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Research Submissions

The Effect of Beginning Treatment With Fremanezumab on Headache and Associated Symptoms in the Randomized Phase 2 Study of High Frequency Episodic Migraine: Post-Hoc Analyses on the First 3 Weeks of Treatment

Stephen D. Silberstein, MD; Alan M. Rapoport, MD; Pippa S. Loupe, PhD; Ernesto Aycardi, MD; Mirna McDonald, MS; Ronghua Yang, PhD; Marcelo E. Bigal, MD, PhD

Background.—Migraine has a substantial impact on daily living, affecting productivity and quality of life for patients and their families. Patients frequently discontinue preventive medications in part because of a delay in headache and symptom relief due to the long dose titration procedures necessary for some migraine preventives.

Objective.—To evaluate the efficacy of fremanezumab, a selective monoclonal CGRP ligand antibody, during the first 3 weeks of therapy in patients with high-frequency episodic migraine (HFEM) to relieve migraine headaches and associated symptoms and to reduce use of acute migraine medications.

Methods.—In a multicenter, randomized, double-blind, placebo-controlled, phase 2 study, patients with HFEM who met inclusion criteria and were 80% compliant with daily headache diary entry were randomized and treated once every 28 days for 3 months with either placebo or fremanezumab 225 or 675 mg. Compared to placebo, both doses of fremanezumab significantly reduced the primary endpoint of the HFEM study, change in the number of migraine days in month 3 relative to baseline. Herein, we performed post-hoc analyses to assess the efficacy of each dose during the first 3 weeks of treatment to reduce migraine headache parameters, associated migraine symptoms, and the consumption of acute migraine medications.

Results.—The sample consisted of 297 study participants. Compared to placebo, decreases in migraine days were seen during the first week of therapy for both fremanezumab doses with least square mean (LSM) differences between fremanezumab 225 mg and placebo of −0.93 (95% CI: −1.36, −0.49) and between 675 mg dose and placebo of −1.02 (95% CI: −1.46, −0.58), both $P < .0001$. This benefit was maintained through the second week of therapy for the 225 and 675 mg doses, respectively, (−0.76 (95% CI: −1.11, −0.40) $P < .0001$, −.79 (95% CI: −1.15, −0.44) $P < .0001$) and the third week of therapy (−0.64 (95% CI: −0.97, −0.30) $P = .0003$ and −0.64 (95% CI: −0.98, −0.30) $P = .0003$). Likewise in the first week, patients recorded reductions in associated migraine symptoms such as nausea, vomiting, photophobia, and phonophobia, which continued through weeks 2 and 3. There were also reductions in days with acute medication use to treat migraine for the 225 and 675 mg fremanezumab doses compared to placebo. In the first week, LSM differences between 225 mg and placebo were −1.02 (95% CI: −1.39, −0.64) and between 675 mg and placebo were −1.06 (95% CI: −1.39, −0.64) $P < .0001$); for the second and third weeks (−1.01 (95% CI: −1.14, −0.55) $P < .0001$; −.90 (95% CI: −1.04, −0.44) $P < .0001$; −.91 (95% CI: −0.92, −0.34) $P < .0001$; and −.83 (95% CI: −0.84, −0.26) $P = .0002$), respectively.

Conclusion.—Fremanezumab treatment resulted in a rapid preventive response in patients with HFEM, with reductions seen in several headache parameters and migraine symptoms within the first week after therapy initiation and continuing during the

From the Jefferson Headache Center, Thomas Jefferson University, Philadelphia, PA, USA (S. Silberstein); David Geffen School of Medicine at UCLA, Los Angeles, CA, USA (A. Rapoport); Global Research and Development Teva Pharmaceuticals Ltd, Overland Park, KS, USA (P. Loupe); Xenon Pharmaceuticals Inc, Boston, MA, USA (E. Aycardi); Global Research and Development Teva Pharmaceuticals Ltd, West Chester, PA, USA (M. McDonald and R. Yang); Purdue Pharma, Stamford, CT, USA (M. Bigal).

Address all correspondence to P. S. Loupe, Global Research and Development, Teva Pharmaceuticals Ltd, 11100 Nall Avenue, Overland Park, KS 66211, USA, email: pippa.loupe@tevapharm.com

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second and third weeks. Patients also were able to rapidly reduce their use of acute medications to treat migraine attacks. The trial is registered at Clinicaltrials.gov as NCT02025556.

Key words: migraine, fremanezumab, TEV-48125, calcitonin-gene-related peptide (CGRP), migraine preventive medication

Abbreviations: CGRP calcitonin-gene-related peptide, CM chronic migraine, EM episodic migraine, HFEM, high-frequency episodic migraine, HIT-6, Headache Impact test, IgG2Δa, immunoglobulin G2Δa, ITT, intent-to-treat, IWRS, interactive web response system, MMRM, mixed effect model of repeated measurement, M/S, moderate-to-severe; MSQ, Migraine-Specific Quality of Life Questionnaire

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INTRODUCTION

Migraine is a debilitating neurologic disease that can transform from an episodic into a chronic form.[1-3] Migraine frequency can be conceptualized as a continuum from low-frequency episodic into high-frequency episodic and then into chronic migraine; one goal of preventive treatment is to avoid this transformation. This is achieved by reducing headache frequency and lowering disability and impact.[4] Risk factors for progression, as well as factors protecting transformation from episodic into chronic migraine, have been identified.[5]

Current preventive treatments for migraine often have unwanted adverse events or contraindications, limiting their use. In addition, they often require slow titration to achieve tolerable dosing and can take up to 4–6 weeks at a minimum to provide relief to patients.[6-9] Adherence to preventive migraine medications is low[8] and lack of initial efficacy, accompanied by adverse events, often results in discontinuation.

Calcitonin-gene related peptide (CGRP) is a neuropeptide involved in the pathophysiology of migraine; it induces trigeminal sensitization and activation of second-order sensory neurons in the brain stem.[10-13] By its effect on trigeminal sensitization, CGRP may be a risk factor for increased headache frequency, predisposing the progression of migraine from an episodic to chronic form.[14-16] Its blockage may be associated with a rapid decreased frequency or remission of migraine, which has been demonstrated for chronic migraine.[17]

Fremanezumab (Ajovy, Teva Pharmaceuticals, Ltd) is a fully humanized immunoglobulin G subclass 2 (IgG2Δa) monoclonal antibody with two mutations in the hinge that reduce effector function.[18] This antibody selectively targets the CGRP ligand and is well-tolerated and effective as a preventive treatment for episodic and chronic migraine in phase 2 and 3 studies.[19-22] Fremanezumab resulted in significant reductions in migraine and headache days within the first month of treatment; additionally, as post-hoc analyses in the phase 2 chronic migraine study suggested, improvement in headache hours occurs as early as 3 days after dosing.[17]

Herein, we conduct similar analyses in the episodic migraine study, to determine the effect of 2 doses of fremanezumab (225 and 675 mg) during the first 3 weeks of therapy on reducing headache parameters and associated symptoms in the phase 2, high-frequency episodic migraine (HFEM) study.

METHODS

Study Design.—The methods for the fremanezumab phase 2 HFEM study have been previously reported.[19] Briefly, the study was performed from January 2014

Conflict of Interest: Dr. Silberstein reports receiving consulting fees from Alder BioPharmaceuticals, Allergan, Amgen, Automatic Technologies, Avanir Pharmaceuticals, Curelator, Depomed, Dr. Reddy's Laboratories, electroCore, Eli Lilly, eNeura, Insys Therapeutics, Supernus Pharmaceuticals, Teva Pharmaceuticals, Theranica BioElectronics, and Trigemina.
Dr. Rapoport reports that he is on the speakers bureau for Amgen, Depomed, Dr. Reddy's, electroCore, Teva, and has been a consultant for Amgen, Autonomic Technologies, Dr. Reddy's, Electrocore, Impax, Teva, and Zosano
P. Loupe and R. Yang are full-time employees of Teva Pharmaceuticals and M. McDonald is a former employee of Teva Pharmaceuticals.
Dr. Aycardi is a full-time employee of Xenon Pharmaceuticals Inc.; he was an employee of Teva Pharmaceuticals at the time of this study.
Dr. Bigal is a full-time employee of Purdue. He was a full-time employee of Teva and of Labrys Biologicals at the time of this

to January 2015 in 62 US sites, including headache centers, neurology clinics, and primary care facilities. The study was conducted in accordance with Good Clinical Practice and US FDA guidelines, and was registered at clinicaltrials.gov as NCT02025556. All protocols were approved by the institutional review boards for each site and patients provided written informed consent before participating in the study.

For patients to be considered eligible participants in the study they had to be men or women aged 18–65 years with confirmed diagnoses of migraine as per the International Classification of Headache Disorders (ICHD III beta).[23] Inclusion criteria consisted of having 8 or more headache days per month for at least 3 months and confirmation of this headache frequency during the 28-day study run-in period. Patients had to have 8–14 days of headache per month fulfilling one of the following criteria (migraine day, headache preceded or accompanied by migraine aura, or headache relieved by an ergot or triptan). Patients were allowed to have used one standard migraine preventive drug at stable doses for at least 2 months prior to study onset and acute migraine medications up to 14 days per month (maximum of 4 days of opioids or barbiturates per month). Patients were excluded if they used onabotulinumtoxinA for migraine or for any medical or cosmetic reasons during the 6 months prior to study entry. They were excluded if they had discontinued >2 medication categories or >3 more preventive medications (within 2 medication categories) due to lack of efficacy or had treatment with an investigational drug or device within 30 days of study entry or had any prior exposure to a monoclonal antibody targeting the CGRP pathway. They were allowed to treat a migraine attack as usual.

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 16-week clinical trial consisting of a 28-day screening period, and a 3-month double-blinded treatment period. Patients who met eligibility criteria were trained during the 28-day screening period to provide daily headache and migraine symptom data using an electronic headache diary. Diary entry involved patients logging into the web-based interactive system (IWRS) every day and answering questions on the occurrence of headache, migraine, associated symptoms, and the use of acute medications during the previous 24 h

enter 1 day of information and was locked thereafter. If patients demonstrated 80% compliance with diary entry during the screening period, they were stratified based on sex and preventive medication use and then randomized into either one of the two fremanezumab arms (225 and 675 mg) or placebo arm by study site coordinators using the IWRS and eClinical Operating System portal. The randomization scheme was developed by a staff member of the contract research organization managing the study (NCGS, Charleston, SC, USA) who had no further role in the study.

As the HFEM study was conducted without prior proof-of-concept for this or other antibodies, in agreement with government regulators, an interim analysis was initially suggested. For randomization, participants were first stratified by sex and use of concomitant preventive drugs. Once the stratification group was determined, randomization was done by block (men using preventive drugs, men not using preventive drugs, women using preventive drugs, women not using preventive drugs). Participants (n = 192) were initially randomized 1:1 to 675 mg or placebo. After the fulfillment of this first cohort, participants (n = 105) were randomized 9:1 to 225 mg or placebo, yielding an approximately 1:1:1 final randomization schedule and an interim analysis for the highest dose. However, since no safety concerns emerged in the chronic migraine study that was being conducted in parallel to this HFEM study (and which enrolled higher doses) and due to the fast rate of enrollment on the current study, it was agreed that the interim analysis was no longer justified, since it would not transfer into any protocol modification while inducing the potential for unblinding and Type I error. IRBs had access to the protocol and SAP. To help keep the blinding, IRBs requested that the patient consent forms indicate a randomization of approximately 1:1:1 ratio.

Study sites had 2 blinded study coordinators at each clinic visit to protect the treatment blind. One study coordinator performed the clinical assessment which included reviewing electronic diary data entry procedures and safety assessments with patients. The second study coordinator performed the treatment administration. Patients were blinded to whether they were receiving placebo or one of the fremanezumab doses; they all received 4 injections

were identical in packaging and appearance regardless of treatment arm. Each active injection contained 225 mg of fremanezumab. Patients in the fremanezumab arms received one of two dosing strategies: once monthly subcutaneous injections of 225 or 675 mg for 3 months.

Outcomes and Statistical Analyses.—The primary efficacy endpoint of the phase 2 HFEM study was the mean change from baseline in the number of migraine days during the third study month. A migraine day was defined as a headache day lasting at least 4 consecutive hours and meeting the criteria for migraine with aura, migraine without aura, or probable migraine; it could also be a headache day of any duration treated with migraine specific medications, such as a triptan or ergot. Key secondary and exploratory endpoints included the change from baseline to month 3 in the number of headache days and hours with headaches of any severity. The number of days with moderate-to-severe (M/S) headaches was an exploratory endpoint in the HFEM and was defined as a day with at least 4 consecutive hours of moderate to severe headache. Other exploratory endpoints included assessment of treatment-related changes in migraine associated symptoms (nausea, vomiting, photophobia, and phonophobia) and a change in the use of acute medications during the study. Patients provided daily information on the use of acute medication consumption by responding to questions in the e-diary regarding the previous day usage and selecting from a list of the most frequently used medications to treat migraine attacks. Patients could enter the name of a used medication if it was not included in the list and could enter information on acute medication use at any hour in the e-diary. For purposes of these post-hoc analyses, missing weekly data were prorated to 7-day rate based on available data within that week.

As one of the questions remaining from the original study was how soon after starting fremanezumab did treatment effects become apparent, we conducted mixed effect model repeated measurement (MMRM) analysis to investigate the earliest significant separation from placebo. The post-hoc analyses included the change from baseline in the efficacy variables at week 1, 2, and 3 as the dependent variable; preventive medication use, sex, visit, an interaction term, acute medication use and years since onset of disease were defined as covariates, with patients treated as random. An unstructured covariance matrix for repeated observations within patients was used and 95% CIs for the least square mean differences between each fremanezumab group and placebo were constructed. All variables were analyzed by the intent-to-treat (ITT) principle, which included all randomized participants who received at least one dose of study drug and provided at least one measurement. One patient received study drug and discontinued prior to providing one measurement and was not included in the ITT cohort analysis. All statistical tests were 2-sided at alpha level of 0.05. As these are post-hoc analyses, the reported *P* values should be interpreted with caution as there were no adjustments for multiplicity. The analyses were conducted with SAS (Version 9.2).

Role of the Funding Source.—The analyses of this paper were designed by all authors, some of whom are employees of the funding source, Teva Pharmaceuticals Ltd. One of the authors, Mirna McDonald, a former employee of Teva Pharmaceuticals conducted the statistical analyses. All authors were involved in writing the manuscript. They had access to all data in the study and there were no agreements with the sponsor which would preclude the authors' ability to analyze and interpret data and publish manuscripts independently when and where they choose.

RESULTS

Patient Disposition.—The HFEM study was conducted in parallel to a study investigating the efficacy of fremanezumab in chronic migraine (CM), thus screening included 1170 patients with a migraine diagnosis. Of these, 264 patients met eligibility criteria for CM and were enrolled in the parallel CM study. An additional 609 patients did not qualify for either the HFEM or CM study and were excluded. A total of 297 individuals were eligible for the HFEM study and were randomized to receive placebo (n = 104), 225 mg (n = 96), or 675 mg (n = 97). Of the patients in the HFEM study randomized into treatment arms, 2 participants did not receive any study medication and so were not included in the ITT or safety cohorts (1 in the 225 mg group and 1 in the 675 mg group) and one

Table 1.—Patient Baseline Demographic and Disease Characteristics

Patient Characteristics[†‡]	Placebo (n = 104)	Fremanezumab 225 mg (n = 96)[§]	Fremanezumab 675 mg (n = 97)[§]
Age – mean (SD) years	42.0 (11.6)	40.8 (12.4)	40.7 (12.6)
Sex			
Male	12 (12%)	9 (9%)	15 (15%)
Female	92 (88%)	87 (91%)	82 (85%)
Ethnic origin			
White	85 (82%)	74 (77%)	74 (76%)
Black or African American	13 (13%)	19 (20%)	18 (19%)
Asian	2 (2%)	1 (1%)	1 (1%)
Other	0	0	0
Years of migraine	21.1 (14.1)	18.9 (12.9)	16.9 (12.3)
Migraine days/month	11.5 (2.2)	11.5 (1.9)	11.3 (2.2)
Migraine days/week	2.9 (.6)	2.9 (.5)	2.8 (.6)
M/S headache days/month[¶]	9.8 (2.7)	10.0 (3.1)	9.6 (2.9)
M/S headache days/week	2.4 (.7)	2.5 (.8)	2.4 (.7)
Headache days/month	12.4 (2.3)	12.6 (3.1)	12.5 (2.7)
Headache days/week	3.1 (.6)	3.1 (.8)	3.1 (.6)
M/S headache hours/month	53.7 (45.7)	45.9 (27.2)	48.4 (27.9)
M/S headache hours/week	13.4 (11.5)	11.5 (6.8)	12.1 (7.0)
Headache hours/month	82 (49.3)	76.1 (36.7)	80.4 (36.6)
Headache hours/week	20.5 (12.4)	19.0 (9.2)	20.1 (9.2)
Days with nausea or vomiting/month	5.8 (4.3)	6.2 (4.1)	5.9 (4.0)
Days with nausea or vomiting/week	1.4 (1.1)	1.5 (1.0)	1.5 (1.0)
Days with photophobia and phonophobia/month	7.6 (4.7)	7.8 (4.3)	7.6 (4.2)
Days with photophobia and phonophobia/week	1.9 (1.2)	1.9 (1.1)	1.9 (1.0)
Days using acute medications/month	10.4 (3.6)	10.4 (3.6)	9.8 (4.0)
Days using acute medications/week	2.6 (.9)	2.6 (.9)	2.4 (1.0)

[†]All *P* values for treatment comparisons of demographic characteristics were >.05.
[‡]Data are mean (SD) of days or hours per month or per week, or number (percentage) of patients.
[§]The intent-to-treat mixed effect model of repeated measurement (ITT MMRM) analyses included 95 patients from fremanezumab 225 mg and 96 from fremanezumab 675 mg groups as one patient from each group withdrew from the study prior to drug treatment.
[¶]M/S, moderate-to severe.

patient was lost to follow-up after the first injection of study medication so there were no diary records; she was included in the safety cohort but not in the ITT cohort of the 225 mg group.

As shown in Table 1, baseline demographics and clinical disease characteristics were similar across treatment arms with a mean (SD) of 11.4 (2.1) migraine days per month. Compliance with diary entry was high throughout the study and similar across groups; for instance, during the first treatment month, 91% of placebo, 89% of 225 mg, and 84% of 675 mg patients provided daily entries at ≥80% compliance rate (≥22 days per 28 day treatment period).

Efficacy.—*Headache Parameters*.—The study has been described in detail.[19] As displayed in Figure 1 and Table 2, the number of migraine days for patients treated with fremanezumab was reduced compared to those treated with placebo in *the first week of therapy* for both fremanezumab doses; LSM differences between placebo and active treatment at week 1 for the 225 mg fremanezumab dose is −0.93 migraine days per week (95% CI: −1.36, −0.49); and for the 675 mg dose −1.02 migraine days per week (95% CI: −1.46, −0.58), both $P < .0001$. This benefit was maintained through the second and third weeks of therapy (all $P < .001$). Likewise there were consistent reductions in

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