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Safety and Tolerability of Fremanezumab in Patients With Migraine and Documented Inadequate Response to 2-4 Classes of Migraine Preventive Medications in the International, Multicenter, Randomized, Placebo-controlled FOCUS Study

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CONCLUSIONS

- **Fremanezumab administered quarterly or monthly was generally safe and well tolerated in patients with episodic migraine (EM) and chronic migraine (CM) and documented inadequate response to 2 to 4 classes of prior migraine preventive medications**
- **Incidences of adverse events (AEs), AEs leading to discontinuation, and serious AEs (SAEs) were similar with both fremanezumab dosing regimens versus placebo**
- **The most commonly reported AEs were injection-site reactions and nasopharyngitis**
- **Incidences of cardiovascular and hepatobiliary AEs, AEs leading to discontinuation, and SAEs were low (≤1%), and no safety signals were identified**

OBJECTIVES

- Although migraine preventive treatment can reduce the symptom burden of migraine,[1] persistence with migraine preventive treatment is poor[2]
  - One of the most common reasons migraine patients discontinue preventive treatment is side effects[3]
- Fremanezumab is a fully humanized monoclonal antibody (IgG2Δa) that selectively targets calcitonin gene-related peptide (CGRP)
  - Approved for the preventive treatment of migraine in adults[4]
- The FOCUS study (ClinicalTrials.gov Identifier: NCT03308968) of fremanezumab was the first and largest study of a migraine preventive treatment in patients with EM and CM who had documented inadequate response to 2 to 4 classes of migraine preventive medications
- In the FOCUS study, the safety and tolerability of subcutaneous (SC) quarterly or monthly fremanezumab were evaluated in EM and CM patients with documented inadequate response to 2 to 4 classes of migraine preventive medications

METHODS

Patients

Table 1. Key Selection Criteria

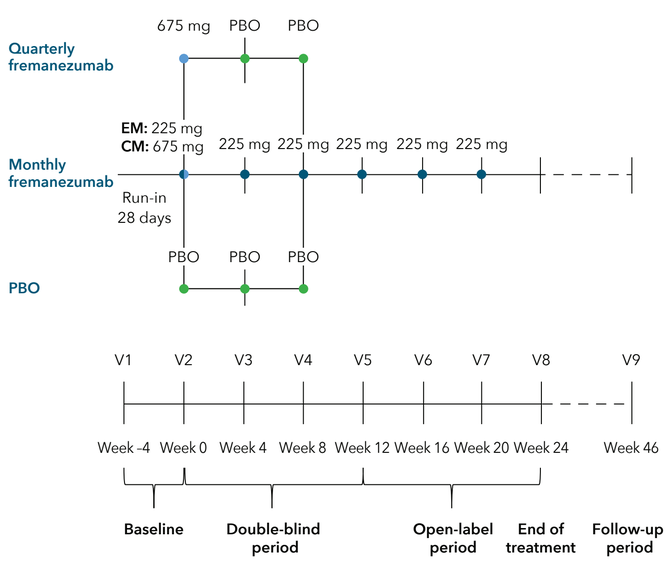
Inclusion criteria	Exclusion criteria
— Adult patients (18-70 years) with a diagnosis of migraine with onset at ≤50 years	— Any migraine preventive treatment for >5 days at screening and plan to continue treatment
— History of migraine for ≥12 months prior to screening and fulfilled criteria for EM or CM at baseline	— OnabotulinumtoxinA during the 3 months prior to screening
— Documented inadequate response (within the past 10 years) to 2-4 classes of prior migraine preventive medications: – Beta-blocker (propranolol, metoprolol, atenolol, bisoprolol) – Anticonvulsant (topiramate) – Tricyclic antidepressant (amitriptyline) – Calcium channel blocker (flunarizine) – OnabotulinumtoxinA – Valproic acid	— Opioid- or barbiturate-containing treatment on >4 days during the run-in period — Intervention/device for migraine during the 2 months prior to screening — Triptans, ergots, or nonsteroidal anti-inflammatory drugs for migraine preventive treatment — Prior exposure to a mAb targeting the CGRP pathway

EM, episodic migraine; CM, chronic migraine; mAb, monoclonal antibody; CGRP, calcitonin gene-related peptide.

Study Design

- International, multicenter, randomized, double-blind, placebo-controlled, phase 3 study
- Included a screening visit; 28-day run-in period; 12-week, double-blind, placebo-controlled treatment period; and 12-week, open-label treatment period (**Figure 1**)
  - Results of the 12-week, double-blind period are presented here
- During the double-blind period, patients were randomized (1:1:1) to SC quarterly fremanezumab, SC monthly fremanezumab, or placebo (**Figure 1**)

Figure 1. Study design and dosing for EM and CM patients.



EM, episodic migraine; CM, chronic migraine; PBO, placebo; V, visit.

Tolerability Assessments

- Tolerability of quarterly and monthly fremanezumab versus placebo was evaluated as a secondary endpoint
- Tolerability was assessed by evaluating reported AEs, AEs leading to discontinuation, SAEs, cardiovascular AEs, and hepatobiliary AEs

RESULTS

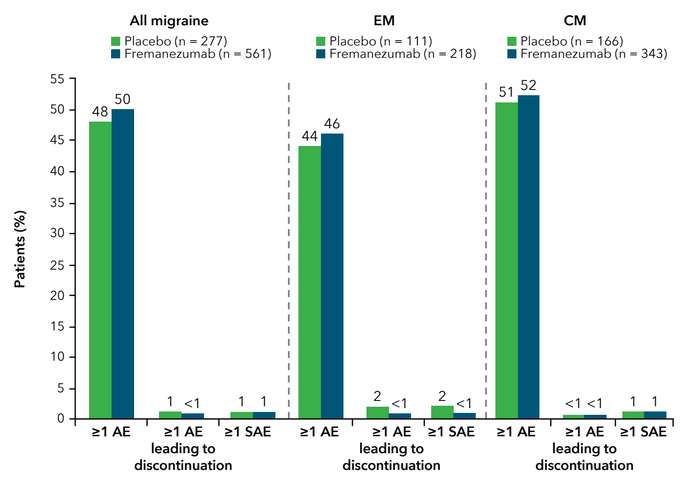
Patients

- Safety population, N = 838 (placebo, n = 277; quarterly fremanezumab, n = 276; monthly fremanezumab, n = 285)
- Demographics and baseline characteristics were well balanced across treatment groups
  - Mean (standard deviation) time since migraine diagnosis, 24.2 (13.4) years
  - EM patients, n = 329 (39%); CM patients, n = 509 (61%)

Tolerability

- Rates of AEs, AEs leading to discontinuation, and SAEs were similar in the fremanezumab and placebo groups in the overall population, as well as in the EM and CM subgroups (**Figure 2**)
- Incidences of AEs, AEs leading to discontinuation, and SAEs were comparable for both fremanezumab dosing regimens and placebo (**Table 2**)
  - AEs leading to discontinuation and SAEs were infrequent (≤1%) across treatment groups
  - No individual AE leading to discontinuation or SAE was reported by ≥1 patient
  - None of the SAEs were considered to be treatment related by investigators, and no safety signals were identified
- The most common AEs (incidence ≥5%) were injection-site erythema, injection-site induration, and nasopharyngitis (**Table 2**)

Figure 2. Rates of AEs, AEs leading to discontinuation, and SAEs with fremanezumab and placebo by migraine classification.



AE, adverse event; SAE, serious adverse event; EM, episodic migraine; CM, chronic migraine.

Table 2. AEs, AEs Leading to Discontinuation, SAEs, and Most Common AEs (Incidence ≥5%)

Patients with ≥1 AE, n (%)	Placebo (n = 277)	Quarterly fremanezumab 675 mg/ placebo/ placebo (n = 276)	Monthly fremanezumab 675/225/ 225 mg (n = 174)	Monthly fremanezumab 225/225/ 225 mg (n = 111)	All fremanezumab (n = 561)
Any AE	134 (48)	151 (55)	85 (49)	44 (40)	280 (50)
AEs leading to discontinuation	3 (1)	1 (<1)	3 (2)	1 (<1)	5 (<1)
SAEs	4 (1)	2 (<1)	3 (2)	1 (<1)	6 (1)
AEs with incidence ≥5% in any treatment/dose group					
Injection-site erythema	15 (5)	19 (7)	12 (7)	4 (4)	35 (6)
Injection-site induration	12 (4)	12 (4)	10 (6)	3 (3)	25 (4)
Nasopharyngitis	11 (4)	13 (5)	6 (3)	1 (<1)	20 (4)

AE, adverse event; SAE, serious adverse event.

- Individual cardiovascular or hepatobiliary AEs were reported by <1% of patients in each treatment group (**Table 3**)
- No clinically relevant electrocardiogram abnormalities were observed in fremanezumab- or placebo-treated patients at any study assessment

Table 3. Cardiovascular and Hepatobiliary AEs

Patients with ≥1 AE, n (%)	Placebo (n = 277)	Quarterly fremanezumab 675 mg/ placebo/ placebo (n = 276)	Monthly fremanezumab 675/225/ 225 mg (n = 174)	Monthly fremanezumab 225/225/ 225 mg (n = 111)	All fremanezumab (N = 561)
Cardiac disorders	3 (1)	2 (<1)	2 (1)	2 (2)	6 (1)
Palpitations	2 (<1)	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Atrial fibrillation	0	0	0	1 (<1)	1 (<1)
SVT	0	1 (<1)	0	0	1 (<1)
Tachycardia	0	0	1 (<1)	0	1 (<1)
Bradycardia	1 (<1)	0	0	0	0
Vascular disorders	6 (2)	7 (3)	3 (2)	2 (2)	12 (2)
Hypertension	2 (<1)	3 (1)	0	1 (<1)	4 (<1)
Hematoma	0	2 (<1)	0	0	2 (<1)
Hot flush	2 (<1)	1 (<1)	1 (<1)	0	2 (<1)
Peripheral venous disease	0	1 (<1)	0	1 (<1)	2 (<1)
Hypotension	1 (<1)	0	1 (<1)	0	1 (<1)
Temporal arteritis	0	0	1 (<1)	0	1 (<1)
Peripheral coldness	1 (<1)	0	0	0	0
Hepatobiliary disorder	0	0	1 (<1)	0	1 (<1)
Cholelithiasis	0	0	1 (<1)	0	1 (<1)

AE, adverse event; SVT, supraventricular tachycardia.

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Disclosures

M.D. Ferrari was an investigator on the FOCUS study, which was sponsored by Teva Pharmaceuticals. J.M. Cohen, X. Ning, M. Galic, and R. Yang are employees of Teva Pharmaceuticals.

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