



CM, chronic migraine.

- Among patients who reverted to no medication overuse, the monthly average number of days with any acute headache medication use significantly decreased with both quarterly and monthly fremanezumab compared with placebo (**Figure 6**)

Figure 6. Change in the Monthly Average Number of Days of Acute Headache Medication Use in CM Patients Who Reverted to No Medication Overuse



Baseline number of days of acute headache medication use, mean (SD)	16.6 (3.4)	16.7 (3.6)	16.6 (3.3)

CM, chronic migraine; SD, standard deviation; SE, standard error.

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Disclosures
Stephen D. Silberstein: Provides consultation to Alder, Allergan, Amgen, Autonomic Technologies, Avanir, Curelater Inc., Depomed, 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.v
Zaza Katsarava: Provides consultation to Allergan, Novartis, Eli Lilly, and Teva Pharmaceuticals.
Sait Ashina: Provides consultation to Allergan, Eli Lilly, Amgen, Novartis, and Promius, and is a speaker for Teva Pharmaceuticals.
Michael J. Seminerio: Employee of Teva Pharmaceuticals.
Joshua M. Cohen: Employee of Teva Pharmaceuticals.

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