IHC-PO-142

Presented at ***International Headache Congress (IHC);*** 5-8 September 2019; Dublin, Ireland.

Long-Term Impact of Fremanezumab on Response Rate, Acute Headache Medication Use, and Disability in Chronic Migraine Patients With Acute Medication Overuse at Baseline: Results of a 1-Year Study

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CONCLUSIONS

- Long-term treatment with fremanezumab quarterly or monthly reduced from baseline the number of headache days of at least moderate severity, the number of migraine days, acute headache medication use, and headache-related disability in patients with chronic migraine (CM) who had acute medication overuse (AMO) at baseline
- Results from this *post hoc* analysis may help to inform clinical decision-making for physicians treating patients with CM who have AMO at baseline

INTRODUCTION

- Overuse of acute headache medications, including triptans, ergot derivatives, opioids, and combination analgesics, is common among patients with CM[1]
- Patients with CM who have AMO have greater disability and further impaired quality of life compared with CM patients who do not have AMO[2]
- While preventive therapy is recommended for patients with AMO,[3] there remains a need for an effective, safe, and well-tolerated preventive therapy that specifically targets the pathophysiology of migraine
- 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 the long-term impact of fremanezumab on response rate, the use of acute headache medication, and disability in patients with CM who had AMO (defined as non-specific acute headache medication use on ≥15 days, migraine-specific acute medication use on ≥10 days, or use of combination medications for headache on ≥10 days) at baseline

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 trials, as well as an additional subset of new patients 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
- 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

Key exclusion criteria

- For rollover patients in a prior Phase 3 (HALO CM) trial:
  - 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 trial, 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 at Weeks 4 and 8
- In the long-term trial, patients who received fremanezumab quarterly or monthly in the prior placebo-controlled trial continued 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

- Proportion of patients with a ≥50% reduction 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
- Mean change from baseline (28-day pre-treatment period) in the monthly average number of days of any acute headache medication use
- Mean change from baseline (Day 0) in six-item Headache Impact Test (HIT-6) scores; higher scores indicate greater disability

Safety and tolerability

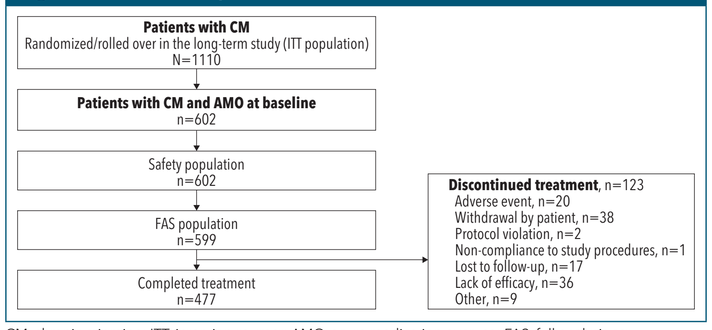
- Adverse events (AEs) and systematic local injection-site assessments (immediately and at 1 hour post-injection)

RESULTS

Patient Demographics and Baseline Characteristics

- Of the 1110 patients with CM enrolled in this study, 602 (54.2%) had AMO at baseline (**Figure 1**)

Figure 1. Patient Disposition[a]



CM, chronic migraine; ITT, intention-to-treat; AMO, acute medication overuse; 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 clinical characteristics were similar between both treatment arms for patients with CM who had AMO at baseline (**Table 1**)

Table 1. Baseline Demographics and Disease Characteristics of Patients With CM Who Had AMO at Baseline

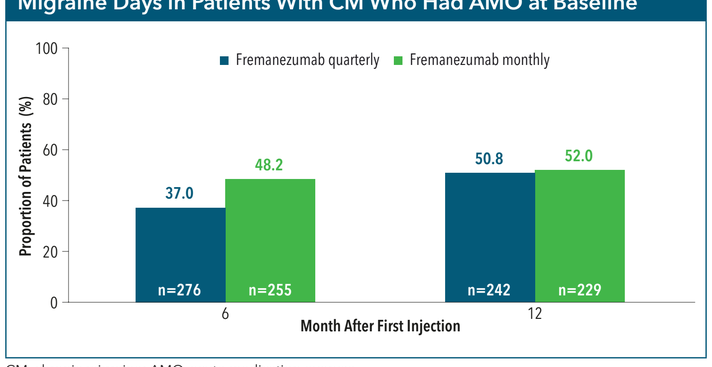
	Fremanezumab quarterly (n=307)	Fremanezumab monthly (n=295)
Patient demographics		
Age, mean (SD), y	46.5 (10.9)	45.9 (10.8)
Sex, female, n (%)	275 (90)	261 (88)
BMI, mean (SD), kg/m^2	26.0 (5.0)	26.1 (5.1)
Disease history		
Years since initial migraine diagnosis, mean (SD)	23.4 (13.5)	23.4 (12.2)
Current preventive medication use, n (%)	83 (28)	77 (25)
Current acute headache medication use, n (%)	307 (100)	295 (100)
Prior topiramate use, n (%)	131 (43)	128 (43)
Prior onabotulinumtoxinA use, n (%)	80 (26)	81 (27)
Disease characteristics during the 28-day pre-treatment period		
Headache days of any severity and duration, mean (SD)	20.9 (4.0)	21.0 (4.3)
Headache days of at least moderate severity, mean (SD)[a]	15.7 (4.8)	15.3 (5.6)
Migraine days, mean (SD)[b]	17.5 (4.7)	17.7 (5.1)
Days with any acute headache medication use, mean (SD)	18.1 (4.2)	18.5 (4.4)
HIT-6 scores, mean (SD)[c]	64.3 (5.1)	64.7 (4.7)

CM, chronic migraine; AMO, acute medication overuse; SD, standard deviation; BMI, body mass index; HIT-6, six-item Headache Impact Test.
[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 an 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 patients 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 medication (triptan or ergot). [c]Data are reported for the full analysis set population (quarterly: n=307; monthly: n=292).

≥50% Response Rates in Patients With CM Who Had AMO at Baseline

- The proportion of patients who had a ≥50% reduction in monthly migraine days with fremanezumab quarterly and monthly was maintained from Month 6 (quarterly: 37%; monthly: 48%) to Month 12 (quarterly: 51%; monthly: 52%) (**Figure 2**)

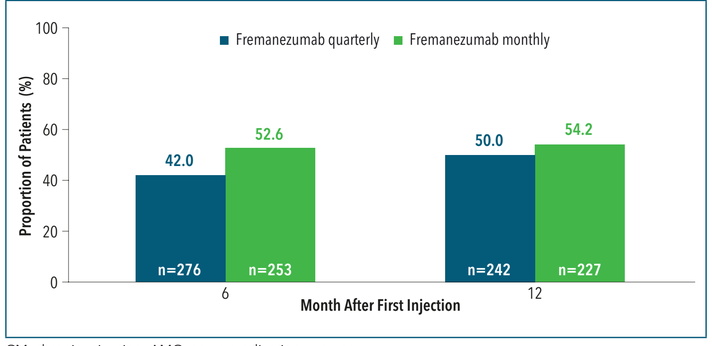
Figure 2. ≥50% Reduction in Monthly Average Number of Migraine Days in Patients With CM Who Had AMO at Baseline



CM, chronic migraine; AMO, acute medication overuse.

- The proportion of patients with a ≥50% reduction in the monthly number of headache days of at least moderate severity with fremanezumab quarterly and monthly was maintained from Month 6 to Month 12 (**Figure 3**)

Figure 3. ≥50% Reduction in the Monthly Average Number of Headache Days of at Least Moderate Severity in Patients With CM Who Had AMO at Baseline

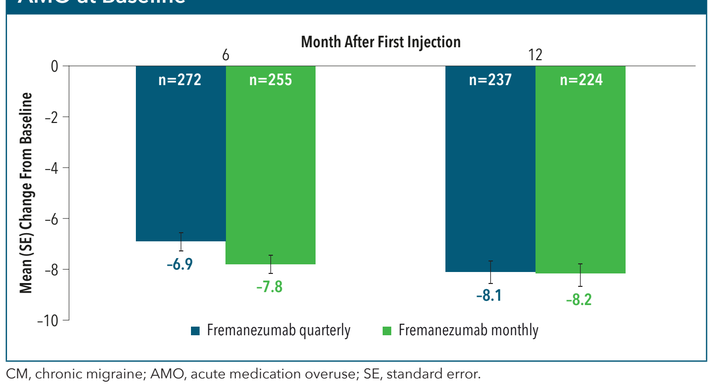


CM, chronic migraine; AMO, acute medication overuse.

Change in Any Acute Headache Medication Use

- In CM patients with AMO at baseline, fremanezumab quarterly and monthly reduced the monthly average number of days of any acute medication use from baseline to Month 6, and reductions were maintained through Month 12 (**Figure 4**)
- Following treatment with fremanezumab, approximately 60% of patients with CM and AMO at baseline had reverted to no AMO at Month 6 (quarterly: 59% [n=163/276]; monthly: 65% [n=166/255]), and reversion was maintained through Month 12 (quarterly: 66% [n=162/244]; monthly: 68% [n=156/231])

Figure 4. Change in the Monthly Average Number of Days of Any Acute Headache Medication Use in Patients With CM Who Had AMO at Baseline

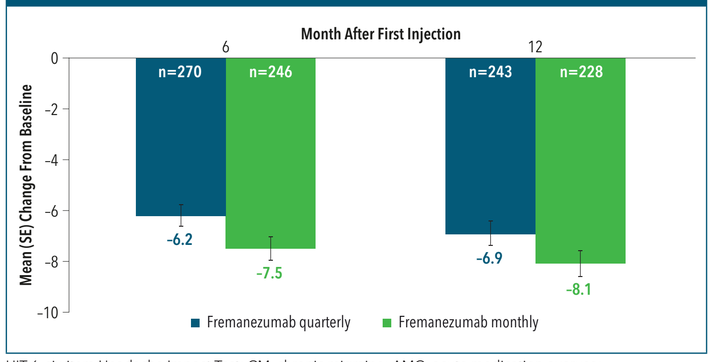


CM, chronic migraine; AMO, acute medication overuse; SE, standard error.

Headache-Related Disability

- Fremanezumab quarterly and monthly treatment reduced headache-related disability in CM patients who had AMO at baseline, as demonstrated by a decrease from baseline in HIT-6 score at Month 6 and Month 12 (**Figure 5**)

Figure 5. Change in HIT-6 Score in Patients With CM Who Had AMO at Baseline



HIT-6, six-item Headache Impact Test; CM, chronic migraine; AMO, acute medication overuse; SE, standard error.

Safety and Tolerability in Patients With CM Who Had AMO at Baseline

- Similar proportions of patients with CM reported at least one AE with fremanezumab quarterly and monthly (**Table 2**)
- The most commonly reported AEs were injection-site reactions, with similar proportions of patients between treatment groups (**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 Who Had AMO at Baseline

	Fremanezumab quarterly (n=307)	Fremanezumab monthly (n=295)
Patients with AEs, n (%)		
At least one AE	263 (86)	262 (89)
At least one treatment-related AE	157 (51)	167 (57)
At least one serious AE	29 (9)	16 (5)
Any AE leading to discontinuation of the study	11 (4)	9 (3)
Injection-site reactions (occurring in >6% of patients in any treatment group), n (%)[a]		
Injection-site induration	88 (29)	103 (35)
Injection-site pain	79 (26)	93 (32)
Injection-site erythema	80 (26)	90 (31)
Injection-site hemorrhage	23 (7)	25 (8)
Injection-site pruritus	18 (6)	21 (7)
Other common AEs (occurring in >6% of patients in any treatment group), n (%)		
Upper respiratory tract infection	38 (12)	33 (11)
Nasopharyngitis	44 (14)	36 (12)
Sinusitis	20 (7)	18 (6)
Urinary tract infection	21 (7)	16 (5)

AE, adverse event; CM, chronic migraine; AMO, acute medication overuse.
[a]Local injection sites were systematically assessed for erythema, induration, ecchymosis, and pain both immediately and 1 hour after dosing.

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Acknowledgments

This study was funded by Teva Pharmaceutical Industries Ltd., Petach Tikva, Israel. We thank the patients, study investigators, and site personnel involved with this study, and Nelson Jen, PhD (Chameleon Communications International with funding from Teva Pharmaceutical Industries Ltd.) for editorial assistance in the preparation of this report.

Disclosures

Stephen D. Silberstein: Provides consultation to Alder, Allergan, Amgen, Autonomic Technologies, Avanir, Curelator 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.
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David Kudrow: Advisor to Eli Lilly, Amgen, Alder. Research support from Amgen, Alder, Eli Lilly, Teva Pharmaceuticals, Zosano, Allergan, Genentech, VM Biopharma, and CoLucid.

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