IHC-PO-168

Long-term Efficacy of Fremanezumab in Chronic and Episodic Migraine Patients With Acute Medication Overuse at Baseline: Results of a 1-year Study

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

Stephen D. Silberstein, MD[1]; Joshua M. Cohen, MD, MPH, FAHS[2]; Michael J. Seminerio, PhD, MBA[2]; Ronghua Yang, PhD[2]; Xiaoping Ning, MD, MS[2]; Messoud Ashina, MD[3]

[1]Jefferson Headache Center, Thomas Jefferson University, Philadelphia, Pennsylvania, USA; [2]Teva Pharmaceutical Industries Ltd., Frazer, Pennsylvania, USA; [3]University of Copenhagen, Copenhagen, Denmark

CONCLUSIONS

- Fremanezumab demonstrated efficacy over 12 months of treatment in patients with migraine, regardless of acute medication overuse (AMO) at baseline
- In both chronic migraine (CM) and episodic migraine (EM) patients with AMO at baseline, reductions in both mean monthly migraine days and mean monthly headache days of at least moderate severity were greater than or equal to reductions in patients without AMO at baseline, suggesting an even greater treatment effect of fremanezumab in patients with AMO
- These results suggest that it may not be necessary to discontinue overused medications prior to initiation of fremanezumab in order to achieve a significant improvement in migraine
- Fremanezumab was well tolerated in patients with CM or EM who had AMO at baseline

INTRODUCTION

- Overuse of acute headache medication, such as triptans, ergot derivatives, opioids, and combination analgesics, can cause medication overuse headache (MOH)[1]
- MOH is disabling and refractory and can lead to the progression from EM to CM; the use of preventive treatment may be beneficial for patients with migraine[1,2]
- 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 migraine 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 versus those who did not

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 (HALO) trials, as well as an additional subset of new patients who were not previously enrolled in the HALO trials

Patient Population

Key inclusion criteria

- 18–70 years of age
- History of migraine (according to International Classification of Headache Disorders, third edition, beta version [ICHD-3 beta] criteria) for ≥12 months prior to screening
- Patients with CM: prospectively confirmed 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 with EM: prospectively confirmed EM during the 28-day pre-treatment baseline period
  - Headache occurring 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
- 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 patients rolling over from the previous HALO 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 EM or CM: 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 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 trial continued the same treatment, while patients who previously received placebo and new patients were randomized 1:1 to either fremanezumab quarterly or monthly

Outcomes

Efficacy

- Mean change from baseline (28-day treatment period) in the monthly average number of migraine days in patients with or without AMO at baseline
- Mean change from baseline (28-day treatment period) in the monthly average number of headache days of at least moderate severity in patients with or without AMO at baseline
- The proportion of patients with CM or EM who reverted from AMO at baseline to no AMO

Safety and tolerability

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

RESULTS

Study Population

- A total of 602/1110 (54%) patients with CM and 100/780 (13%) patients with EM reported AMO at baseline (**Figure 1**)
- Baseline patient demographics and clinical characteristics were similar among treatment arms in patients with CM or EM who had AMO at baseline and those without AMO at baseline (**Table 1**)

Table 1. Baseline Demographics and Clinical Characteristics for CM and EM Patients With AMO and Those Without AMO at Baseline[a]

	AMO at Baseline				No AMO at Baseline			
	CM		EM		CM		EM	
	Fremanezumab quarterly (n=307)	Fremanezumab monthly (n=292)	Fremanezumab quarterly (n=58)	Fremanezumab monthly (n=42)	Fremanezumab quarterly (n=244)	Fremanezumab monthly (n=264)	Fremanezumab quarterly (n=336)	Fremanezumab monthly (n=344)
Patient demographics								
Age, mean (SD), y	46.5 (10.9)	45.9 (10.8)	47.5 (11.8)	50.1 (9.8)	40.1 (12.3)	38.9 (11.9)	42.6 (11.1)	44.1 (12.4)
BMI, mean (SD), kg/m^2	26.0 (5.0)	26.1 (5.1)	24.9 (4.2)	26.0 (4.6)	27.0 (5.5)	26.7 (5.1)	27.2 (5.1)	26.3 (5.2)
Sex, female, n (%)	275 (90)	261 (88)	49 (84)	38 (90)	209 (86)	233 (88)	293 (87)	287 (83)
Disease history								
Years since initial migraine diagnosis, mean (SD)	23.4 (13.5)	23.4 (12.2)	28.0 (13.9)	27.9 (14.1)	19.4 (13.0)	18.8 (11.5)	20.5 (12.1)	21.1 (12.5)
Current preventive medication use, n (%)	77 (25)	83 (28)	15 (26)	11 (26)	51 (21)	59 (22)	74 (22)	81 (24)
Prior topiramate use, n (%)	131 (43)	128 (43)	25 (43)	17 (40)	74 (30)	76 (29)	63 (19)	83 (24)
Prior onabotulinumtoxinA use, n (%)	80 (26)	81 (27)	8 (14)	7 (17)	47 (19)	41 (16)	20 (6)	20 (6)
Disease characteristics during the 28-day pre-treatment period								
Migraine days, mean (SD)[b]	17.5 (4.7)	17.7 (5.1)	12.2 (1.8)	12.3 (1.8)	15.0 (5.2)	15.0 (5.2)	8.7 (2.4)	8.7 (2.6)
Headache days of at least moderate severity, mean (SD)[c]	15.7 (4.8)	15.3 (5.6)	11.8 (11.8)	11.5 (2.0)	11.2 (5.5)	11.5 (5.8)	6.7 (2.7)	6.8 (2.7)
Days with any acute headache medication use, mean (SD)	18.1 (4.2)	18.5 (4.4)	12.1 (1.9)	12.2 (1.5)	7.7 (4.4)	7.3 (4.5)	7.4 (3.3)	7.5 (3.3)
Days with acute migraine-specific headache medication use, mean (SD)[d]	10.8 (7.6)	10.3 (7.8)	11.1 (2.7)	11.0 (2.9)	2.5 (3.2)	2.0 (3.2)	3.0 (3.4)	3.2 (3.4)

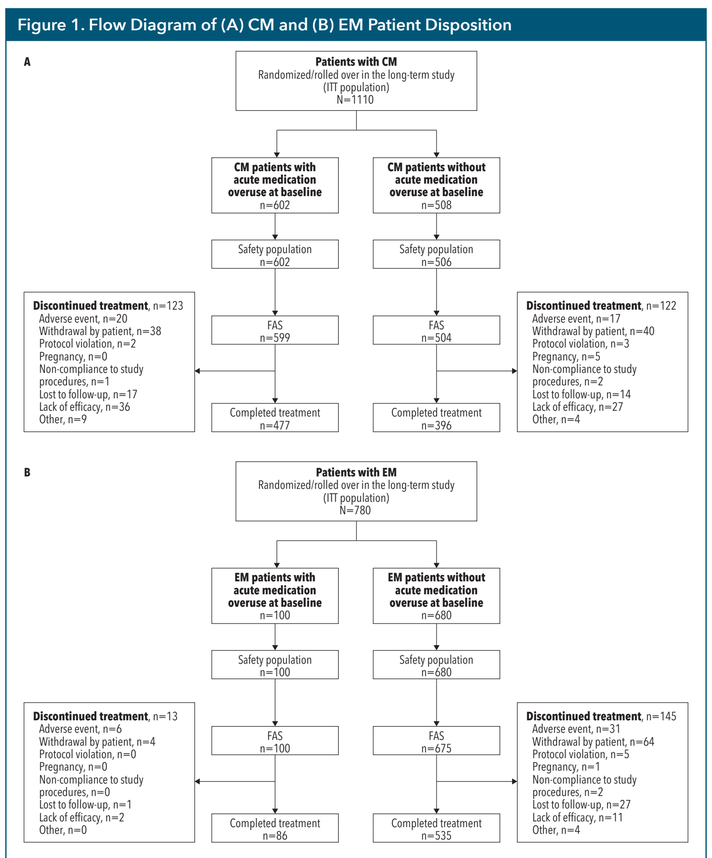
AMO, acute medication overuse; BMI, body mass index; CM, chronic migraine; EM, episodic migraine; ITT, intention-to-treat; SD, standard deviation.
[a]Data reported in the ITT population. [b]A calendar day in which the patient reported either headache pain that lasted ≥4 hours (CM) or ≥2 hours (EM) consecutively, 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]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. [d]Data reported for patients who used acute migraine-specific headache medications (triptan or ergot) at baseline.

Table 2. AEs for CM and EM Patients With AMO and Those Without AMO at Baseline[a]

	AMO at Baseline				No AMO at Baseline			
	CM		EM		CM		EM	
	Fremanezumab quarterly (n=307)	Fremanezumab monthly (n=292)	Fremanezumab quarterly (n=58)	Fremanezumab monthly (n=42)	Fremanezumab quarterly (n=243)	Fremanezumab monthly (n=263)	Fremanezumab quarterly (n=336)	Fremanezumab monthly (n=344)
Patients with AEs, n (%)								
At least one AE	263 (86)	262 (89)	48 (83)	35 (83)	197 (81)	236 (90)	281 (84)	288 (84)
At least one treatment-related AE	157 (51)	167 (57)	29 (50)	26 (62)	142 (58)	161 (61)	184 (55)	197 (57)
At least one serious AE	29 (9)	16 (5)	3 (5)	2 (5)	8 (3)	19 (7)	18 (5)	18 (5)
Any AE leading to discontinuation from the study	11 (4)	9 (3)	2 (3)	4 (10)	8 (3)	9 (3)	18 (5)	14 (4)
Injection-site reactions (occurring in >3% of patients in any treatment group), n (%)[b]								
Injection-site pain	79 (26)	93 (32)	17 (29)	18 (43)	78 (32)	89 (34)	101 (30)	105 (31)
Injection-site induration	88 (29)	103 (35)	15 (26)	15 (36)	77 (32)	93 (35)	98 (29)	130 (38)
Injection-site erythema	80 (26)	90 (31)	13 (22)	15 (36)	58 (24)	81 (31)	72 (21)	88 (26)
Injection-site hemorrhage	23 (7)	25 (8)	2 (3)	4 (10)	19 (8)	19 (7)	15 (4)	24 (7)
Injection-site pruritus	18 (6)	21 (7)	2 (3)	2 (5)	8 (3)	18 (7)	13 (4)	33 (10)
Other common AEs (occurring in >5% of patients in any treatment group), n (%)								
Nasopharyngitis	44 (14)	36 (12)	10 (17)	7 (17)	20 (8)	24 (9)	31 (9)	44 (13)
Upper respiratory tract infection	38 (12)	33 (11)	6 (10)	4 (10)	37 (15)	38 (14)	53 (16)	41 (12)
Urinary tract infection	21 (7)	16 (5)	3 (5)	4 (10)	18 (7)	11 (4)	19 (6)	20 (6)
Sinusitis	20 (7)	18 (6)	2 (3)	1 (2)	20 (8)	21 (8)	16 (5)	16 (5)
Bronchitis	13 (4)	9 (3)	1 (2)	2 (5)	9 (4)	16 (6)	17 (5)	17 (5)
Influenza	11 (4)	15 (5)	3 (5)	1 (2)	12 (5)	15 (6)	7 (2)	10 (3)
Vertigo	2 (<1)	1 (<1)	2 (3)	3 (7)	1 (<1)	1 (<1)	6 (2)	3 (<1)
Ligament sprain	4 (1)	6 (2)	2 (3)	3 (7)	6 (2)	5 (2)	4 (1)	5 (1)
Anxiety	7 (2)	6 (2)	2 (3)	3 (7)	4 (2)	4 (2)	8 (2)	8 (2)

AE, adverse event; AMO, acute medication overuse; CM, chronic migraine; EM, episodic migraine.
[a]Data reported in the safety population. [b]Local injection sites were systematically assessed for erythema, induration, ecchymosis, and pain both immediately and 1 hour after dosing.

Figure 1. Flow Diagram of (A) CM and (B) EM Patient Disposition

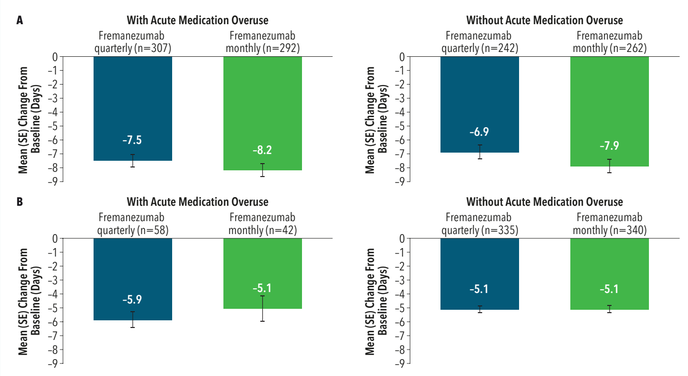


CM, chronic migraine; EM, episodic migraine; FAS, full analysis set; ITT, intention-to-treat.

Monthly Average Number of Migraine Days

- At Month 12, sustained reductions from baseline were seen in the monthly average number of migraine days in patients with CM who had AMO at baseline and who did not have AMO at baseline (**Figure 2A**)
- Similar reductions in migraine days were also seen in patients with EM who had AMO at baseline and who did not have AMO at baseline (**Figure 2B**)

Figure 2. Change in the Monthly Average Number of Migraine Days in (A) CM Patients and (B) EM Patients With and Without AMO at Baseline

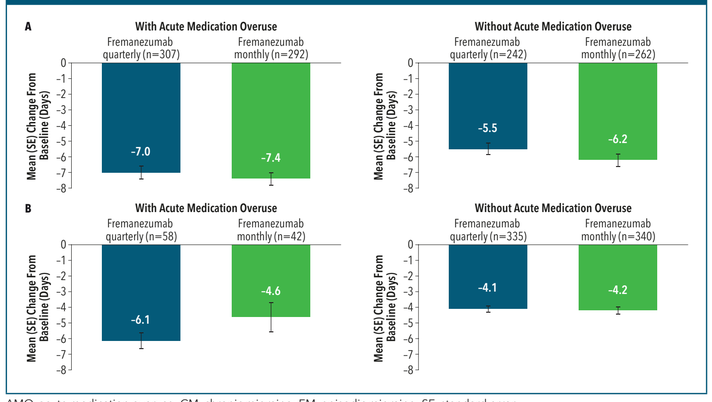


AMO, acute medication overuse; CM, chronic migraine; EM, episodic migraine; SE, standard error.

Monthly Average Number of Headache Days of at Least Moderate Severity

- At Month 12, sustained reductions from baseline in the monthly average number of headache days of at least moderate severity were seen in patients with CM who had AMO at baseline and who did not have AMO at baseline (**Figure 3A**)
- Reductions in headache days of at least moderate severity were also seen in patients with EM who had AMO at baseline vs those who did not have AMO at baseline (**Figure 3B**)

Figure 3. Change in the Monthly Average Number of Headache Days of at Least Moderate Severity in (A) CM Patients and (B) EM Patients With and Without AMO at Baseline



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

Reversion From AMO at Baseline to No AMO

- Approximately 60% of patients with CM and AMO at baseline 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])
- Following treatment with fremanezumab, more than 60% of patients with EM and AMO at baseline reverted to no AMO at Month 6 (quarterly: 85% [n=45/53]; monthly: 61% [n=23/38]), and reversion was maintained through Month 12 (quarterly: 86% [n=42/49]; monthly: 77% [n=27/35])

Safety and Tolerability

- >80% of patients with CM or EM who had AMO at baseline reported at least one AE in each treatment arm (**Table 2**)
- The most commonly reported AEs were injection-site reactions, with similar proportions of patients across treatment groups (**Table 2**)

References

1. Saper JR, Da Silva AN. *CNS Drugs* 2013;27:867-877.
2. Estemalik E, Tepper S. *Neuropsychiatr Dis Treat* 2013;9:709-720.
3. Hoy SM. *Drugs* 2018;78:1829-1834.
4. AJOVY® (fremanezumab) [prescribing information]. Teva Pharmaceuticals USA, Inc.; 2018.
5. AJOVY (fremanezumab) [Summary of Product Characteristics]. Teva Pharmaceuticals GmbH; 2019.

Acknowledgments

This study was funded by Teva Pharmaceutical Industries Ltd., Petach Tikva, Israel. We thank the patients and site personnel involved with this study, and Sarah Qamar, 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, Curelater Inc., Depomed, Dr. Reddy's Laboratories, Ensured Inc., electroCore Medical LLC, eNeura Therapeutics, INSYS Therapeutics, Lilly USA LLC, Supernus Pharmaceuticals Inc., Teva Pharmaceutical Industries Ltd., Theranica, and Trigemina Inc.

Joshua M. Cohen: Teva Branded Pharmaceutical Products R&D, Inc. (USA).

Michael J. Seminerio: Employee of Teva Pharmaceutical Industries Ltd.

Ronghua Yang: Employee of Teva Pharmaceutical Industries Ltd.

Xiaoping Ning: Teva Branded Pharmaceutical Products R&D, Inc. (USA).

Messoud Ashina: Speaker fees from Allergan, Amgen, Novartis, and Teva Pharmaceutical Industries Ltd.

For a copy of this poster, scan the QR code with your Android™ phone, Blackberry®, or iPhone®. No personal information will be collected. This is not associated with any marketing or promotional activity.