IHC-DP-034

Long-Term Efficacy of Fremanezumab in Migraine Patients With and Without Concomitant Oral Preventive Medication Use: Results of a 1-Year Study

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

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CONCLUSIONS

- In patients with and without concomitant preventive medication use, long-term treatment with fremanezumab quarterly or monthly reduced from baseline the number of headache days of at least moderate severity and the number of migraine days
- The adverse event (AE) profile of fremanezumab was similar between patients who used concomitant preventive medication and those who did not
- This analysis demonstrated that adding fremanezumab to an existing oral migraine preventive medication regimen results in sustained efficacy for up to 15 months with no safety signals

INTRODUCTION

- Migraine preventive treatment is recommended for patients with frequent or disabling headache days and aims to reduce the frequency, severity, and duration of headache days[1,2]
  - Oral preventive therapies are generally considered first line; however, some patients may experience a partial response or AEs at higher dosages[1]
  - In these cases, migraine preventive medication from a different class may provide additional therapeutic benefit[1]
- 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 of fremanezumab in subgroups of patients with and without concomitant preventive medication use

METHODS

Study Design

- This was a 12-month, multicenter, randomized, double-blind, parallel-group Phase 3 study (NCT02638103)
  - Patients who completed the HALO CM (NCT02621931) and HALO EM (NCT02629861) pivotal efficacy studies had the option to enter this long-term HALO study ("rollover patients"), and a subset of additional "new patients" could directly enroll

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 CM during the 28-day pre-treatment baseline period
  - Headache of any severity and duration on ≥15 days
  - ≥8 days fulfilling ICHD-3 beta criteria for migraine or probable migraine or use of triptan or ergot medications
- Patients with EM: prospectively confirmed EM during the 28-day pre-treatment baseline period
  - Headache of any severity and duration on 6–14 days (rollover patients) or on 4–14 days (new patients)
  - ≥4 days fulfilling ICHD-3 beta criteria for migraine or 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
  - Patients using migraine preventive medications were encouraged to continue their preventive medication regimen without change for the duration of the study; however, if discontinuation was clinically indicated by the investigator, the medication could be stopped
  - Patients not using migraine preventive medications were asked not to initiate preventive medications during the study

Key exclusion criteria

- For rollover patients from previous phase 3 (HALO EM and HALO CM) 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 due to lack of efficacy in two or more of the following four 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
- The above exclusion criteria did not apply to new patients

Study Treatment

- In the initial placebo-controlled HALO CM and EM 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 study, rollover patients who received fremanezumab quarterly or monthly in the placebo-controlled trials continued the same treatment, while rollover patients who previously received placebo and new patients were randomized 1:1 to either fremanezumab quarterly or monthly
- All patients remained blinded as to which dosing regimen they received during the long-term study

Outcomes

Efficacy

- Mean change 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 in patients with and without concomitant preventive medication use at baseline

Safety and tolerability

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

RESULTS

Study Population

- A total of 270 (24%) of 1110 patients with CM and 181 (23%) of 780 patients with EM were using concomitant preventive medication at baseline (**Figure 1**)
- Within each migraine diagnosis group, baseline demographics and disease characteristics were generally similar across treatment groups (**Table 1**)
  - By definition, current preventive medication use differed between subgroups
  - A greater percentage of patients using concomitant preventive medications had previously used onabotulinumtoxinA, especially among patients with CM
- The most commonly used concomitant preventive medication for patients with CM and patients with EM was topiramate (CM, 37%; EM, 37%), followed by amitriptyline-containing compounds (CM, 22%; EM, 17%)

Headache Days of at Least Moderate Severity

- Fremanezumab treatment resulted in reductions from baseline in the monthly average number of headache days of at least moderate severity in patients with **CM** who were using concomitant preventive medication (**Figure 2A**) and those who were not (**Figure 2B**)
- Fremanezumab treatment resulted in reductions from baseline in the monthly average number of headache days of at least moderate severity in patients with **EM** who were using concomitant preventive medication **(Figure 3A**) and those who were not (**Figure 3B**)

Table 1. Baseline Demographics and Disease Characteristics for CM and EM Patients by Concomitant Preventive Medication Use[a]

	CM				EM			
	With concomitant use		Without concomitant use		With concomitant use		Without concomitant use	
	Fremanezumab quarterly (n=128)	Fremanezumab monthly (n=142)	Fremanezumab quarterly (n=423)	Fremanezumab monthly (n=417)	Fremanezumab quarterly (n=89)	Fremanezumab monthly (n=92)	Fremanezumab quarterly (n=305)	Fremanezumab monthly (n=294)
Patient demographics								
Age, mean (SD), y	43.7 (11.3)	44.8 (11.5)	43.7 (12.2)	41.8 (11.9)	45.7 (12.3)	47.6 (12.3)	42.6 (11.0)	43.8 (12.1)
Sex, female, n (%)	115 (90)	128 (90)	369 (87)	366 (88)	79 (89)	82 (89)	263 (86)	243 (83)
BMI, mean (SD), kg/m^2	25.8 (5.1)	25.2 (4.9)	26.6 (5.3)	26.8 (5.1)	27.8 (5.2)	26.3 (5.2)	26.6 (5.0)	26.3 (5.2)
Disease history								
Years since initial migraine diagnosis, mean (SD)	20.1 (13.1)	23.0 (12.7)	22.1 (13.5)	20.6 (11.8)	23.0 (13.6)	22.7 (14.4)	21.2 (12.4)	21.6 (12.3)
Current preventive medication use, n (%)[b]	128 (100)	142 (100)	0	0	89 (100)	92 (100)	0	0
Antiepileptics	55 (43)	71 (50)	–	–	45 (51)	45 (49)	–	–
Antidepressants	58 (45)	70 (49)	–	–	34 (38)	31 (34)	–	–
Beta-blockers	38 (30)	30 (21)	–	–	17 (19)	25 (27)	–	–
Calcium channel blockers or benzocycloheptene	1 (1)	1 (1)	–	–	3 (3)	2 (2)	–	–
Current acute headache medication use, n (%)	127 (>99)	138 (97)	401 (95)	390 (94)	87 (98)	89 (97)	295 (97)	280 (95)
Prior topiramate use, n (%)	48 (38)	49 (35)	157 (37)	155 (37)	20 (22)	24 (26)	68 (22)	76 (26)
Prior onabotulinumtoxinA use, n (%)	39 (30)	45 (32)	88 (21)	77 (18)	10 (11)	9 (10)	18 (6)	18 (6)
Disease characteristics during the 28-day pre-treatment period								
Headache days of any severity and duration, mean (SD)	20.2 (4.3)	21.0 (4.4)	20.4 (4.1)	20.3 (4.4)	11.1 (2.4)	11.0 (2.5)	11.3 (2.4)	10.9 (2.6)
Headache days of at least moderate severity, mean (SD)[c]	14.2 (5.8)	14.7 (6.0)	13.5 (5.5)	13.1 (6.0)	7.5 (2.9)	7.8 (3.0)	7.4 (3.2)	7.2 (3.0)
Migraine days, mean (SD)[d]	16.6 (5.0)	17.1 (5.8)	16.3 (5.2)	16.2 (5.2)	9.1 (2.6)	9.3 (2.7)	9.3 (2.6)	9.0 (2.7)

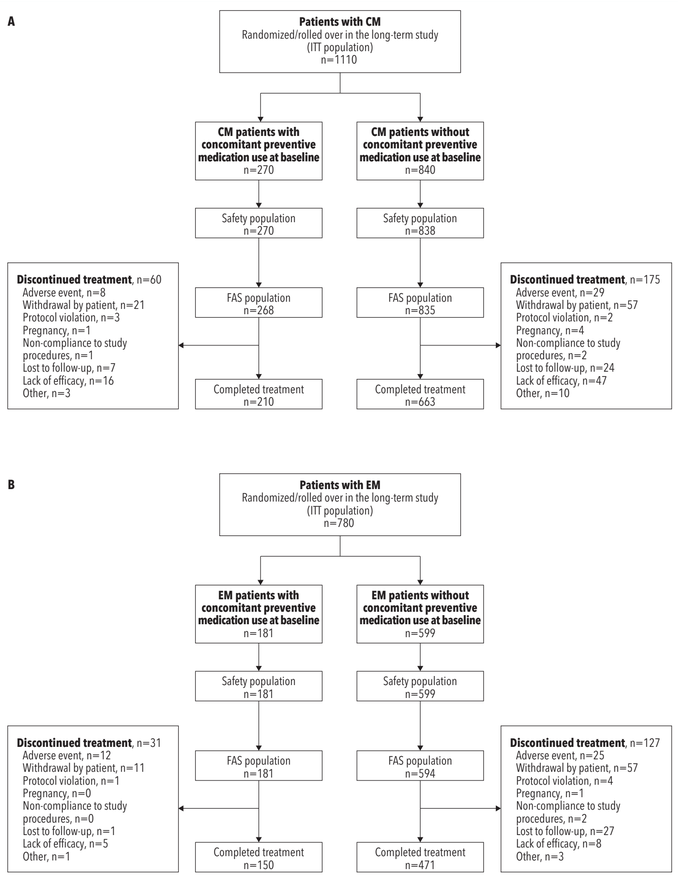
BMI, body mass index; CM, chronic migraine; EM, episodic migraine; ITT, intention-to-treat; SD, standard deviation.
[a]In the ITT population. [b]Patients flagged for preventive medication use at baseline who did not have their medication recorded in the medication database were not included in the analysis of preventive medication by therapeutic class (CM: quarterly n=1, monthly, n=4; EM: quarterly n=1, monthly n=2). [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 an acute migraine-specific medication (triptan or ergot) was used to treat a headache of any severity or duration. [d]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).

Table 2. Summary of AEs and AEs of Interest in the Safety Population for CM and EM Patients by Concomitant Preventive Medication Use

	CM				EM			
	With concomitant use		Without concomitant use		With concomitant use		Without concomitant use	
	Fremanezumab quarterly (n=128)	Fremanezumab monthly (n=142)	Fremanezumab quarterly (n=422)	Fremanezumab monthly (n=416)	Fremanezumab quarterly (n=89)	Fremanezumab monthly (n=92)	Fremanezumab quarterly (n=305)	Fremanezumab monthly (n=294)
Patients with AEs, n (%)								
At least one AE	104 (81)	125 (88)	357 (85)	373 (90)	75 (84)	77 (84)	255 (84)	246 (84)
At least one treatment-related AE	69 (54)	87 (61)	230 (55)	241 (58)	43 (48)	55 (60)	170 (56)	168 (57)
At least one serious AE	12 (9)	8 (6)	26 (6)	27 (6)	5 (6)	7 (8)	16 (5)	14 (5)
Any AE leading to discontinuation	4 (3)	4 (3)	16 (4)	14 (3)	6 (7)	6 (7)	14 (5)	12 (4)
Death	0	0	0	0	0	0	0	0
Injection-site reactions (occurring in >6% of patients in any treatment group), n (%)[a]								
Injection-site induration	30 (23)	51 (36)	135 (32)	145 (35)	18 (20)	32 (35)	95 (31)	113 (38)
Injection-site pain	38 (30)	50 (35)	119 (28)	132 (32)	23 (26)	31 (34)	95 (31)	92 (31)
Injection-site erythema	30 (23)	41 (29)	108 (26)	130 (31)	20 (22)	20 (22)	65 (21)	83 (28)
Injection-site hemorrhage	9 (7)	10 (7)	33 (8)	34 (8)	5 (6)	4 (4)	12 (4)	24 (8)
Injection-site pruritus	8 (6)	11 (8)	18 (4)	28 (7)	3 (3)	10 (11)	12 (4)	25 (9)
Other common AEs (occurring in >6% of patients in any treatment group), n (%)								
Upper respiratory tract infection	16 (13)	13 (9)	61 (14)	59 (14)	12 (13)	7 (8)	47 (15)	38 (13)
Nasopharyngitis	13 (10)	11 (8)	51 (12)	50 (12)	11 (12)	14 (15)	30 (10)	37 (13)
Bronchitis	5 (4)	6 (4)	18 (4)	19 (5)	8 (9)	2 (2)	13 (4)	12 (4)
Urinary tract infection	9 (7)	6 (4)	30 (7)	22 (5)	5 (6)	4 (4)	17 (6)	20 (7)
Sinusitis	15 (12)	9 (6)	25 (6)	30 (7)	7 (8)	5 (5)	12 (4)	13 (4)
Influenza	7 (5)	13 (9)	15 (4)	17 (4)	3 (3)	4 (4)	8 (3)	7 (2)
Diarrhea	7 (5)	10 (7)	7 (2)	6 (1)	1 (1)	3 (3)	6 (2)	4 (1)
Fatigue	1 (<1)	1 (<1)	9 (2)	7 (2)	2 (2)	6 (7)	5 (2)	6 (2)

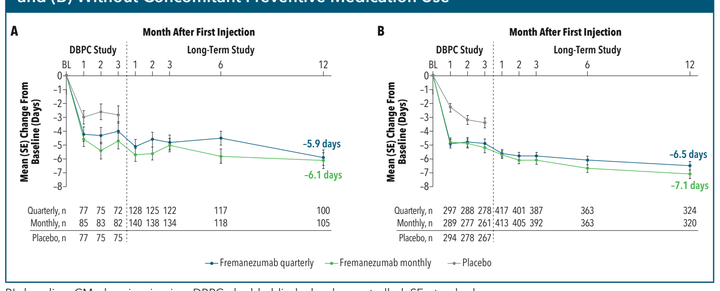
AE, adverse event; CM, chronic migraine; EM, episodic migraine.
[a]Local injection sites were systematically assessed for erythema, induration, ecchymosis, and pain both immediately and 1 hour after dosing.

Figure 1. Patient Disposition for Patients (A) With CM and (B) With EM[a]



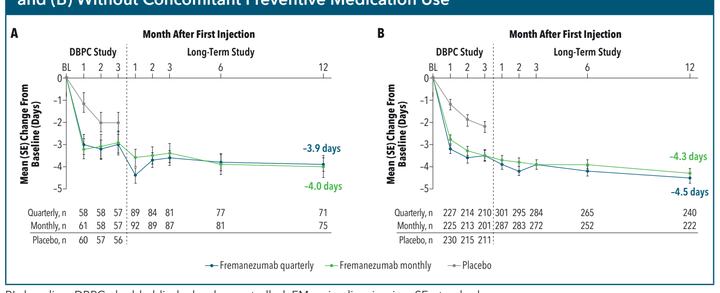
CM, chronic migraine; EM, episodic migraine; FAS, full analysis set; ITT, intention-to-treat.
[a]Patient flow was based on an interim analysis with some patients' complete status unknown (missing or ongoing); group numbers may not sum to total.

Figure 2. Change From Baseline in the Monthly Average Number of Headache Days of at Least Moderate Severity in CM Patients (A) With Concomitant Preventive Medication Use and (B) Without Concomitant Preventive Medication Use



BL, baseline; CM, chronic migraine; DBPC, double-blind, placebo-controlled; SE, standard error.

Figure 3. Change From Baseline in the Monthly Average Number of Headache Days of at Least Moderate Severity in EM Patients (A) With Concomitant Preventive Medication Use and (B) Without Concomitant Preventive Medication Use

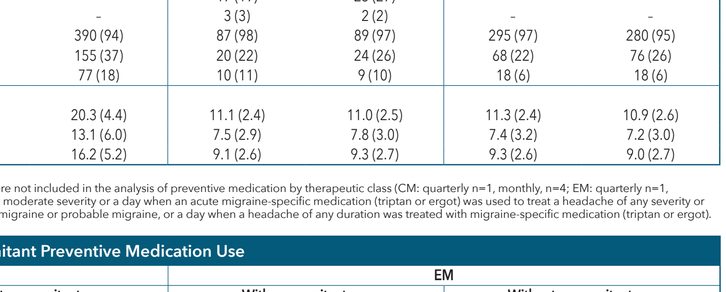


BL, baseline; DBPC, double-blind, placebo-controlled; EM, episodic migraine; SE, standard error.

Migraine Days

- Fremanezumab quarterly or monthly resulted in reductions from baseline in the monthly average number of migraine days in patients with CM who were using concomitant preventive medication (**Figure 4A**) and those who were not (**Figure 4B**)

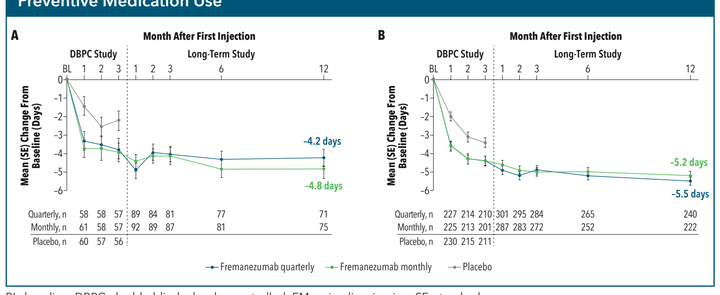
Figure 4. Change From Baseline in the Monthly Average Number of Migraine Days in CM Patients (A) With Concomitant Preventive Medication Use and (B) Without Concomitant Preventive Medication Use



BL, baseline; CM, chronic migraine; DBPC, double-blind, placebo-controlled; SE, standard error.

- Fremanezumab quarterly or monthly resulted in reductions from baseline in the monthly average number of migraine days in patients with EM who were using concomitant preventive medication (**Figure 5A**) and those who were not (**Figure 5B**)

Figure 5. Change From Baseline in the Monthly Average Number of Migraine Days in EM Patients (A) With Concomitant Preventive Medication Use and (B) Without Concomitant Preventive Medication Use



BL, baseline; DBPC, double-blind, placebo-controlled; EM, episodic migraine; SE, standard error.

Safety and Tolerability

- AEs were reported for 81–88% of patients who used concomitant preventive medication and 84–90% of patients who did not (**Table 2**)
- Treatment-related AEs occurred in 48–61% of patients who used concomitant preventive medication and 55–58% of patients who did not (**Table 2**)
- Serious AEs and AEs leading to study discontinuation were infrequent, with similar proportions of patients across groups (**Table 2**)
- Injection-site reactions (induration, pain, erythema) were the most frequently reported AEs across all groups (**Table 2**)

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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 who participated in this study, and Lindsay Tannenholz, PhD (Chameleon Communications International with funding from Teva Pharmaceutical Industries Ltd.) for editorial assistance in the preparation of this report.

Disclosures

Peter J. Goadsby: Reports grants and personal fees from Amgen and Eli Lilly and Company, and personal fees from Alder Biopharmaceuticals, Allergan, Autonomic Technologies, Inc., Biohaven Pharmaceuticals Inc., Dr. Reddy's Laboratories, electroCore LLC, eNeura, Impel NeuroPharma, MundiPharma, Novartis, Teva Pharmaceuticals, Trigemina, Inc., W.L.Gore, medicolegal work, Massachusetts Medical Society, UpToDate, Oxford University Press, and Wolters Kluwer; he holds a patent for magnetic stimulation for headache assigned to eNeura without fee.

David W. Dodick: Personal fees: Amgen, Association of Translational Medicine, University Health Network, Daniel Edelman Inc., Autonomic Technologies, Inc., Axsome, Aural Analytics, Allergan, Alder, Biohaven, Charleston Laboratories, Dr. Reddy's Laboratories/Promius, electroCore LLC, Eli Lilly, eNeura, Neurolief, Novartis, Ipsen, Impel, Satsuma, Supernus, Sun Pharma (India), Theranica, Teva Pharmaceuticals, Vedanta, WL Gore, Nocira, PSL Group Services, University of British Columbia, Zosano, ZP Opco, Foresite Capital, and Oppenheimer. CME fees or royalty payments: HealthLogiX, Medicom Worldwide, Medlogix Communications, Mednet, Miller Medical, PeerView, WebMD Health/Medscape, Chameleon, Academy for Continued Healthcare Learning, Universal Meeting Management, Haymarket, Global Scientific Communications, Global Life Sciences, Global Access Meetings, UpToDate (Elsevier), Oxford University Press, Cambridge University Press, and Wolters Kluwer Health. Stock options: Aural Analytics, Healint, Theranica, Second Opinion/Mobile Health, Epien, GBS/Nocira, Matterhorn/Ontologics, and King-Devick Technologies. Consulting without fee: Aural Analytics, Healint, Second Opinion/Mobile Health, and Epien. Board of Directors: Epien, Matterhorn/Ontologics, and King-Devick Technologies. Patent: 17189376.1-1466.v Title: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis, without fee. Professional society fees or reimbursement for travel: American Academy of Neurology, American Brain Foundation, American Headache Society, American Migraine Foundation, International Headache Society, and Canadian Headache Society. Use agreement through employer: Myndshft.

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Stephen D. Silberstein: Provides consultation to Alder, Allergan, Amgen, Autonomic Technologies, Inc., 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.

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