

# Efficacy and safety of eptinezumab in patients with chronic migraine

## PROMISE-2

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## Abstract

### Objective

To evaluate the efficacy and safety of eptinezumab, a humanized anti-calcitonin gene-related peptide monoclonal antibody, in the preventive treatment of chronic migraine (CM).

### Methods

The Prevention of Migraine via Intravenous ALD403 Safety and Efficacy-2 (PROMISE-2) study was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Adults with CM were randomly assigned to receive IV eptinezumab 100 mg, eptinezumab 300 mg, or placebo administered on day 0 and week 12. The primary endpoint was change from baseline in mean monthly migraine days (MMDs) over weeks 1 to 12.

### Results

Among treated participants ( $n = 1,072$ ), baseline mean number of MMDs was  $\approx 16.1$  across groups. Treatment with eptinezumab 100 and 300 mg was associated with significant reductions in MMDs across weeks 1 to 12 compared with placebo (placebo  $-5.6$ , 100 mg  $-7.7$ ,  $p < 0.0001$  vs placebo; 300 mg  $-8.2$ ,  $p < 0.0001$  vs placebo). Treatment-emergent adverse events (TEAEs) were reported by 43.5% (100 mg), 52.0% (300 mg), and 46.7% (placebo) of patients. Nasopharyngitis was the only TEAE reported for  $>2\%$  of eptinezumab-treated patients at an incidence of  $>2\%$  over placebo; it occurred in the 300 mg eptinezumab arm (eptinezumab 9.4%, placebo 6.0%).

### Conclusion

In patients with CM, eptinezumab 100 and 300 mg was associated with a significant reduction in MMDs from the day after IV administration through week 12, was well tolerated, and demonstrated an acceptable safety profile.

### Classification of evidence

This study provides Class I evidence that for patients with CM, a single dose of eptinezumab reduces MMDs over 12 weeks of treatment.

### ClinicalTrials.gov identifier

NCT02974153.

### MORE ONLINE

#### → Class of Evidence

Criteria for rating therapeutic and diagnostic studies

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## Glossary

**ADA** = anti-drug antibody; **AE** = adverse event; **ANCOVA** = analysis of covariance; **CGRP** = calcitonin gene-related peptide; **CM** = chronic migraine; **eDiary** = electronic diary; **HIT-6** = 6-item Headache Impact Test; **ICHD-3** = International Classification of Headache Disorders, 3rd edition; **MMD** = monthly migraine day; **NAb** = ADA with neutralizing potential; **PROMISE** = Prevention of Migraine via Intravenous ALD403 Safety and Efficacy; **SAE** = serious AE; **TEAE** = treatment-emergent AE.

Migraine is a common, disabling neurologic disorder<sup>1</sup>; its most burdensome form is chronic migraine (CM), clinically defined by the presence of headache on  $\geq 15$  d/mo for  $\geq 3$  months, with  $\geq 8$  d/mo of headaches linked to migraine.<sup>2</sup> Relative to episodic migraine, CM is associated with significantly greater disability, higher rates of comorbidity, and increased direct and indirect costs.<sup>3</sup>

Reducing the burden of CM is an important goal of preventive treatment, although randomized trials in CM are a recent phenomenon.<sup>4–7</sup> Currently, onabotulinumtoxinA and calcitonin gene-related peptide (CGRP)-targeted monoclonal antibodies are the only agents approved for the prevention of CM. In the United States, diagnosis and treatment rates for CM are low, and migraine preventive treatment is frequently discontinued prematurely.<sup>8–13</sup>

The Prevention of Migraine via Intravenous ALD403 Safety and Efficacy (PROMISE) phase 3 studies were randomized, double-blind, placebo-controlled trials designed to evaluate the efficacy, safety, and pharmacokinetics of repeat IV administration of the monoclonal antibody eptinezumab (ALD403) for migraine prevention in patients with episodic migraine (PROMISE-1) and CM (PROMISE-2). Eptinezumab is a monoclonal antibody that binds to the CGRP ligand.<sup>14,15</sup> Blockade of the CGRP pathway is an established method in the acute and preventive treatment of migraine.<sup>16</sup> This report presents the primary results of the PROMISE-2 study.

## Methods

### Standard protocol approvals, registrations, and patient consents

The study was approved by the independent ethics committee or institutional review board for each study site. All clinical work was conducted in compliance with current Good Clinical Practices as referenced in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines, local regulatory requirements, and the principles of the Declaration of Helsinki. All patients enrolled in the study provided written informed consent before their participation. All clinical sites were required to sign a study-specific site blinding plan. This study is registered on ClinicalTrials.gov (NCT02974153).

### Study design and patients

This phase 3, double-blind, randomized, placebo-controlled, parallel-group, efficacy and safety study was performed at 128 sites in 13 countries (United States, Spain, Ukraine, Russian Federation, United Kingdom, Republic of Georgia, Hungary, Italy, Slovakia, Germany, Czech Republic, Denmark, and Belgium) during the period of November 30, 2016, to April 20, 2018.

Adults 18 to 65 years of age (inclusive) with a diagnosis of migraine at or before 50 years of age were eligible for participation if they had a history of CM for  $\geq 12$  months before screening, completed the headache electronic diary (eDiary) on  $\geq 24$  of the 28 days after screening visit and before randomization (the screening period), and experienced  $\geq 15$  to  $\leq 26$  headache days and  $\geq 8$  migraine days during the 28-day screening period.<sup>2</sup> Patients taking prescription or over-the-counter medication for acute or preventive treatment of migraine were eligible only if the medications had been prescribed or recommended by a health care professional; migraine preventive medication use had to be stable for  $\geq 3$  months before screening. Hormonal therapy (e.g., contraceptive, hormone replacement) was also permitted if it was stable and ongoing  $\geq 3$  months before screening. Patients using barbiturates or prescription opioids  $\leq 4$  d/mo were eligible for participation if use was stable for  $\geq 2$  months before screening, and this restriction was maintained through week 24 of the study. Other medications for the treatment of acute migraine such as triptans, nonsteroidal anti-inflammatory drugs, and simple analgesics were not restricted. Patients with CM and medication-overuse headache with the exception of the overuse of barbiturates or opioids were eligible for inclusion. The study steering committee wished to include patients using opioids and barbiturates because more than one-third of people in the United States who have migraine use these medications as acute prescription treatments. The study steering committee chose to limit opioid and barbiturate use because high use often makes the patient refractory to preventive treatments. In pursuit of a balance between generalizability and enrolling the target population, patients using opioids or barbiturates  $\geq 5$  d/mo were excluded.

Individuals were excluded from participation if they had a confounding pain disorder or clinically significant pain syndromes; uncontrolled or untreated psychiatric conditions; acute or active temporomandibular disorders; history or diagnosis of a headache or migraine disorders that did not meet the International Classification of Headache Disorders, 3rd edition (ICHD-3)

beta version (2013) Section 1.3 criteria for CM; present or previous malignancies (except history of squamous or basal cell carcinoma with excision for cure or breast or cervical cancer  $\geq 10$  years since diagnosis/treatment without evidence of recurrence); any active, progressive, or unstable cardiovascular, neurologic, or autoimmune disorder; newly diagnosed or uncontrolled hypertension (mild primary hypertension that was well controlled for  $\geq 6$  months before screening was allowed); history or evidence of substance abuse or dependence; clinically significant abnormal ECG findings; a concurrent medical condition or laboratory abnormality during the screening period or before dosing on day 0; body mass index  $\geq 39$  kg/m<sup>2</sup>; or recent or planned surgery requiring general anesthesia within 8 weeks before screening or during the duration of the study. Also excluded were patients who had received any experimental, unregistered therapy within 30 days or 5 plasma half-lives before screening or who had used any prohibited devices, neuromodulation, neurostimulation, or injectable therapy within 2 months before screening or during the screening period; botulinum toxin (any type) for migraine or for any other medical/cosmetic reasons requiring injections within 4 months before screening or during the screening period; monoamine oxidase inhibitors, ketamine, methylergonovine, or nimesulide within 3 months before screening or during the screening period; any monoclonal antibody treatment within 6 months of screening; or eptinezumab or any monoclonal antibody targeting the CGRP pathway. Women who were pregnant, breastfeeding, or planning to become pregnant during the study were excluded from participation, as were patients participating in any other clinical study or who were positive for HIV, hepatitis B surface antigen, or hepatitis C.

Women of childbearing potential and men with partners of childbearing potential agreed to use adequate contraception throughout study participation and for  $\geq 6$  months after the last dose of study drug.

### Study procedures

Patients used an eDiary to document headaches and migraines for 4 weeks after the screening visit to confirm eligibility criteria and to establish baseline values. Eligible patients were then randomly assigned to receive eptinezumab 100 mg, eptinezumab 300 mg, or placebo in a 1:1:1 ratio. Randomization was stratified by the number of migraine days recorded during the screening period ( $\leq 17$  vs  $> 17$  days) and preventive medication use during the 3 months before screening (use vs no use). The total duration of the study was 32 weeks, with 10 scheduled visits (screening, day 0, and weeks 2, 4, 8, 12, 16, 20, 24, and 32). After the last patient completed the week 12 visit, the analysis of the primary endpoint was performed.

Patients received up to 2 treatments of eptinezumab or placebo (administered IV on day 0 and at week 12). Assignment was concealed. Investigational product (either eptinezumab 100 mg or placebo) was shipped frozen on dry ice as a single-use, preservative-free solution in a tamper-proof 2-mL type I glass vial. Each individual vial was labeled with protocol-

specific information to meet International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and country-specific requirements. On randomization, study sites were provided with enough appropriate investigational product for 1 patient to be dosed, with subsequent treatment packs shipped automatically before the next scheduled treatment visit. Investigational treatments were reconstituted in a total volume of 100 mL 0.9% saline and administered over a period of 30 minutes (plus an additional 15 minutes, per protocol, if required) by the blinded investigator. Patients were monitored for  $\geq 2$  hours after treatment. All research participants, clinicians, and research personnel were blinded and remained blinded throughout the duration of the clinical trial.

### Outcome measures

Patients completed a daily eDiary from the time of screening through week 24; this included a daily evening report (completed regardless of whether the patient had a headache) and a headache report, which was event based (i.e., per headache). In addition to capturing headache episodes and migraine attacks, the daily eDiary captured acute medication use (including type). A migraine day was defined using information from the eDiary and followed the definition of a CM outlined in ICHD-3. Specifically, a migraine day had to meet 3 criteria: (1) lasted  $\geq 4$  hours or lasted 30 minutes to 4 hours and believed by the patient to be a migraine that was relieved by acute medication; (2) had  $\geq 2$  of the following: unilateral location, pulsating quality, moderate or severe pain intensity, and aggravation by or causing avoidance of routine physical activity; and (3) had  $\geq 1$  of the following: nausea and/or vomiting or photophobia and phonophobia.

Monthly results (e.g., monthly migraine days [MMDs]) were based on the results of the 4-week intervals. If the headache diary was completed for  $\geq 21$  days of a 4-week interval, the observed frequency was normalized to 28 days. If the diary was completed for  $< 21$  days of a 4-week interval, the results were a weighted function of the observed data for the current interval and the results from the previous interval, with the weight proportional to how many days the diary had been completed.

The primary efficacy endpoint was the change from baseline in MMDs over weeks 1 to 12, assessed with eDiary data. eDiary data also were used for evaluating several of the key secondary efficacy endpoints:  $\geq 75\%$  migraine responder rate over weeks 1 to 4,  $\geq 75\%$  migraine responder rate over weeks 1 to 12,  $\geq 50\%$  migraine responder rate over weeks 1 to 12, percentage of patients with a migraine on the day after dosing, change from baseline in daily migraine prevalence from baseline to week 4, and acute migraine medication use during weeks 1 to 12.

During the scheduled visits, patients completed several patient-reported outcome measures, including the 6-item Headache Impact Test (HIT-6), the 36-item Short-Form Health Survey (version 2.0), the EuroQol 5-Dimensions 5-Levels, and the Patient Global Impression of Change. The

Most Bothersome Symptom was evaluated as a tertiary endpoint and is not reported here.

The HIT-6<sup>17,18</sup> version 1.0, an  $\alpha$  control endpoint in this study for the 300 mg treatment group, was administered at screening, day 0, and at week 4, 12, 16, 24, and 32 visits to measure the impact of headaches on the ability to function normally in daily life. Patients rated the HIT-6 items using a Likert-type scale anchored by “never” and “always” and including the following response scores: never = 6, rarely = 8, sometimes = 10, very often = 11, and always = 13. Response scores were summed to produce a total score. Scores  $\geq 60$  were indicative of severe life impact, 56 to 59 of substantial life impact, 50 to 55 of some life impact, and  $\leq 49$  of little to no life impact.

Safety was assessed throughout the study via adverse event (AE) monitoring, clinical laboratory tests, vital sign measurements, physical examinations, 12-lead ECGs, the Columbia-Suicide Severity Rating Scale,<sup>19</sup> and concomitant medication use. AEs of special interest also were monitored and included AEs associated with the Columbia-Suicide Severity Rating Scale score, cardiovascular AEs, hepatic AEs, and those associated with study drug administration, including hypersensitivity and anaphylaxis AEs.

Blood samples for immunogenicity analyses were collected on day 0 and at week 2, 4, 8, 12, 24, and 32, including monitoring development of anti-eptinezumab antibodies and assaying for neutralizing potential.

## Statistical methods

A total of 350 patients per group provided at least 90% power for the primary endpoint for each comparison, assuming a treatment effect of  $\geq 1$  day and a common SD of  $\leq 4$  days. These sample size calculations were performed with PASS 2008<sup>20</sup> and were based on a *t* test that approximated the analysis of covariance (ANCOVA) used for the primary endpoint.<sup>20</sup>

All patients who received study medication were included in the safety and efficacy populations. For the safety analyses, patient results were summarized within the group representing the treatment they received; if they received 2 different doses, they were summarized in the treatment arm of the highest dose received. For the efficacy population, patients' results were summarized within the treatment group to which they were randomly assigned.

A serial procedure was used to account for multiplicity associated with  $>1$  dose level and for multiple endpoints (figure 1). Statistical testing was conducted to maintain a study-wide 2-sided 5%  $\alpha$  level. The procedure first evaluated the 300 mg vs placebo comparison for the primary endpoint. If this was significant, testing continued to the first subset of key secondary endpoints for 300 mg. If a significant difference was detected for all tests within this series, the procedure then moved on to the second subset of key secondary endpoints for 300 mg. The procedure then moved on to the 100 mg group for the primary

endpoint and subsequently the key secondary endpoint groups for 100 mg. If these endpoints were significant, the procedure moved to the final key secondary endpoints for 300 mg. Within each endpoint group, the Holm procedure<sup>21</sup> was used.

The primary efficacy endpoint was the change from baseline in MMDs (weeks 1–12) in an ANCOVA model. Key secondary efficacy endpoints were  $\geq 75\%$  migraine responder rates during weeks 1 to 4 and 1 to 12,  $\geq 50\%$  migraine responder rates during weeks 1 to 12, percentage of patients with a migraine on the day after dosing, reduction in average daily percentage of patients with migraine from baseline to week 4, change in HIT-6 total score from baseline to week 12 (300 mg dose only), and acute migraine medication use from baseline to week 12 (300 mg dose only). A  $\geq 50\%$  or  $\geq 75\%$  migraine responder was defined as a patient who achieved  $\geq 50\%$  reduction or  $\geq 75\%$  reduction in MMDs from baseline, respectively. These reductions were evaluated by comparing the baseline frequency of migraine days to the migraine frequency in 4-week intervals. Results from these 4-week intervals will be combined to produce 12-week responder endpoints. The week 1 to 4, 5 to 8, and 9 to 12 changes from baseline measures were averaged, and the average value was compared to baseline. A percent change from baseline was determined, which was used to determine the responder status.

For the key secondary endpoints (migraine responder rates and percentage of patients with a migraine on the day after dosing), testing was based on Cochran-Mantel-Haenszel/extended Cochran-Mantel-Haenszel tests. The tests were stratified by the randomization stratification factor. For the HIT-6 and Acute Migraine Medication endpoints, an ANCOVA model similar to the one used for the primary endpoint was used for testing. Exploratory and safety endpoints were summarized with descriptive statistics. All analyses were conducted with SAS software (SAS Institute, Inc, Cary, NC) version 9.2 or higher. Appendix 2 available from Dryad ([doi.org/10.5061/dryad.ck84q23](https://doi.org/10.5061/dryad.ck84q23)) provides additional information on the statistical analysis.

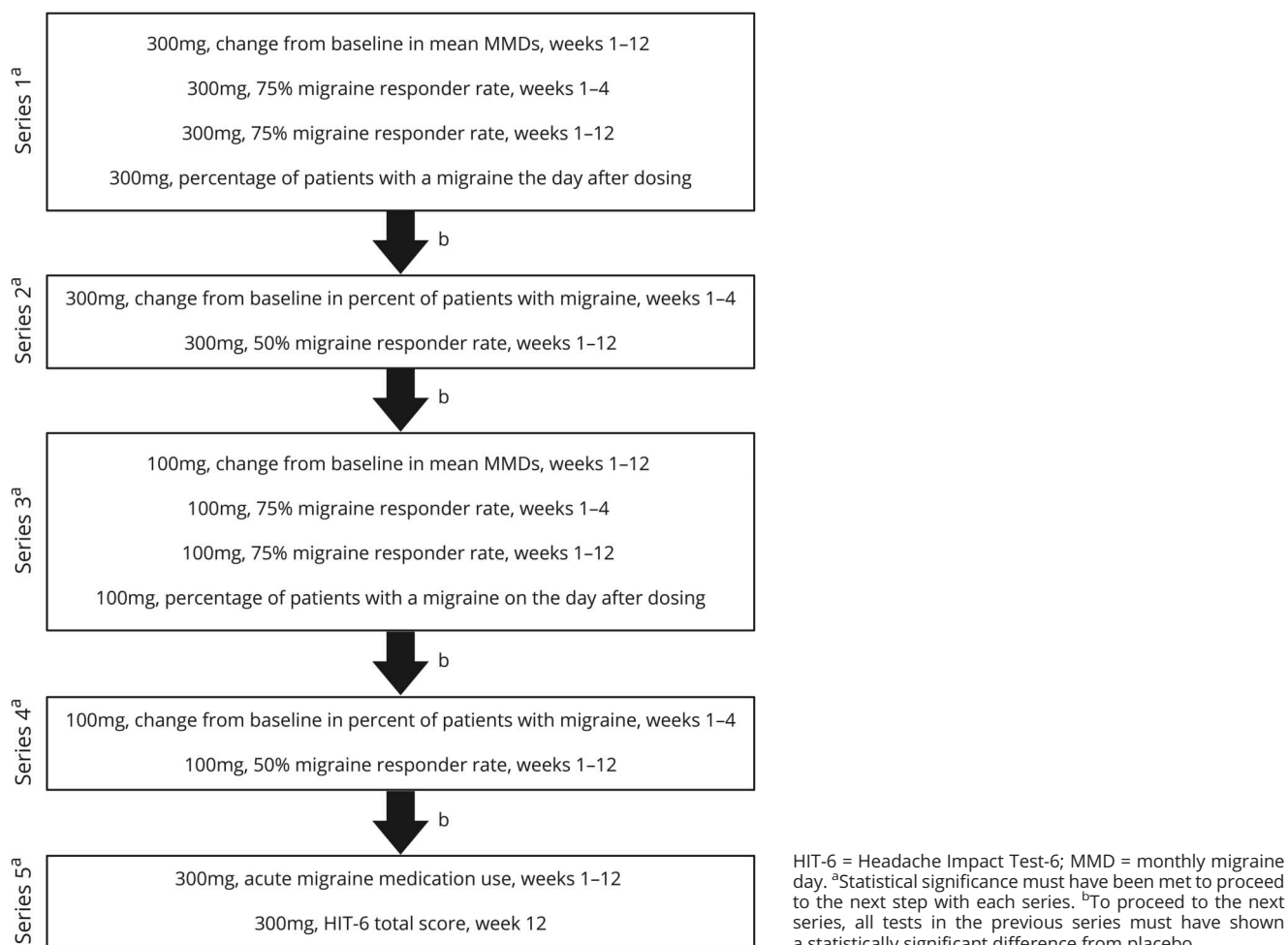
## Data availability

The data reported are part of an ongoing, global sponsor-led clinical development and registration program. Deidentified participant data are not available for legal and ethical reasons.

## Results

A total of 1,121 patients were randomly assigned; 1,072 received treatment and were included in the safety and full analysis populations (figure 2). Reasons that patients were randomized but not treated included withdrawal by the patient (19 patients), loss to follow-up (3 patients), and other (e.g., randomization errors and protocol violations 27 patients). Overall, 1,049 patients (93.6%) remained in the study until week 12, the end of the primary efficacy period. A total of 1,000 patients (89.2%) attended the week 24 visit, and 878 patients (78.3%) attended the week 32 visit.

**Figure 1** Decision rule for dose levels (primary and key secondary endpoints)



Demographic and baseline clinical characteristics are summarized in table 1. The mean age was 40.5 years; 65.7% of patients were >35 years of age. The majority of patients were female (88.2%), white (91.0%), and not Hispanic or Latino (92.0%). Migraine history was well balanced across treatment groups. The mean age at migraine diagnosis was 22.5 years, and the mean duration of migraine diagnosis was 18.1 years. A total of 479 patients (44.7%) used concomitant prophylactic medication. A total of 431 patients (40.2%) had a diagnosis of medication-overuse headache at baseline. Diagnosis was made at screening by the study investigator using ICHD-3 beta criteria for medication-overuse headache and was confirmed by analyses of acute medication use over the baseline period.

Nearly all patients (99.7%) reported using  $\geq 1$  concomitant medications during the study; concomitant medication use was well balanced across treatment groups at the drug class level. The most frequently reported concomitant medications were nervous system medications (93.9%), musculoskeletal system medications (57.8%), alimentary tract and metabolism medications (33.5%), respiratory system medications

(29.2%), genitourinary system and sex hormone medications (26.1%), and cardiovascular system medications (22.9%).

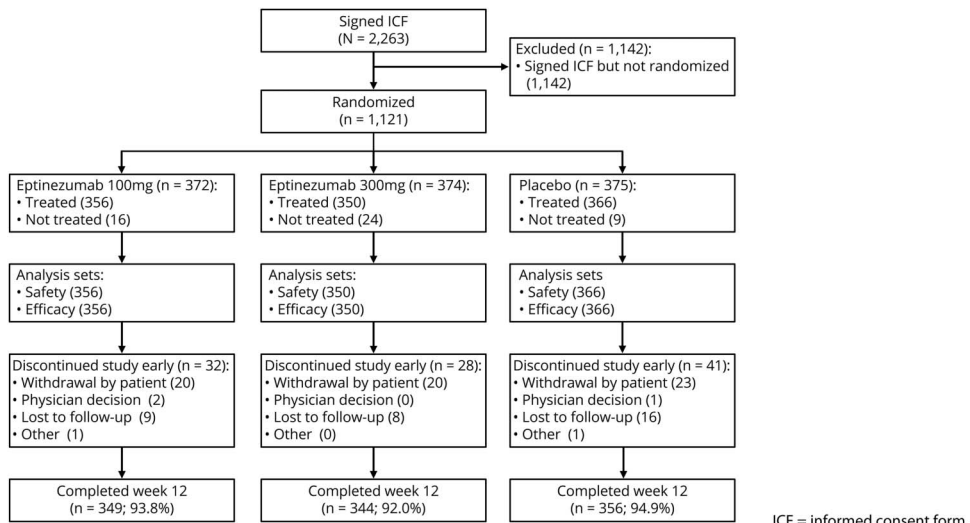
### Efficacy findings

Because the largest  $p$  value within the  $\alpha$ -controlled primary and key secondary endpoints was 0.0001 based on the decision rule outlined in figure 1, the results for the primary efficacy endpoint and all key secondary endpoints for both eptinezumab dose groups were statistically significant (table 2).

### Primary efficacy endpoint

Both 100 and 300 mg of eptinezumab demonstrated statistically significant reductions in MMDs during weeks 1 to 12 ( $p < 0.0001$ ; figure 3 and table 2). MMDs decreased from 16.1 to 8.5 days in the eptinezumab 100 mg group, from 16.1 to 7.9 days in the eptinezumab 300 mg group, and from 16.2 to 10.5 days in the placebo group. Relative to placebo, eptinezumab reduced mean (95% confidence interval) MMDs from baseline (during the 28-day screening period) by  $-2.0$  ( $-2.9$  to  $-1.2$ ) days for the 100 mg dose and  $-2.6$  ( $-3.4$  to  $-1.7$ ) days for the 300 mg dose. A post hoc analysis of the primary efficacy endpoint in patients with no barbiturate or opioid use at any time during

**Figure 2** Patient disposition



the clinical trial identified a similar reduction in mean MMDs from baseline compared to placebo (100 mg  $-2.3$  [ $-3.2$  to  $-1.4$ ],  $p < 0.0001$ ; 300 mg  $-2.8$  [ $-3.7$  to  $-1.9$ ],  $p < 0.0001$ ).

### Key secondary efficacy endpoints

The  $\geq 75\%$  migraine responder rates (weeks 1–4 and 1–12) and  $\geq 50\%$  migraine responder rates (weeks 1–12) are summarized in figure 4 and table 2. Patients in both eptinezumab dose groups were more likely to achieve  $\geq 75\%$  migraine response during weeks 1 to 4 than were patients in the placebo group (common odds ratios [95% confidence interval] 2.4 [1.7–3.5] for eptinezumab 100 mg and 3.2 [2.2–4.6] for eptinezumab 300 mg). They also were more likely to achieve  $\geq 75\%$  migraine response during weeks 1–12 (common odds ratios [95% confidence interval] 2.0 [1.4–3.0] for eptinezumab 100 mg and 2.8 [1.9–4.0] for eptinezumab 300 mg) and  $\geq 50\%$  migraine response during weeks 1 to 12 (common odds ratios [95% confidence interval] 2.1 [1.6–2.8] for eptinezumab 100 mg and 2.4 [1.8–3.3] for eptinezumab 300 mg).

The migraine preventive effect of eptinezumab was statistically significant for the 100 and 300 mg doses of eptinezumab vs placebo after the first day after dosing (figure 4). During the 28-day screening period, the average daily percentage of patients with a migraine was 58%. The percentage of patients with a migraine on the day after dosing was 28.6% in the eptinezumab 100 mg group and 27.8% in the eptinezumab 300 mg group vs 42.3% in the placebo group (both  $p < 0.0001$  vs placebo). Estimated mean changes in the average daily percentage of patients with a migraine from baseline over weeks 1, 2, 3, and 4 were  $-27.1\%$  in the eptinezumab 100 mg group (mean difference [95% confidence interval] from placebo  $-8.3\%$  [ $-11.48$  to  $-5.05$ ],  $p < 0.0001$ ),  $-29.8\%$  in the eptinezumab 300 mg group (mean difference from placebo  $-11.0\%$  [ $-14.2$  to  $-7.8$ ],  $p < 0.001$ ), and  $-18.8\%$  in the placebo group. Furthermore, the

average daily percentage of patients with migraine was lower in the eptinezumab groups than in the placebo group during each of the first 4 weeks after dosing (figure 4).

Most patients had HIT-6 total scores in the severe range at baseline (eptinezumab 100 mg 89.6%, eptinezumab 300 mg 88.6%, and placebo 87.4%). The mean HIT-6 scores at baseline were 65.0 (eptinezumab 100 mg), 65.1 (eptinezumab 300 mg), and 64.8 (placebo). By week 12, the percentage of patients with HIT-6 scores in the severe range had been reduced to 51.4% in the eptinezumab 100 mg treatment group, 42.9% in the eptinezumab 300 mg treatment group, and 60.1% in the placebo group. Patients in the eptinezumab 300 mg group demonstrated a statistically significant improvement on the HIT-6 at week 12, with an estimated mean difference from placebo (95% confidence interval) of  $-2.9$  ( $-3.9$  to  $-1.8$ ,  $p < 0.0001$ ). The estimated mean difference from placebo for the 100 mg treatment group (a prespecified endpoint) was  $-1.7$  and was nominally significant ( $p = 0.001$ ), although this comparison was not formally included within the prespecified testing algorithm.

Both eptinezumab dose groups reduced acute medication days from baseline to week 12 (100 mg  $-3.3$  days, 300 mg  $-3.5$  days). The reduction in the 100 mg group was greater than that in the placebo group ( $-1.2$  [ $-1.7$  to  $-0.6$ ],  $p < 0.0001$ ) but was not formally tested. The reduction in the eptinezumab 300 mg group was significantly greater than that in the placebo group (mean difference from placebo [95% confidence interval]  $-1.4$  [ $-1.9$  to  $-0.9$ ],  $p < 0.0001$ ).

### Safety and tolerability

A total of 1,072 patients received  $\geq 1$  doses of study medication. The majority of patients received both doses of eptinezumab (100 mg  $n = 340$  [95.5%], 300 mg  $n = 338$  [96.6%]) or placebo ( $n = 342$  [93.4%]).

**Table 1** Demographics and baseline clinical characteristics (safety population)

	Eptinezumab 100 mg (n = 356)	Eptinezumab 300 mg (n = 350)	Placebo (n = 366)	Total population (n = 1,072)
Mean (SD) age, y	41.0 (11.7)	41.0 (10.4)	39.6 (11.3)	40.5 (11.2)
<b>Sex, n (%)</b>				
Male	49 (13.8)	36 (10.3)	41 (11.2)	126 (11.8)
Female	307 (86.2)	314 (89.7)	325 (88.8)	946 (88.2)
<b>Ethnicity, n (%)</b>				
Hispanic or Latino	33 (9.3)	18 (5.1)	35 (9.6)	86 (8.0)
Not Hispanic or Latino	323 (90.7)	332 (94.9)	331 (90.4)	986 (92.0)
<b>Race, n (%)</b>				
White	332 (93.3)	322 (92.0)	321 (87.7)	975 (91.0)
Black or African American	21 (5.9)	23 (6.6)	38 (10.4)	82 (7.6)
Asian	1 (<1)	1 (<1)	1 (<1)	3 (<1)
American Indian or Alaska Native	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Native Hawaiian or other Pacific Islander	0	1 (<1)	0	1 (<1)
Multiple races	1 (<1)	2 (<1)	4 (1.1)	7 (<1)
Other	0	0	1 (<1)	1 (<1)
Mean (SD) weight, kg	73.3 (15.6)	72.7 (15.3)	74.8 (16.2)	73.6 (15.8)
Mean (SD) height, cm	166.2 (8.2)	166.1 (7.9)	166.3 (7.9)	166.2 (8.0)
Mean (SD) BMI, kg/m <sup>2</sup>	26.4 (5.0)	26.2 (5.0)	27.0 (5.6)	26.6 (5.2)
Mean (SD) age at migraine diagnosis, y	22.8 (10.6)	22.0 (9.3)	22.6 (10.0)	22.5 (10.0)
Mean (SD) duration of migraine diagnosis at baseline, y	18.3 (12.2)	19.0 (11.5)	17.0 (11.6)	18.1 (11.8)
Mean (SD) duration of CM at baseline, y	11.6 (11.7)	12.4 (11.2)	11.6 (10.9)	11.8 (11.2)
Mean (SD) No. of headache days <sup>a</sup>	20.4 (3.1)	20.4 (3.2)	20.6 (2.99)	20.5 (3.1)
Mean (SD) No. of migraine days <sup>a</sup>	16.1 (4.6)	16.1 (4.8)	16.2 (4.6)	16.1 (4.6)
Medication-overuse headache diagnosis, n (%)	139 (39.0)	147 (42.0)	145 (39.6)	431 (40.2)
<b>Baseline triptan use, n (%)</b>				
≥33% of days	124 (34.8)	125 (35.7)	116 (31.7)	365 (34.0)
<33% of days	231 (64.9)	225 (64.3)	250 (68.3)	706 (65.9)
Use of opioids or barbiturates at any time, n (%)	46 (12.9)	39 (11.1)	48 (13.1)	133 (12.4)

Abbreviations: BMI = body mass index; CM = chronic migraine.

<sup>a</sup> Full analysis population; mean electronic diary–reported migraine and headache characteristics during the 28-day screening period.

### Adverse events

Overall, 508 patients (47.4%) experienced ≥1 treatment-emergent AEs (TEAEs). The incidence of TEAEs was generally balanced among treatment groups (table 3).

A total of 122 patients (11.4%) had ≥1 TEAEs considered by the investigator to be related to the study drug: 93 patients (13.2%) in the eptinezumab groups and 29

patients (7.9%) in the placebo group. The most frequently reported study drug-related TEAEs were fatigue (eptinezumab n = 13 [1.8%], placebo n = 3 [<1%]) and nausea (eptinezumab n = 11 [1.6%], placebo n = 1 [<1%]). The remaining study drug-related TEAEs occurred in <1% of patients.

No deaths were reported in this study. A total of 10 patients (<1%) experienced a serious TEAE (7 patients who received

**Table 2** Efficacy outcomes (efficacy population)

	Eptinezumab 100 mg (n = 356)	Eptinezumab 300 mg (n = 350)	Placebo (n = 366)
<b>Mean MMDs, weeks 1–12</b>			
<b>Actual</b>			
Mean	8.5	7.9	10.5
<b>Change from baseline</b>			
Mean	–7.7	–8.2	–5.6
Difference from placebo (95% CI)	–2.0 (–2.9 to –1.2)	–2.6 (–3.4 to –1.7)	
p Value vs placebo	<0.0001	<0.0001	
<b>Mean headache days, weeks 1–12</b>			
<b>Actual</b>			
Mean	12.2	11.7	14.1
<b>Change from baseline</b>			
Mean	–8.2	–8.8	–6.4
Difference from placebo (95% CI)	–1.7 (–2.6 to –0.9)	–2.3 (–3.2 to –1.4)	
<b>Percentage of patients with migraine, day 1</b>			
<b>Actual</b>			
Mean	28.6	27.8	42.3
p Value vs placebo	<0.0001	<0.0001	
<b>Average daily migraine prevalence, weeks 1–4, %</b>			
<b>Actual</b>			
Mean	30.6	27.9	10.5
<b>Change from baseline</b>			
Mean	–27.1	–29.8	–18.8
Difference from placebo (95% CI)	–8.3 (–11.5 to –5.0)	–11.0 (–14.2 to –7.8)	
p Value vs placebo	<0.0001	<0.0001	
<b>75% Migraine responder rate, weeks 1–4</b>			
Patients, n (%)	110 (30.9)	129 (36.9)	57 (15.6)
Difference from placebo (95% CI)	15.3 (9.3 to 21.4)	21.3 (15.0 to 27.6)	
p Value vs placebo	<0.0001	<0.0001	
Odds ratio vs placebo	2.4	3.2	
<b>75% Migraine responder rate, weeks 1–12</b>			
Patients, n (%)	95 (26.7)	116 (33.1)	55 (15.0)
Difference from placebo (95% CI)	11.7 (5.8 to 17.5)	18.1 (12.0 to 24.3)	
p Value vs placebo	0.0001	<0.0001	
Odds ratio vs placebo	2.0	2.8	
<b>50% Migraine responder rate, weeks 1–12</b>			
Patients, n (%)	205 (57.6)	215 (61.4)	144 (39.3)
Difference from placebo (95% CI)	18.2 (11.1 to 25.4)	22.1 (14.9 to 29.2)	

Continued



**Table 2** Efficacy outcomes (efficacy population) (continued)

	Eptinezumab 100 mg (n = 356)	Eptinezumab 300 mg (n = 350)	Placebo (n = 366)
<b>p Value vs placebo</b>	<0.0001	<0.0001	
<b>Odds ratio vs placebo</b>	2.1	2.4	
<b>Mean acute medication days, weeks 1–12</b>			
<b>Actual</b>			
<b>Mean</b>	3.3	3.2	4.3
<b>Change from baseline</b>			
<b>Mean</b>	–3.3	–3.5	–1.9
<b>Difference from placebo (95% CI)</b>	–1.2 (–1.7 to –0.6)	–1.4 (–1.9 to –0.9)	
<b>p Value vs placebo</b>	<0.0001	<0.0001	
<b>HIT-6 score, week 4</b>			
<b>Actual</b>			
<b>Mean</b>	58.0	56.4	60.3
<b>Change from baseline</b>			
<b>Mean</b>	–6.9	–8.6	–4.6
<b>Difference from placebo (95% CI)</b>	–2.3 (–3.4 to –1.2)	–4.0 (–5.1 to –2.8)	
<b>HIT-6 score, week 12</b>			
<b>Actual</b>			
<b>Mean</b>	58.8	57.6	60.5
<b>Change from baseline</b>			
<b>Mean</b>	–6.2	–7.3	–4.5
<b>Difference from placebo (95% CI)</b>	–1.7 (–2.8 to –0.7)	–2.9 (–3.9 to –1.8)	
<b>p Value vs placebo</b>	0.0010	<0.0001	

Abbreviations: CI = confidence interval; HIT-6 = Headache Impact Test-6; MMD = monthly migraine day.

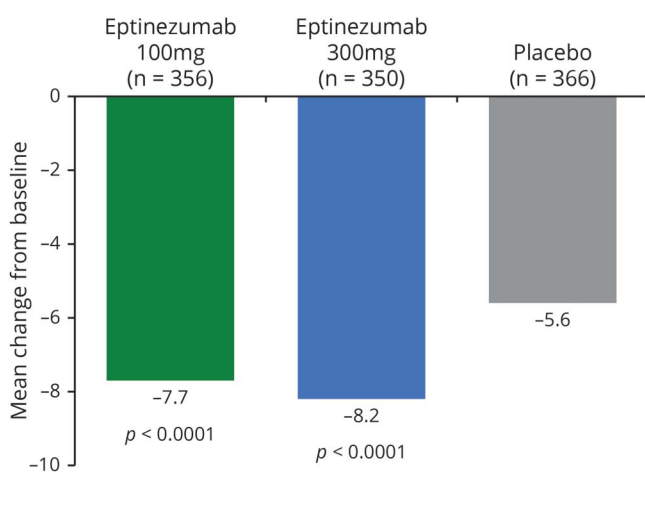
eptinezumab and 3 who received placebo). The most frequently reported serious TEAEs were in the system organ class of nervous system disorders (eptinezumab n = 4 [ $<1\%$ ], placebo n = 1 [ $<1\%$ ]); injury, poisoning, and procedural complications (eptinezumab n = 2 [ $<1\%$ ], placebo n = 0); and psychiatric disorders (eptinezumab n = 2 [ $<1\%$ ], placebo n = 0). One serious AE (SAE) was assessed as related to the study drug by both the investigator and the sponsor. This was a single episode of worsening migrainous visual phenomena in a patient with a medical history of migraine with visual aura, considered part of the disease under study, which occurred 126 days after the second dose of eptinezumab 300 mg and lasted 4 days. No patients had life-threatening SAEs.

A total of 13 patients (1.2%) experienced a TEAE that led to study drug withdrawal: 3 ( $<1\%$ ) in the eptinezumab 100 mg group, 8 (2.3%) in the eptinezumab 300 mg group, and 2 ( $<1\%$ )

in the placebo group. A total of 6 patients (1.7%) who received eptinezumab 300 mg had the study drug withdrawn due to hypersensitivity. Three of these events occurred after the first dose and 3 after the second dose. All were mild to moderate in severity, were considered related to the study drug, and occurred on the treatment day. Five of the 6 events resolved on the same day as onset (1 resolved within 2 days). The occurrence of individual symptoms or symptom constellations coded as the preferred term of hypersensitivity was based on the sponsor's established framework for evaluating treatment day events. The clinical presentation of these events was most commonly reported as nonspecific allergy-type reactions. Hypersensitivity symptoms (i.e., immunoglobulin E mediated) such as hives, angioedema, and documented respiratory manifestations were rare.

One patient who received eptinezumab 300 mg experienced an SAE of seizure that required hospitalization and led to

**Figure 3** Primary endpoint: Change from baseline to week 12 in mean monthly migraine days (full analysis population)



study drug withdrawal. This SAE was assessed by the investigator as not related to the study drug and resolved on the same day as the hospitalization. All TEAEs of special interest occurred in <1% of the total eptinezumab and placebo groups.

### Anti-drug antibodies

The incidence of anti-eptinezumab antibodies was maximal at 24 weeks (eptinezumab 100 mg 56 of 326 patients, eptinezumab 300 mg 56 of 329 patients) and then declined despite continuation of dosing (week 32: eptinezumab 100 mg 37 of 325, eptinezumab 300 mg 29 of 321 patients). There was no clear dose-response trend in the number of patients with anti-drug antibody (ADA)-positive results. Among ADA-positive patients, 26 in the eptinezumab 100 mg group and 19 in the eptinezumab 300 mg group had ADAs with neutralizing potential (NABs). The incidence of NABs generally increased over time from week 2 to 24 (except at week 4). Of the 112 ADA-positive patients at week 24, NAB-positive status was reported in 24 patients (21.4%). Formation of ADAs with or without neutralizing potential did not affect efficacy (change in MMDs over weeks 1–12 for ADA-positive vs ADA-negative patients: eptinezumab 100 mg –6.1 vs –8.1, eptinezumab 300 mg –9.3 vs –8.1, respectively). Similarly, the results showed no evidence of an impact from the development of ADA, including NABs, on the safety profile of eptinezumab.

## Discussion

PROMISE-2 demonstrated that both the 100 and 300 mg doses of eptinezumab resulted in significant reductions in the primary endpoint, MMDs, over weeks 1 to 12 after the first IV administration. The  $\geq 75\%$  and  $\geq 50\%$  migraine responder rates for the eptinezumab 100 mg and 300 mg dose groups

were greater than for placebo. These findings are consistent with previous results from the phase 2 study of CM.<sup>22</sup>

The preventive effects of eptinezumab in patients with CM were demonstrated on the first day after administration. During the baseline run-in phase, patients experienced a migraine headache on 57.5% of days. On day 1 after administration, 42.3% of placebo-treated patients reported having a migraine headache compared with 28.6% of patients treated with eptinezumab 100 mg and 27.8% of patients treated with eptinezumab 300 mg. This >50% reduction in migraine the day after dosing is statistically significant. The reduction in migraine that occurred on day 1 was maintained throughout the study. Over weeks 1 to 4, migraine occurred in 30.6% in the eptinezumab 100 mg group, 27.9% in the eptinezumab 300 mg group, and 38.9% in the placebo group.

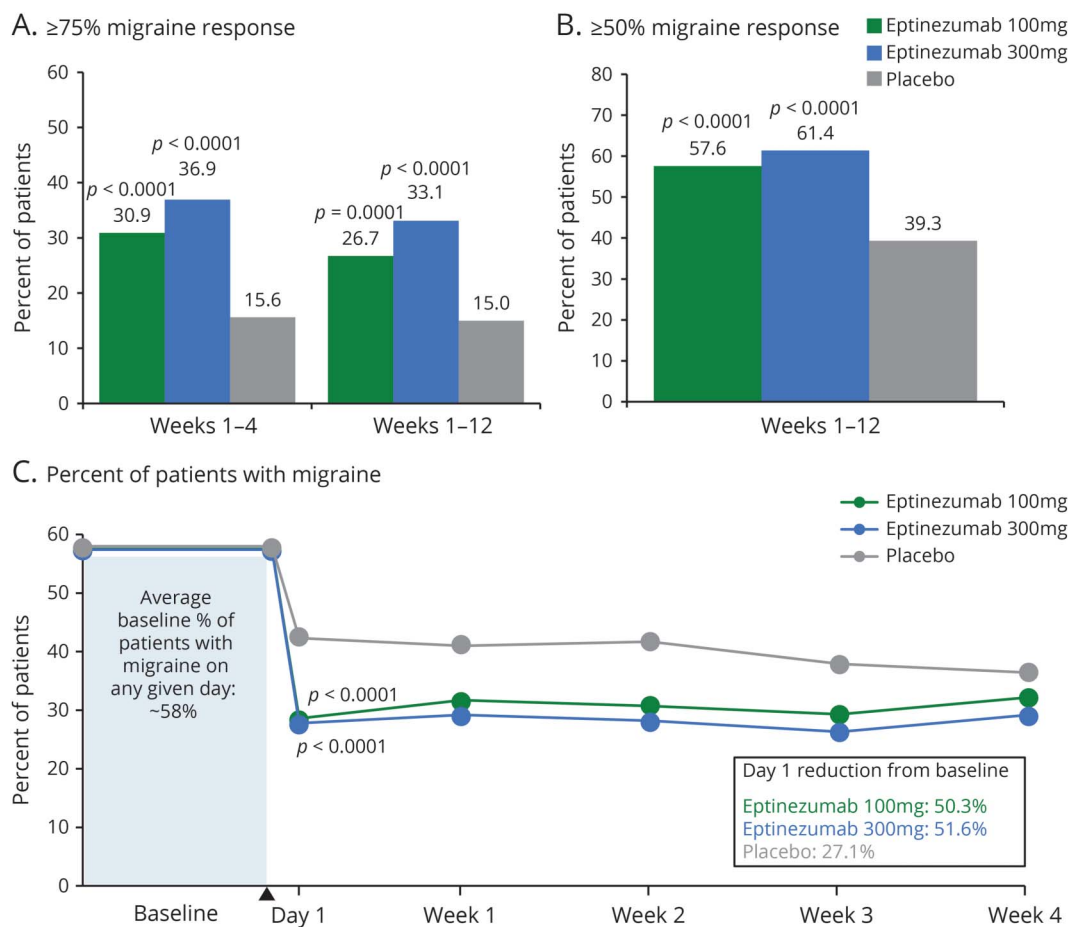
Speed of onset of preventive benefit is viewed by patients as desirable, second only to effectiveness.<sup>23</sup> Current oral preventive therapies usually require dose titration and develop benefits over weeks to months.<sup>24</sup> Early onset of effect with eptinezumab may translate into meaningful benefits for patients with CM, allowing them to get back to work, school, household, and family obligations sooner than with previously available options.

Treatment with either dose of eptinezumab was associated with reductions in days of acute medication use. Reduction in acute medication use is an important benefit because overuse of acute medication is associated with headache exacerbation, side effects, and cost.<sup>25</sup> Reduction in acute medication use has been identified as a positive factor influencing patient acceptance of preventive therapy.<sup>26</sup> Eptinezumab was well tolerated in this study. The percentages of patients with any TEAEs were similar across the active and placebo groups; most events were mild or moderate in severity, and no deaths were reported. Eptinezumab was similarly well tolerated in previous clinical study reports.<sup>22,27</sup>

The immune response to eptinezumab was characterized by positive ADA results at every time point through week 32 (peak at week 24), with no clear dose-response trend in the number of patients with ADA. The data show a remarkably consistent treatment response to both the 100 and 300 mg doses of eptinezumab, with no impacts on the safety or efficacy profiles of the drug.

PROMISE-2 was designed for consistency with guidelines recently (2018) updated by the International Headache Society Clinical Trials Standing Committee.<sup>28</sup> It should be noted that individuals with a history or evidence of significant cardiovascular disease or any clinically significant concurrent medical condition were excluded from participation; thus, the findings may not be indicative of safety and efficacy in patients with excluded comorbid conditions.

**Figure 4** Key secondary endpoints (full analysis population)



(A) ≥75% migraine responder rates, (B) ≥50% migraine responder rates, and (C) patients with migraine on day 1 and during weeks 1 to 4.

The overall response to placebo was high in this trial. High placebo rates may be attributed to a number of factors, including the novelty of treatment, route of administration, number of active treatment arms increasing patient expectations, and number of patients previously naive to preventive

therapy.<sup>29-35</sup> The intensive amount of patient contact with migraine care experts throughout the trial also may have contributed to the higher-than-expected placebo response, including professionally supervised IV administration and frequent follow-up contact via telephone and in-person visits.

**Table 3** TEAEs reported in ≥2% of patients in any treatment group (safety population)

	Eptinezumab 100 mg (n = 356), n (%)	Eptinezumab 300 mg (n = 350), n (%)	Placebo (n = 366), n (%)	Total study (n = 1,072), n (%)
<b>Any event</b>	155 (43.5)	182 (52.0)	171 (46.7)	508 (47.4)
<b>Nasopharyngitis</b>	19 (5.3)	33 (9.4)	22 (6.0)	74 (6.9)
<b>Upper respiratory tract infection</b>	15 (4.2)	19 (5.4)	20 (5.5)	54 (5.0)
<b>Sinusitis</b>	7 (2.0)	9 (2.6)	15 (4.1)	31 (2.9)
<b>Migraine</b>	6 (1.7)	8 (2.3)	16 (4.4)	30 (2.8)
<b>Urinary tract infection</b>	8 (2.2)	12 (3.4)	6 (1.6)	26 (2.4)
<b>Nausea</b>	6 (1.7)	12 (3.4)	7 (1.9)	25 (2.3)
<b>Fatigue</b>	8 (2.2)	6 (1.7)	7 (1.9)	21 (2.0)

Abbreviation: TEAE = treatment-emergent adverse event.

Despite the high placebo rates, statistical significance was achieved for eptinezumab 100 mg and 300 mg for the primary and all secondary endpoints.

The results of this study demonstrate that IV eptinezumab (100 and 300 mg) is associated with a clinically meaningful migraine preventive effect over multiple efficacy measures, is well tolerated, and has an acceptable safety profile in adult patients with CM. The migraine preventive effect of eptinezumab 100 and 300 mg was observed as early as day 1 after administration, with >50% of patients reporting a significant decrease in migraine incidence compared to baseline levels. Furthermore, during the first month after the initial administration, more than one-third of patients in the eptinezumab 100 and 300 mg groups experienced a  $\geq 75\%$  reduction in migraine days. Similar meaningful results were reported for clinical and patient-reported outcomes as early as month 1. The migraine preventive effect of eptinezumab 100 and 300 mg was maintained throughout the full 12-week dosing interval, with patients who received a single dose of eptinezumab experiencing significantly greater reductions from baseline in mean migraine days during weeks 1 to 12 relative to those receiving placebo.

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<b>Peter J. Goadsby, MD, PhD</b>	NIHR-Wellcome Trust King's Clinical Research Facility, King's College London, UK	Major role in the acquisition, analysis, or interpretation of data; revised manuscript critically for important intellectual content
<b>Jeff Smith, MD, FRCP</b>	Lundbeck Seattle BioPharmaceuticals, Inc, Dublin, Ireland	Major role in the conception or design of the study; revised manuscript critically for important intellectual content
<b>Barbara A. Schaeffler, MBA</b>	Lundbeck Seattle BioPharmaceuticals, Inc, Bothell, WA	Major role in the acquisition, analysis, or interpretation of data; revised manuscript critically for important intellectual content
<b>David M. Biondi, DO</b>	Cohen Veterans Bioscience, Cambridge, MA	Major role in the conception and study design and the acquisition, analysis, interpretation of data; revised manuscript critically for important intellectual content
<b>Joe Hirman, PhD</b>	Pacific Northwest Statistical Consulting, Inc, Woodinville, WA	Major role in the acquisition, analysis, or interpretation of data; revised manuscript critically for important intellectual content. Responsible for biostatistical analysis

## Appendix (continued)

Name	Location	Contribution
<b>Susan Pederson, BS</b>	Lundbeck Seattle BioPharmaceuticals, Inc, Bothell, WA	Major role in the acquisition, analysis, or interpretation of data; revised manuscript critically for important intellectual content
<b>Brent Allan, DO</b>	Global Safety Docs, Paradise Valley, AZ	Major role in the acquisition, analysis, or interpretation of data; revised manuscript critically for important intellectual content
<b>Roger Cady, MD</b>	Lundbeck Seattle BioPharmaceuticals, Inc, Bothell, WA	Major role in study design, the acquisition, analysis, interpretation of data; revised manuscript critically for important intellectual content

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