Preventive migraine treatment with eptinezumab reduced acute headache medication and headache frequency to below diagnostic thresholds in patients with chronic migraine and medication-overuse headache

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Abstract
Objective: This post hoc analysis in patients medically diagnosed with chronic migraine (CM) and medication-overuse headache (MOH) evaluated reductions in the use of acute headache medication (AHM) and sustained changes in the diagnostic status of CM and MOH following eptinezumab treatment in the PROMISE-2 study.

Background: Eptinezumab, a monoclonal antibody that inhibits calcitonin gene-related peptide, is approved in the United States for the preventive treatment of migraine. A previous analysis showed that eptinezumab reduced monthly migraine days and was well tolerated in the subgroup of PROMISE-2 patients diagnosed with both CM and MOH.

Methods: The phase 3, double-blind, placebo-controlled PROMISE-2 study (NCT02974153) randomized adults with CM to eptinezumab 100 mg, 300 mg, or placebo (administered intravenously every 12 weeks for up to two doses). MOH was prospectively diagnosed at screening by trained physicians based on 3 months of medication history and International Classification of Headache Disorders-3β criteria. This post hoc analysis evaluated changes in total and class-specific days of AHM usage, the percentage of patients using AHM at or above MOH diagnostic thresholds, and the percentage of patients experiencing monthly headache and migraine day frequency below diagnostic thresholds for MOH and/or CM.

Results: In PROMISE-2, 431/1072 (40.2%) patients with CM were diagnosed with MOH (eptinezumab 100 mg, n = 139; 300 mg, n = 147; placebo, n = 145) and were included in this analysis. Total monthly AHM use decreased from 20.6 days/month at baseline to 10.6 days/month over 24 weeks of treatment (49% decrease) with eptinezumab 100 mg, from 20.7 to 10.5 days/month (49% decrease) with eptinezumab 300 mg, and from 20.7 to 10.9 days/month (49% decrease) with placebo.
INTRODUCTION

Medication-overuse headache (MOH) is a secondary headache disorder associated with excessive acute use of analgesics or other drugs used to treat migraine. The International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria for a diagnosis of MOH is ≥15 headache days/month in a patient with a preexisting headache disorder, with >3 months of regular overuse of ≥1 drug that can be taken for acute and/or symptomatic treatment of headache or ≥15 days/month for nonopioid (simple) analgesics, or ≥10 days/month for triptans, ergots, opioids, and/or combination analgesics, as well as combinations of different classes of headache medications. The resolution of MOH is typically regarded as reduction of acute medication below the levels defined by ICHD-3 thresholds for three consecutive months.

MOH occurs in 0.5%–7.2% of the total population (median estimate of 1%–2%), depending on the country and age range of the subjects in the various settings evaluated. MOH most commonly affects women, with a peak incidence in those who are 50–60 years of age. The disorder may lead to considerable disability, medical and societal costs, as well as often making headache refractory to treatment. MOH is considered by many to be the most costly headache disorder.

Frequent medication use and increased headache frequency are common events among patients who experience migraine. Clinic-based studies have shown an association between the frequent use of analgesics and the development of MOH. Although not all patients who overuse acute headache medications (AHMs) will transform from episodic migraine to chronic migraine (CM) with MOH, an important goal of treatment is to prevent this transition. It is, however, not clear whether the frequent intake of medication leads to MOH or whether patients with more frequent headaches take more medications. Furthermore, it is not clear whether patients who develop MOH have a genetic predisposition and hypersensitivity to pain stimuli that may indicate increased risk. In addition, overuse of most acute medications, such as triptans, combination analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and others may increase the risk of MOH. MRI studies of the brain structure of patients with MOH reveal evidence of structural and functional changes in the areas of the brain associated with pain and addiction. Those abnormalities associated with pain appear to return to normal after MOH is resolved, but the areas associated with addiction may still be abnormal. An unmet need clearly exists to prevent MOH from developing, which may be achieved by using new treatments with high levels of sustained efficacy, high tolerability, and delivery methods that improve patient adherence to treatment.

Eptinezumab is a humanized IgG1 monoclonal antibody that selectively binds to and durably inhibits the calcitonin gene-related peptide (CGRP) ligand with high affinity. Eptinezumab is approved in the United States for the preventive treatment of migraine in adults. In pivotal phase 3 studies, eptinezumab 100 and 300 mg met the primary efficacy endpoint by significantly reducing mean monthly migraine days over Weeks 1–12, compared with placebo, in patients with episodic migraine (PROMISE-1) and CM (PROMISE-2). On average, the percentage of patients experiencing a migraine on the day following infusion was reduced by >50% in both studies and for both the 100 and 300 mg doses in both episodic migraine and CM, which was sustained across the 12-week treatment period. Those receiving eptinezumab treatment were more likely to achieve ≥75% migraine response during Weeks 1–4 and Weeks 1–12 than were patients receiving placebo. A population pharmacokinetic analysis using data from eight trials of eptinezumab found that patient characteristics (including demographics and disease state) had no clinically significant effects on pharmacokinetic parameters, concluding that no dose adjustments were needed.
METHODS

Study overview, design, and patients

The detailed methodology for PROMISE-2 (NCT02974153) has been published previously. Briefly, PROMISE-2 was a randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of eptinezumab for migraine prevention in adults with CM. Written informed consent was obtained from all participants prior to study initiation; consent forms used at each site were approved by the Independent Ethics Committee/Institutional Review Board for each study site in accordance with local legal requirements. Enrolled patients were treated with eptinezumab 100 mg, 300 mg, or placebo every 12 weeks for up to two doses. The subgroup of patients with CM in these analyses included those who were diagnosed at the screening visit as having MOH and to assess whether eptinezumab treatment sustained changes in the diagnostic status of CM and MOH as identified at screening in the PROMISE-2 study.

Thus, no patients had MOH based exclusively on either of these drug classes. Active treatment for MOH (e.g., behavioral or psychological interventions, or pharmacological treatment other than the study drugs) was not a part of the PROMISE-2 study protocol.

Outcomes

Analyses in the MOH subgroup included the change in monthly AHM days, in total and by class (triptan, ergotamine, simple analgesics, combination analgesics [combination of drugs of different classes acting as analgesics or adjuvants], and opioids); the percentage of patients using AHM at or above MOH diagnostic thresholds, as well as the number of study months (4-week intervals) patients used AHM below MOH diagnostic thresholds; the percentage of patients experiencing a monthly headache and migraine day frequency below diagnostic thresholds for CM, as well as the number of study months patients reported migraine frequency below CM diagnostic thresholds; and the percentage of patients reporting AHM use and headache/migraine day frequency that were below both CM and MOH diagnostic thresholds, including the number of successive study months for which this was achieved.

MOH diagnostic thresholds were defined by ICHD-3β criteria (Table S1), which is ≥10 days/month of triptans, ergots, opioids, and/or combination analgesics and/or ≥15 days/month of simple analgesics. For analysis of patients diagnosed with MOH, days of acute medication use were counted separately for each class. Within the ≥10 days/month group, if multiple drug classes were taken on a single day, the count was reported as a multiple of days. Thus, if 5 days of sumatriptan and 5 days of combination analgesics were taken per month, this would be counted as 10 days, and the diagnosis would be MOH. Simple analgesics were analyzed separately from other acute medications and used a 15 days/month cutoff. The CM diagnostic threshold was defined as ≥15 headache days/month, including ≥8 migraine days/month per ICHD-3 criteria. Additionally, if a migraine resolved in less than 4 hours because of triptan use, the classification of a “migraine day” is still applied.

Statistical analyses

Daily AHM use was captured in a daily eDiary, as were headache and migraine days. Use of AHM was captured each day regardless of whether a patient had a headache on that day. Descriptive statistics (including mean, standard deviation, and percentage) were used to report data. Analyses were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

AHM use was analyzed over time for the full MOH population. For analyses of specific drug classes, the patient population was limited to those who reported any use of the specific drug class during the baseline period. For analyses across dosing intervals (12 weeks), two methods were used to determine if a patient met diagnostic thresholds for MOH or CM; these comprised the average over the
Missing data imputation was used for the endpoints related to headache and migraine days, as described in the primary report of PROMISE-2. Briefly, the rate of headache and migraine was assumed to be the same on days when the diary was not completed as on days when it was completed. In cases where patients provided limited eDiary data in a given month (i.e., <21 days), the assumed migraine/headache rate was a weighted function of the data from the current month and prior month where the weight was a function of how much data were missing in the current month. As missing data were always imputed, results for headache and migraine endpoints were available for all patients at all time points.

Similar logic was used for the medication endpoints (i.e., medication usage rates days were assumed to be the same on days without data as those with data). However, in this case, if the eDiary was completed for ≥50% of days in the study month, any days the patient failed to complete the diary were assumed to be the same as the previous reported days, but if a patient failed to report medication data for ≥50% of days in a study month, the data were not imputed and were classified as missing.

RESULTS

Acute headache medication use at baseline in patients with MOH

Of 1072 patients with CM treated in the PROMISE-2 trial, 431 (40.2%) had a diagnosis of MOH at screening, as determined by the study investigator, including 139 patients who received eptinezumab 100 mg, 147 who received eptinezumab 300 mg, and 145 who received placebo. Of these, 135, 144, and 142 patients, respectively, provided sufficient data to allow baseline medication use to be determined. The demographics and disposition of the patients in the MOH analyses are shown in Table 1. The MOH subgroup was primarily female (87.2%; 376/431) and white (93.5%; 403/431).

Mean (standard deviation) baseline acute medication days were similar for the eptinezumab 100 mg, 300 mg, and placebo groups: 16.4 (6.5), 16.7 (5.9), and 16.1 (6.7), respectively (Table 1). In the respective treatment groups of eptinezumab 100 mg, 300 mg, and placebo, 18.7% (26/139), 12.9% (19/147), and 20.7% (30/145) of patients were overusing simple analgesics at baseline and 59.7% (83/139), 71.4% (105/147), and 60.7% (88/145) were overusing triptans, ergots, opioids, and/or combination analgesics. The overuse of both categories at baseline was reported in 7.9% (11/139; 100 mg), 7.5% (11/147; 300 mg), and 9.7% (14/145; placebo) of patients.

Acute headache medication use by patients with MOH after treatment

Prophylactic and acute concomitant headache medication use during the study is shown in Table 2 for those diagnosed with MOH at baseline. In patients with MOH, eptinezumab treatment resulted in numerically larger reductions compared with placebo in mean days of total AHM use over Weeks 1–12, and these reductions were sustained over Weeks 13–24 (Figure 1). Total monthly AHM use decreased from 20.6 days/month (100 mg) and 20.7 days/month (300 mg) at baseline in the eptinezumab groups to 10.6 and 10.5 days/month, respectively, over Weeks 13–24 (both decreases of 49%); in the placebo group, total monthly AHM use decreased from 19.8 to 14.0 days/month (a decrease of 29%).

Across all drug classes, there were numerically larger decreases in monthly use with eptinezumab, compared with placebo, over 24 weeks of treatment; decreases were observed as early as Weeks 1–4 and were maintained or improved over the subsequent monthly periods. At baseline, for patients using triptans, usage rates were generally high, at 13.2 days/month for those in the eptinezumab 100 mg group (n = 92), 11.8 days/month for eptinezumab 300 mg (n = 112), and 11.5 days/month (n = 105) for those in the placebo group.
group. By Week 24, the triptan usage among these patients dropped to 6.3 days/month (a decrease of 6.9 days/month), 5.1 days/month (a decrease of 6.7 days), and 7.0 days/month (a decrease of 4.5 days) for eptinezumab 100 mg (n = 78), eptinezumab 300 mg (n = 96), and placebo (n = 85), respectively (Figure 2A). For patients who reported use of simple analgesics at baseline, usage was 10.2 days/month for those in the eptinezumab 100 mg group (n = 101), 9.3 days/month for eptinezumab 300 mg (n = 95), and 11.1 days/month (n = 98) for those in the placebo group. By Week 24, simple analgesic usage dropped to 5.3, 5.9, and 7.4 days/month for eptinezumab 100 mg (n = 80), eptinezumab 300 mg (n = 80), and placebo (n = 78), respectively (Figure 2B). The use of combination analgesics at baseline was 7.8 days/month for those in the eptinezumab 100 mg group (n = 64), 8.7 days/month for eptinezumab 300 mg (n = 79), and 7.5 days/month (n = 63) for those in the placebo group. By Week 24, combination analgesic usage dropped to 4.3, 3.2, and 4.7 days/month for eptinezumab 100 mg (n = 51), eptinezumab 300 mg (n = 64), and placebo (n = 50), respectively (Figure 2C).

Consistency of response and diagnostic resolution after treatment

The decreases in acute medication usage observed during the study resulted in patients no longer meeting the monthly MOH medication threshold based on ICHD-3β criteria. Across the study, the

### TABLE 2 Preventive and acute medication use in patients with medication-overuse headache

|                      | Eptinezumab 100 mg n = 139 | Eptinezumab 300 mg n = 147 | Placebo n = 145 | Total N = 431 |
|----------------------|-----------------------------|-----------------------------|-----------------|---------------|
| **Preventive medication** |                             |                             |                 |               |
| Prior use            | 139 (100%)                  | 147 (100%)                  | 143 (98.6%)     | 429 (99.5%)   |
| Concomitant use      | 68 (48.9%)                  | 80 (54.4%)                  | 80 (55.2%)      | 228 (52.9%)   |
| **Acute medication** |                             |                             |                 |               |
| Triptan/ergot        | 103 (74.1%)                 | 114 (77.6%)                 | 111 (76.6%)     | 328 (76.1%)   |
| Opioid<sup>b</sup>   | 13 (9.4%)                   | 15 (10.2%)                  | 16 (11.0%)      | 44 (10.2%)    |
| Butalbital<sup>b</sup> | 6 (4.3%)                    | 6 (4.1%)                    | 3 (2.1%)        | 15 (3.5%)    |
| Combination nonopiod analgesic | 36 (25.9%) | 45 (30.6%) | 41 (28.3%) | 122 (28.3%) |
| Simple analgesic     | 35 (25.2%)                  | 37 (25.2%)                  | 34 (23.4%)      | 106 (24.6%)   |
| NSAID                | 83 (59.7%)                  | 88 (59.9%)                  | 84 (57.9%)      | 255 (59.2%)   |
| Other                | 2 (1.4%)                    | 1 (0.7%)                    | 1 (0.7%)        | 4 (0.9%)      |

Abbreviation: NSAID, nonspecific anti-inflammatory drug.

<sup>a</sup>Patients (n [%]) with ≥1 use of medication during the study over Weeks 1–32.

<sup>b</sup>Intake of four or fewer days per month per protocol.
percentage of patients with MOH overusing medication was generally consistent during eptinezumab treatment, with numerically fewer patients treated with eptinezumab (25.6%–37.3%) using acute medication at or above MOH monthly thresholds than patients who received placebo (36.3%–50.7%) across all time points (Figure 3). The percentage of patients experiencing headache and migraine day frequency below CM thresholds during Weeks 1–4 was 46.8% (100 mg, 65/139) and 47.6% (300 mg, 70/147) for patients treated with eptinezumab and 29.0% (42/145) for patients who received placebo (Figure 4). More than 50% of patients treated with eptinezumab remained below the CM threshold across each study month following Weeks 1–4; the percentage of patients below the CM threshold was numerically larger in the eptinezumab treatment groups compared with placebo at each time point.

When the rates of freedom from both CM and MOH combined were analyzed over Weeks 1–12, 26.6%–29.3% of patients treated with eptinezumab were free of CM and MOH for each of the three study months as well as 8.3% of patients who received placebo (Figure 5). The proportions of patients remaining free of both CM and MOH further increased (33.8%–34.0%) over Weeks 13–24.

**FIGURE 2** Mean days/month of acute headache medication use by class, in patients with any of that class during baseline. (A) *Triptan use*. Analysis includes patients who reported ≥1 day of triptan use during the 28-day screening period. Sample sizes at baseline: eptinezumab 100 mg, n = 92; eptinezumab 300 mg, n = 112; placebo, n = 105. (B) *Simple analgesic use*. Analysis includes patients who reported ≥1 day of simple analgesic use during the 28-day screening period. Sample sizes at baseline: eptinezumab 100 mg, n = 101; eptinezumab 300 mg, n = 95; placebo, n = 98. (C) *Combination analgesic use*. Analysis includes patients who reported ≥1 day of combination analgesic use during the 28-day screening period. Sample sizes at baseline: eptinezumab 100 mg, n = 64; eptinezumab 300 mg, n = 79; placebo, n = 63. SE, standard error [Color figure can be viewed at wileyonlinelibrary.com]
across eptinezumab treatment arms. Of patients with available data across the entire treatment period, 29.0% (58/200) of patients treated with eptinezumab (100 mg, 27/93; 300 mg, 31/107) never reached diagnostic thresholds for either CM or MOH during Weeks 1–24, as well as 6.3% (6/96) of patients who received placebo.

Safety

Full details of the safety outcomes in PROMISE-2 have been reported.\textsuperscript{15} No differences in treatment-emergent adverse events were seen between the MOH subgroup in these analyses and the overall PROMISE-2 study population.

FIGURE 3 Rates of medication overuse in patients with chronic migraine and medication-overuse headache (MOH), by study month. Medication overuse was defined by MOH thresholds in the ICHD-3β criteria (including section 8.2.6). Classes of medication included triptan, ergot, opioid, simple analgesic, and combination analgesic, and were counted separately for days of use; simple analgesics were counted separately as ≥15 days/month [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 4 Patients experiencing below chronic migraine (CM) thresholds by study month. CM diagnostic thresholds were defined as ≥15 headache days/month and ≥8 migraine days/month per ICHD-3β criteria [Color figure can be viewed at wileyonlinelibrary.com]

DISCUSSION

Reducing AHM use and its associated burden of overuse is an important goal for patients with CM and MOH. In addition to the risk of developing MOH, the various AHM drug classes have also been associated with sometimes serious adverse events, including gastrointestinal bleeding, cardiovascular risk, and renal or hepatic toxicity,\textsuperscript{19,20} adding complexity to migraine management and increasing the overall burden of this condition. The historical approach to treating MOH has been to request patients to discontinue or wean the use of acute medications, potentially leading to unpleasant symptoms or withdrawal depending on the drug class.\textsuperscript{21} This series of post hoc analyses was conducted to evaluate the impact of migraine
prevention with eptinezumab compared with placebo on AHM use and overuse and its potential for resolving CM and MOH diagnoses in the subgroup of PROMISE-2 patients with a dual diagnosis of CM and MOH at baseline. These analyses showed that fewer patients treated with eptinezumab used acute medication at levels that support an MOH diagnosis than patients who received placebo across all study time points, from Weeks 1–4 and continuing through Weeks 21–24. Eptinezumab treatment was also associated with a large reduction in the percentage of patients overusing AHM, as well as a numerically greater percentage of patients transitioning from CM to episodic migraine compared with placebo. In total, 50.5% of those patients treated with eptinezumab 100 mg and 49.5% of those treated with eptinezumab 300 mg were consistently below MOH diagnostic thresholds for AHM use for the entirety of the 24-week treatment period compared with 27.1% of patients who received placebo. More than one-fourth (29.0%) of patients treated with eptinezumab and 6.3% of patients who received placebo demonstrated resolution of both diagnoses, experiencing 24 weeks without overusing AHM per MOH diagnostic thresholds and without experiencing CM diagnostic thresholds for headache and migraine days. These post hoc analyses provide initial evidence that eptinezumab could be an effective treatment for patients with CM and MOH, providing early and sustained reduction in AHM use in addition to the reduction in migraine frequency.

Reduction of AHM use in patients with CM and MOH has previously been analyzed in secondary and post hoc analyses with onabotulinumtoxinA (medication overuse only),22–26 erenumab (a monoclonal antibody against the CGRP receptor),27,28 and fremanezumab (a monoclonal antibody against CGRP).29; these analyses did not include double-blind, placebo-controlled trials, and/or did not diagnose patients with MOH formally or monitor the consistency of response for individuals with MOH over time. In a 3-year study, patients with MOH treated with onabotulinumtoxinA showed sustained improvements in migraine symptoms; however, it was not a placebo-controlled trial, and given that continued patient participation was likely linked to onabotulinumtoxinA efficacy, the results are more difficult to evaluate.27 Two placebo-controlled studies of erenumab27,28 and one of fremanezumab29 included patients with medication overuse, but the ICHD diagnostic criteria were not formally applied for MOH; in these analyses of patients with acute medication overuse, no efforts were made to assess the sustained response over the entire study period.27,28

Although the extent to which medication overuse contributes to migraine progression is often difficult to determine,30 education can effectively treat MOH in a proportion of patients and is often used as adjuvant treatment. When education is used alone, rates of MOH remission over 60% have been reported in some studies.31,32 In the PROMISE-2 clinical trial, investigators avoided advising or educating patients about MOH to avoid a placebo response. Geographic differences in healthcare systems, variations in AHM prescribing, referral pathways, and access to headache specialists also add to the complexity of managing MOH, and may impact patient outcomes.3,33 Furthermore, patients who overuse centrally acting analgesics, such as codeine preparations or opioids, commonly display the characteristics of substance dependence,34 which makes successful reduction or withdrawal of AHM less likely.

Within the ongoing debate around actively treating MOH, validation of any strategy in controlled clinical trials has been lacking.1,35 and the paucity and inconsistency of available data has resulted in the deployment of numerous management techniques. Some clinicians recommend medication weaning in combination with patient education as the first step,21,36 whereas others

**FIGURE 5** Percentage of patients who did not experience chronic migraine (CM) nor medication-overuse headache (MOH) thresholds for an entire dosing interval. Subgroup includes patients with MOH who reported headache and migraine days below CM thresholds, as well as acute medication use below MOH thresholds, for each individual study month within the respective dosing interval. Medication overuse was defined by MOH thresholds in the ICHD-3β criteria (including section 8.2.6). Classes of medication included triptan, ergot, opioid, simple analgesic, and combination analgesic, and were counted separately for days of use; simple analgesics were counted separately as ≥15 days/month. CM diagnostic thresholds were defined as ≥15 headache days/month and ≥8 migraine days/month per ICHD-3β criteria [Color figure can be viewed at wileyonlinelibrary.com]
recommend starting migraine-preventive treatment along with education, and then gradual detoxification. A third strategy is to treat MOH aggressively with migraine prevention, the acute use of short-term acute treatment such as antiemetics or corticosteroids, and patient education. The key arguments for weaning prior to initiating migraine prevention is that (1) oral preventives may cause significant adverse events such as sedation or cognitive slowing, which could exacerbate withdrawal symptoms; and (2) oral preventives are typically titrated over a period of several weeks. The rapid onset of efficacy of eptinezumab (as early as Day 1) and its 12-week dosing interval, with no known central nervous system adverse events, make eptinezumab a promising option for treating patients with MOH. The data raise the possibility of a change in the MOH treatment paradigm, that of engaging in the beginning with an anti-CGRP ligand monoclonal antibody such as eptinezumab and allowing the use of AHMs to decline over months and then re-evaluating, before further intervention.

Limitations

Limitations of this analysis include those inherent in the nature of post hoc and exploratory analyses; all analyses herein were descriptive to reflect this limitation. Another factor to be considered when making inferences from these study data was that although thresholds for MOH were defined similarly in the ICHD-3β (2013) and ICHD-3 (2018) criteria for MOH, there were some changes in drug definitions between the two sets of criteria (Table S1). In ICHD-3 (2018), simple analgesics were put in a category called nonopioid drugs, and in section 8.2.6 simple/nonopioid are among the list limited at ≥10 days/month instead of the ≥15 threshold; this change would have resulted in an increase in the number of patients in PROMISE-2 diagnosed with MOH. Although this list does not include combination analgesics, it is not expected that the results would significantly change should the data have been analyzed using the ≥10 days/month threshold for simple analgesics. Lastly, opioid and barbiturate use was limited to ≤4 days/month during the screening and treatment periods of PROMISE-2: therefore, patients with opioid-overuse headache were excluded, making the results less generalizable to individuals with migraine who use opioids or barbiturate-containing combination analgesics regularly.

This post hoc analysis showed a large placebo response, which is quite often observed in migraine treatment studies; however, the placebo effect was less pronounced in patients with MOH in this analysis compared with the overall PROMISE-2 population (difference from placebo in change from baseline in monthly migraine days: −3 days in the MOH subgroup vs. −2−2.5 in PROMISE-2). Furthermore, eptinezumab efficacy after subtracting the placebo value was >3 days, and the same response was observed for both the 100 and 300 mg doses.

Another limitation is that patients who used opioids for more than 4 days per month were excluded, because of their potential for higher rates of adverse events and poor outcomes. As a result, a class of patients with MOH that can be found in the general population were omitted from this evaluation; however, another post hoc analysis of PROMISE-2 showed no change in the primary efficacy endpoint in patients who had no barbiturate or opioid use at any time during the study compared with those who did. Opioid or barbiturate use, as well as the presence of significant mood or personality disorders, complicates the management of migraine with MOH and may warrant a different treatment strategy. Finally, an integrated treatment plan for these patients was not provided, which could affect outcomes in a clinical setting.

Conclusions

In patients with CM diagnosed with MOH, preventive migraine treatment with eptinezumab, with either 100 or 300 mg doses, provided meaningful reductions from baseline in AHM use. Reductions were observed during the first 4 weeks and were sustained over 24 weeks of treatment. A sustained resolution of both CM and MOH diagnoses over the entire 24 weeks of treatment was observed for 29.0% of patients treated with eptinezumab (placebo, 6.3%). These post hoc analyses suggest that eptinezumab could be an effective treatment for these patients with difficult to treat migraine.

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CONFLICT OF INTEREST

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Novartis, Satsuma, Zosano; Consultant and/or Advisory Boards (honoraria): Aeon, Align Strategies, Allergan/Abbvie, Alphashights, Amgen, Aperture Venture Partners, Araleza Pharmaceuticals Canada, Axsome Therapeutics, Becker Pharmaceutical Consulting, BioDelivery Sciences International, Biohaven, ClearView Healthcare Partners, CoolTech, CRG, Currax, Decision Resources, DeepBench, DRG, Eli Lilly, Equinox, ExpertConnect, GLG, Guidepoint Global, Healthcare Consultancy Group, Health Science Communications, HMP Communications, Impel, Interactive Forums, Krog and Partners, Lundbeck, M3 Global Research, Magellan Rx Management, Medicix, Navigant Consulting, Neurelief, Nordic BioTech, Novartis, Pulmatrix, Reckner Healthcare, Relevale, SAI MedPartners, Satsuma, Slingshot Insights, Spherix Global Insights, Sudler and Hennessy, Synapse Medical Communications, System Analytic, Teva, Theranica, Thought Leader Select, Trinity Partners, Unity HA, XOC, Zosano: Salary: Dartmouth-Hitchcock Medical Center, American Headache Society, Thomas Jefferson University; CME honoraria: American Academy of Neurology, American Headache Society, Cleveland Clinic Foundation, Diamond Headache Clinic, Elsevier, Forefront Collaborative, Hamilton General Hospital, Ontario, Canada, Headache Cooperative of New England, Henry Ford Hospital, Detroit, Inova, Medical Learning Institute Peerview, Medical Education Speakers Network, Miller Medical Communications, North American Center for CME, Physicians' Education Resource, Rockpointe, ScientiaCME, WebMD/Medscape. M. L. Diamond: Advisory board member: Amgen, Assertio, Eli Lilly, Lundbeck, Promius Pharma, Supernus Pharmaceuticals, Teva, and Upsher-Smith Laboratories; Consultant: Amgen, Eli Lilly, Lundbeck, Promius Pharma, and Teva; Speaker’s bureau: Amgen, Assertio, Eli Lilly, Supernus Pharmaceuticals, and Teva. A. J. Starling: Consulting fees: Alder, Amgen, eNeura, Eli Lilly, Impel, Lundbeck, Novartis, Theranica. J. Hirman: Contracted service provider of biostatistical resources: Lundbeck Seattle BioPharmaceuticals. L. Mehta and R. Cady: Full-time employee: H. Lundbeck A/S or one of its subsidiary companies. T. Brevig: Full-time employee and stockholder: Lundbeck.

AUTHOR CONTRIBUTIONS

Study concept and design: Michael J. Marmura, Hans-Christoph Diener, Joe Hirman, Lahar Mehta, Roger Cady. Acquisition of data: Michael J. Marmura. Analysis and interpretation of data: Michael J. Marmura, Hans-Christoph Diener, Robert P. Cowan, Stewart J. Tepper, Merle L. Diamond, Amaal J. Starling, Joe Hirman, Lahar Mehta, Thomas Brevig, Roger Cady. Drafting of the manuscript: Michael J. Marmura, Hans-Christoph Diener, Robert P. Cowan, Stewart J. Tepper, Merle L. Diamond, Amaal J. Starling, Joe Hirman, Lahar Mehta, Thomas Brevig, Roger Cady. Revising it for intellectual content: Michael J. Marmura, Hans-Christoph Diener, Robert P. Cowan, Stewart J. Tepper, Merle L. Diamond, Amaal J. Starling, Joe Hirman, Lahar Mehta, Thomas Brevig, Roger Cady. Final approval of the completed manuscript: Michael J. Marmura, Hans-Christoph Diener, Robert P. Cowan, Stewart J. Tepper, Merle L. Diamond, Amaal J. Starling, Joe Hirman, Lahar Mehta, Thomas Brevig, Roger Cady.

CLINICAL TRIALS REGISTRATION NUMBER

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.