

Reduction in migraine-associated burden after eptinezumab treatment in patients with chronic migraine

Cephalalgia
42(10) 1005–1012
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DOI: 10.1177/03331024221089567
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Abstract

Objective: To examine changes in the occurrence, severity, and symptoms of headache episodes in patients with chronic migraine following eptinezumab treatment.

Methods: PROMISE-2 was a double-blind, placebo-controlled, parallel-group trial that randomized adults with chronic migraine to eptinezumab 100 mg, 300 mg, or placebo IV every 12 weeks for up to 24 weeks (2 infusions). Headache episodes (migraine and non-migraine) and their characteristics were reported in daily electronic diaries during the 28-day baseline and throughout the 24-week treatment period.

Results: A total of 1072 patients were included in this post hoc analysis. Mean monthly headache days decreased by 8.9 (100 mg) and 9.7 (300 mg) compared to a 7.3 decrease in placebo over the first 4-week interval post initial dose and reductions were maintained throughout the 24-week treatment period. Mean monthly headache episodes also decreased by 8.4 (100 mg) and 9.0 (300 mg) compared to a decrease of 7.1 with placebo. The proportion of headache episodes that were migraine attacks decreased by 11.2% (100 mg), 12.4% (300 mg), and 3.9% (placebo), and among remaining headaches decreases in severe pain, nausea, phonophobia, photophobia, and physical activity limitations were numerically greater than placebo.

Conclusions: Patients with chronic migraine treated with eptinezumab decreased the monthly severity and frequency of headache days and episodes more than placebo. Beyond decreased headache frequency, patients treated with eptinezumab reported a reduction in the percent of remaining headache episodes that were migraine attacks, as well as a decrease in burdensome symptoms of headache episodes, indicating additional decreased headache severity after eptinezumab treatment.

Trial registration: ClinicalTrials.gov Identifier: NCT02974153; registered November 23, 2016.

Keywords

Eptinezumab, chronic migraine, migraine burden

Date received: 8 November 2021; revised: 15 February 2022; accepted: 5 March 2022

Introduction

Neurological disorders are one of the leading causes of disability-adjusted life years, contributing 276 million globally in 2016, with migraine one of the largest neurological contributors at 16.3% (1). Migraine, in general, is highly burdensome due to high prevalence, overall impact (i.e. reduced quality of life or disability), impact on work or school activities, family life, interictal burden, and disease costs (2). Chronic migraine (CM) is characterized by frequent headaches, with diagnosed patients experiencing 15 or more headache days each month, at least 8 of which satisfy the International Classification of Headache Disorders

criteria for migraine (3). Disability, comorbidity, and costs associated with CM are significantly greater in CM than those associated with episodic migraine

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(EM). In the longitudinal CaMEO survey (4,5), individuals with CM were 2–3 times more likely than those with EM to indicate that headaches interfered with their careers and/or finances, relationships, and care-taking responsibilities, and were significantly less likely to report very good or excellent overall health.

Migraine commonly presents as a moderate to severe headache that is unilateral and throbbing in nature, generally lasting between 4 and 72 hours, and is associated with nausea/vomiting and/or photophobia and phonophobia (3). In addition to these defining symptoms of migraine, patients may also experience sensory disturbances (aura), cognitive symptoms (fatigue, lethargy, difficulty concentrating), changes in mood (depression, anxiety, stress), and autonomic symptoms (excessive lacrimation, facial flushing, eye reddening) before, during, and/or after the headache pain phase of a migraine attack (6). Most, but not all, patients report these various symptoms during the premonitory phase (ranging from 14–88% of patients) (7), which adds significantly to the burden associated with migraine (7,8) and is associated with a considerable reduction in patient quality of life (9–11).

Eptinezumab is a calcitonin gene-related peptide (CGRP) antagonist approved for the preventive treatment of migraine, with infusions once every 12 weeks (12). In the PROMISE-2 clinical study, eptinezumab significantly reduced migraine frequency when administered to patients with CM, with a rapid onset of sustained preventive efficacy demonstrated in the 24 hours after dosing and with benefits of treatment maintained throughout the 6-month (2-dose) trial (13–15). Eptinezumab treatment was also associated with greater reductions in acute medication use and improvements in patient-reported outcome measures of daily functioning, including greater reduction in severe headache-related life impact (6-item Headache Impact Test [HIT-6]) and greater improvements in patient-identified most bothersome symptom (patient-identified MBS) and overall health (Patient Global Impression of Change) compared with placebo (14). This post hoc analysis of PROMISE-2 examined changes in the occurrence, severity, and symptoms associated with headache episodes in patients with CM following eptinezumab treatment.

Methods

The full methodology of PROMISE-2 has been previously published (13,14); the key elements are reviewed here. PROMISE-2 (NCT02974153) was a randomized, double-blind, placebo-controlled, parallel-group trial that evaluated the preventive efficacy, tolerability, and safety of eptinezumab in adults with CM (13,14). The independent ethics committee or institutional

review board for each study site approved the study. The study was conducted in accordance with the standards of Good Clinical Practice as defined by International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines, the principles of the Declaration of Helsinki, and all applicable national and local regulations. All patients provided written informed consent prior to participation in the trial. Chronic migraine was defined using Section 1.3 of the International Classification for Headache Disorders (ICHD) beta version (16). Eligible patients were randomized to receive eptinezumab 100 mg, 300 mg, or placebo IV every 12 weeks for up to 2 doses (24 weeks of treatment).

Patients completed a daily electronic diary (eDiary) from the time of screening through Week 24 that captured the incidence, categorization, characteristics, and/or severity of headache and acute headache medication use. Patients could record in their daily eDiary entry any headache episode that started that day or the day prior but were unable to record a headache episode that started before that time (i.e. recall was limited to 1 day). Missing eDiary data was balanced across treatment groups across the study; the baseline rate was 2.08% and 18.67% at month 6. Headache data were entered into the eDiary in the order they occurred, and, after the resolution of a headache, the patient answered questions about the headache that allowed it to be classified as a migraine or non-migraine headache.

Migraine is a subset of headache. Per ICHD guidelines, migraine attacks were defined by the following characteristics to separate them from non-migraine headache episodes: 1) lasted 4 hours or more; or from 30 minutes to 4 hours with the migraine being relieved by medication; 2) had at least 2 of the following symptoms: unilateral location, pulsating quality, moderate or severe pain intensity, or aggravation by or causing avoidance of routine physical activity; 3) had at least 1 of the following: nausea and/or vomiting, photophobia and phonophobia. In accordance with guidelines, the headache characteristics assessed were aura, nausea, vomiting, photophobia, phonophobia, pulsations, unilateral location, aggravated by or caused avoidance of physical activity, and moderate or severe pain. Headache severity was collected on a scale categorizing the pain as mild, moderate, or severe. A notable limitation in defining migraine days in randomized clinical trials (RCT) is the impact acute medication may have on reported migraine symptomatology.

Outcomes included the incidence of monthly headache days (MHDs) and monthly headache episodes—which include both migraine and headache events—and changes in the characteristics and classification of headache episodes before versus after

treatment. A headache episode or migraine attack was defined as a single continuous headache event, which lasted at least 30 minutes and could continue for more than 1 day, with migraine attack having specific features as detailed above. One headache episode or migraine attack may have resulted in multiple headache or migraine days, respectively. A headache day was defined as any study day during which the symptoms of headache were present.

The number of headache days per headache episode within a 4-week interval was used to determine the MHD and monthly headache episode frequency. The change from baseline was calculated as the difference in frequency between baseline and these headache counts within these 4-week intervals. The 12-week change from baseline was the difference in the frequency between baseline and the average of the included 4-week intervals. All outcomes in this post hoc analysis were summarized using descriptive statistics, such as means and percentages. For changes from baseline in MHDs and monthly headache episodes, an analysis of covariance model identical to the model used for the primary endpoint for this study was used to test for a difference between treatment arms. This model included the change from baseline measure as the response variable and included treatment and variables measuring the stratification factors concepts, baseline migraine days (continuous covariate), and prophylactic medication use (binary covariate: use versus no use) were the independent variables. All analyses were conducted with SAS software (SAS Institute, Inc, Cary, NC) version 9.2 or higher.

Results

Study population

A total of 1072 patients with CM (eptinezumab 100 mg, $n=356$; eptinezumab 300 mg, $n=350$; placebo, $n=366$) received treatment in PROMISE-2 and were

included in this analysis (Table 1). The mean age of study participants was 40.5 years; patients were predominantly white (91.0%) and female (88.2%).

Changes in headache occurrence

As reported during the screening period, mean MHDs at baseline were 20.4, 20.4, and 20.6 with eptinezumab 100 mg, 300 mg, and placebo, respectively, where 25.5–26.7% of baseline headache episodes were non-migraine. Over the entire study period (Weeks 1–24), mean MHDs decreased to 11.5 (eptinezumab 100 mg), 10.8 (eptinezumab 300 mg), and 13.3 (placebo), representing changes of -8.9 , -9.7 , and -7.3 days, respectively. These reductions in MHDs were evident during the first 4-week interval following the initial dose and were maintained throughout the 6-month study period (Figure 1). Mean reductions in MHDs in the patients treated with eptinezumab were greater than reductions in those receiving placebo for all 4-week intervals (Weeks 1–4: 100 mg: -2.0 days, 95% Confidence Intervals [CI]: -3.0 , -1.1 ; 300 mg: -2.8 days; CI: -3.9 , -1.9 ; Weeks 5–8: 100 mg: -2.0 days, CI: -3.0 , -1.0 ; 300 mg: -2.3 days, CI: -3.4 , -1.2 ; Weeks 9–12: 100 mg: -1.8 days, CI: -2.9 , -0.8 ; 300 mg: -2.3 , CI: -3.4 , -1.2 ; Weeks 13–16: 100 mg: -2.5 days, CI: -3.7 , -1.4 ; 300 mg: -3.3 days, CI: -4.4 , -2.1 ; Weeks 17–20: 100 mg: -1.5 days, CI: -2.6 , -0.4 ; 300 mg: -2.5 days, CI: -3.6 , -1.4 ; Weeks 21–24: 100 mg: -1.0 days, CI: -2.1 , 0.18 ; 300 mg: -2.0 days, CI: -3.1 , -0.8), with most treatment differences significant ($P < 0.05$).

Mean monthly headache episodes, at baseline were 16.7, 16.8, and 16.2 with eptinezumab 100 mg, 300 mg, and placebo, respectively. Over Weeks 1–24, mean monthly headache episodes decreased to 8.2 (eptinezumab 100 mg), 7.7 (eptinezumab 300 mg), and 9.0 (placebo), representing changes of -8.4 , -9.0 , and -7.1 episodes, respectively. Reductions in the eptinezumab treatment groups were greater than the reductions in the placebo group for all 4-week intervals (Figure 2)

Table 1. Demographics and baseline clinical characteristics.

	Eptinezumab 100 mg ($n = 356$)	Eptinezumab 300 mg ($n = 350$)	Placebo ($n = 366$)
Mean (SD) age, y	41.0 (11.7)	41.0 (10.4)	39.6 (11.3)
Sex, % female	86.2	89.7	88.8
Race, %			
White	93.3	92.0	87.7
Black or African American	5.9	6.6	10.4
Asian	<1	<1	<1
Other	<1	1.1	1.4
Mean (SD) headache days	20.4 (3.1)	20.4 (3.2)	20.6 (3.0)
Mean (SD) headache episodes	16.7 (6.3)	16.8 (6.1)	16.2 (5.9)

SD, standard deviation.

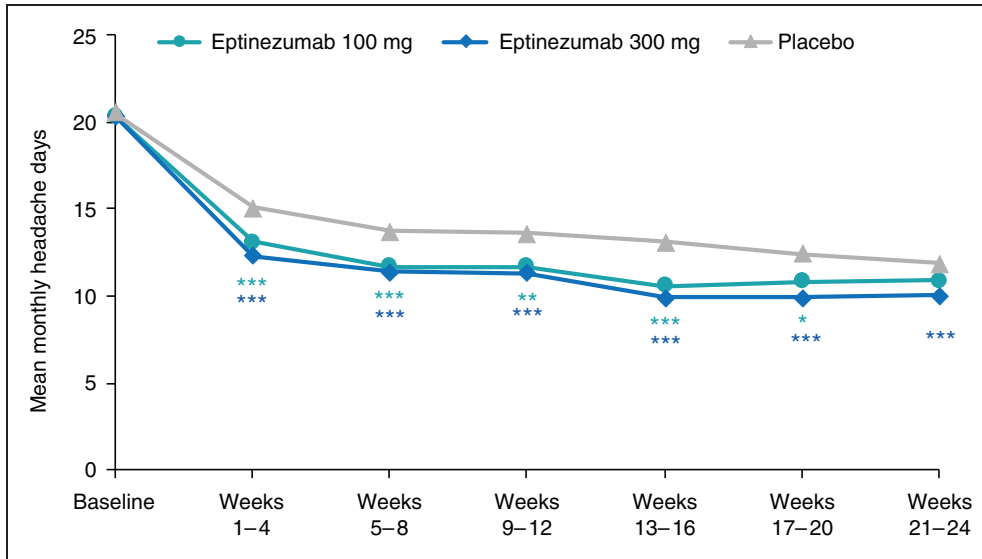


Figure 1. Mean monthly headache days (MHDs), by 4-week interval. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs placebo (color-coded by dose).

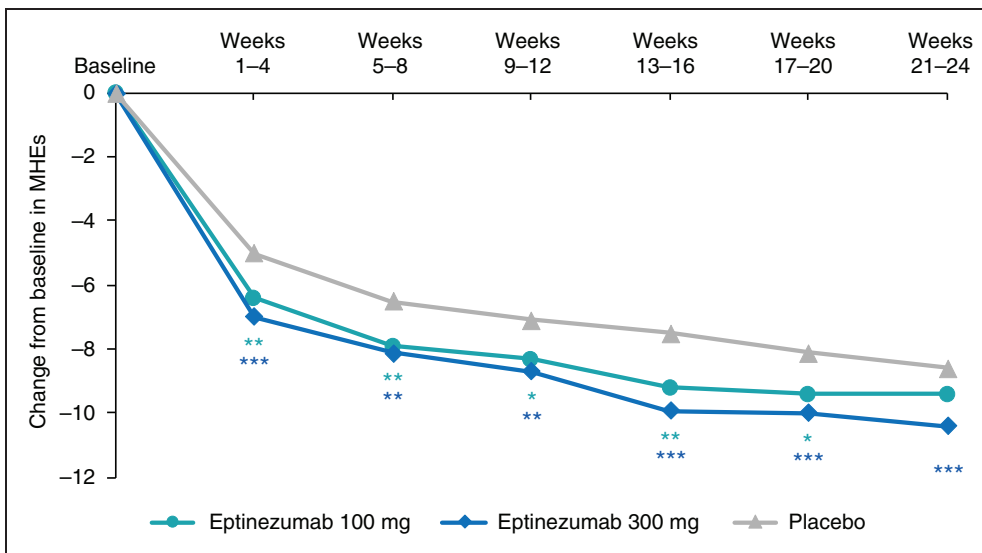


Figure 2. Mean change from baseline in monthly headache episodes (MHEs), by 4-week interval. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs placebo (color-coded by dose).

($P < 0.05$), except between the eptinezumab 100 mg and placebo groups for Weeks 21–24.

Changes in headache characteristics

At baseline, patients reported that 73.3–74.5% of baseline headache episodes were migraine rather than non-migraine headache episodes, 36.3–38.5% included severe pain, 58.1–61.0% included nausea, 73.5–75.0% included phonophobia, and 76.7–78.1% included photophobia (Figure 3A). Across Weeks 1–24, the percentage of headache episodes that were migraine decreased

to 63.3% (eptinezumab 100 mg; change, –11.2%), 61.4% (eptinezumab 300 mg; change, –12.4%), and 69.4% (placebo; change, –3.9%) on average. Numerically greater decreases from baseline in the mean percent of headache episodes with severe pain, nausea, phonophobia, photophobia, and physical activity limitations were also noted for patients treated with eptinezumab compared to patients who received placebo (Figure 3B). Most patients continued to use acute medications when they had headaches, with the percentage of episodes during which acute headache medications were used declining by 0.3% with

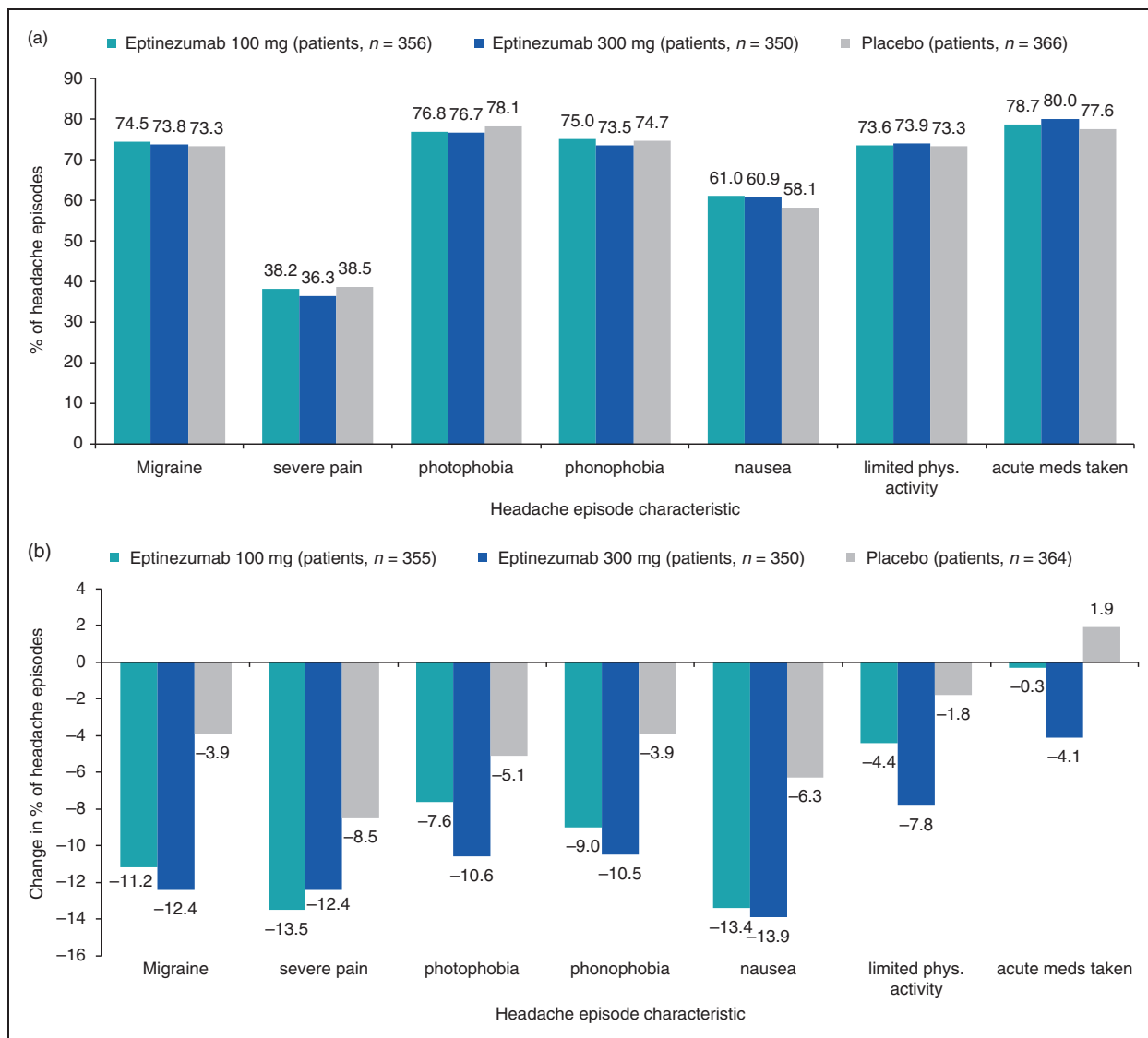


Figure 3. Average headache episode characteristics of patients in PROMISE-2: (a) at baseline and (b) mean change from baseline over Weeks 1–24.

eptinezumab 100 mg and 4.1% with eptinezumab 300 mg and increasing by 1.9% with placebo.

Discussion

This post hoc analysis in the changes of the occurrence, severity, and symptoms of headache episodes in patients with CM treated with eptinezumab or placebo in the PROMISE-2 study suggests that eptinezumab not only robustly reduces migraine and headache frequency in a sustained way, but the remaining headache episodes showed lower severity and burdensome features (i.e. severe pain, photophobia, phonophobia, nausea, and limited physical activity). This suggests that eptinezumab, beyond reduction in the frequency, also reduces headache severity. This is in line with

findings from the RELIEF study, in which patients eligible for preventive migraine treatment were treated with eptinezumab during a migraine attack. There, patients reported shorter time to headache pain freedom, pain relief, and absence of most bothersome symptom (of nausea/vomiting, photophobia, and phonophobia) compared with those receiving placebo (17). Reductions in headache pain and other associated symptoms should reduce the impact of headaches on daily life, and likely was related to the 47.2% reduction in the percentage of patients reporting severe impact (HIT-6 total score ≥ 60) following 2 doses of eptinezumab in PROMISE-2 (14). In addition, 59.6% of patients in PROMISE-2 treated with eptinezumab reported an improvement in their patient-identified MBS (which included symptoms beyond migraine

diagnostic symptoms of nausea, photophobia, and phonophobia) at week 24, compared to 39.3% of patients reporting improvement in placebo (14,18). Similarly, 61.5% of patients treated with eptinezumab reported an improvement in their Patient Global Impression of Change scores, which measured patient-perceived improvements in disease status, compared to 40.9% of patients for placebo (14). Finally, in the follow-up, long-term PREVAIL study of eptinezumab in patients with chronic migraine, impact on Migraine Disability Assessment scores, which quantified migraine-related disability in patients' daily lives, indicated that the majority of patients (~60%) reported little or no disability or mild disability from week 12 to week 104 of assessment (19).

These findings, which focused on the overall burden of headache, are consistent with previously published post hoc analyses of other anti-CGRP monoclonal antibodies (fremanezumab and galcanezumab) that narrowly focus on migraine alone. In previous analyses, observed benefits among patients with CM included reductions in the severity of remaining migraine headache days (fremanezumab, over 3 months; galcanezumab, beginning at month 1), the number of remaining migraine headache days with nausea/vomiting (galcanezumab), and total pain burden (galcanezumab, severity-weighted duration beginning at month 1) (20–22).

Although overall acute headache medication use declined with eptinezumab therapy in PROMISE-2—likely due to reduced migraine and headache frequency—the results of the current analysis indicate that the

majority of patients continued to use acute headache medications when headaches occurred. Changes in acute medication type, dose level, and duration were not examined further, and our analysis did not account for headache occurring over multiple days. One area for future research is the evaluation of changes in the efficacy of acute medication when used concomitantly with eptinezumab. Because acute headache medication use is not without potential complications (e.g. side effects, overuse) (23), this is an area deserving of further investigation. In addition, this was a post hoc analysis; thus, additional prospectively designed trials will be needed to confirm these findings. Because certain patient populations were excluded, such as patients with BMI ≥ 39 kg/m² at screening or with cardiovascular, neurologic, or hypertensive disorders that may present in a clinic setting, the ability to generalize these results to all adults with chronic migraine is limited. In future studies, it may be useful to identify which migraine and headache symptoms have the most impact on daily life.

Conclusions

Chronic migraine patients treated with eptinezumab decreased the monthly frequency of headache days and episodes more than placebo. In addition, patients treated with eptinezumab reported a reduction in the percent of remaining headache episodes that were migraine attacks, as well as a decrease in the severity and burdensome symptoms of headache episodes across the 24-week treatment period.

Key findings

- Patients with chronic migraine in the PROMISE-2 study treated with 100 mg or 300 mg of eptinezumab reported decreased monthly severity and frequency of headache days and episodes compared with placebo.
- Patients treated with eptinezumab reduced the percentage of headache episodes reported as migraine attacks and reported a decrease in burdensome symptoms of headache episodes across the 24-week treatment period.

Abbreviations

CGRP: calcitonin gene-related peptide; CM: chronic migraine; EM: episodic migraine; HIT-6: 6-item Headache Impact Test; ICHD: International Classification for Headache Disorders; IV: intravenously; MBS: most bothersome symptom; MHDs: monthly headache days; MHEs: monthly headache episodes.

Author contributions

JH was responsible for the statistical analysis. All authors had a major role in the acquisition, analysis or interpretation

of data; reviewed and provided critical revision of all manuscript drafts for important intellectual content; and read and approved the final manuscript for submission.

Acknowledgements

Assistance with manuscript preparation was provided by Mary Tom, PharmD, and Nicole Coolbaugh, CMPP, of The Medicine Group, LLC (New Hope, PA, USA) for providing medical writing support, which was funded by H Lundbeck A/S (Copenhagen, Denmark) in accordance with Good Publication Practice guidelines.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article:

PM has received personal fees and research support from AbbVie, Amgen/Novartis, Biohaven, Eli Lilly, Lundbeck, and Teva; consulting fees from Aeon; Speakers Bureau fees from AbbVie, Biohaven, Eli Lilly, Lundbeck, and Teva; and has received stock or an ownership interest from Precept.

DK has received personal compensation for serving on a Scientific Advisory or Data Safety Monitoring board for Amgen, Biohaven, Eli Lilly, Lundbeck, and Novartis; and Speakers Bureau fees from Allergan, Amgen, Biohaven, Eli Lilly, Lundbeck, and Teva.

RC was an employee of Lundbeck or one of its subsidiary companies at the time of study and manuscript development.

AE is an employee of H Lundbeck A/S.

JH is an employee of Pacific Northwest Statistical Consulting, Inc., and a contracted service provider of biostatistical resources for H Lundbeck A/S.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The clinical trial was funded by Lundbeck Seattle BioPharmaceuticals, Inc., Bothell, WA, USA. The publication was supported by H Lundbeck A/S, Copenhagen, Denmark.

Data availability

In accordance with EFPIA's and PhRMA's Principles for Responsible Clinical Trial Data Sharing guidelines, Lundbeck is committed to responsible sharing of clinical trial data in a manner that is consistent with safeguarding the privacy of patients, respecting the integrity of national regulatory systems, and protecting the intellectual property of the sponsor. The protection of intellectual property ensures continued research and innovation in the pharmaceutical industry. Deidentified data are available to those whose request has been reviewed and approved through an application submitted to <https://www.lundbeck.com/global/our-science/clinical-data-sharing>

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