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Eptinezumab in episodic migraine: A randomized, double-blind, placebo-controlled study (PROMISE-1)

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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 episodic migraine.

Methods: The PRevention Of Migraine via Intravenous ALD403 Safety and Efficacy-1 (PROMISE-1) study was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Adults with episodic migraine were randomized to eptinezumab 30 mg, 100 mg, 300 mg, or placebo for up to four intravenous (IV) doses administered every 12 weeks. The primary endpoint was change from baseline in monthly migraine days (MMDs) over weeks 1–12.

Results: A total of 888 patients received treatment across 84 study sites. Mean MMDs at baseline was ~8.6 across treatment groups. Eptinezumab 100 mg and 300 mg met the primary endpoint, significantly reducing MMDs across weeks 1–12 compared with placebo (30 mg, −4.0; 100 mg, −3.9, $p = 0.0182$; 300 mg, −4.3; placebo, −3.2, $p = 0.0001$). Treatment-emergent adverse events were reported by 58.4% (30 mg), 63.2% (100 mg), 57.6% (300 mg), and 59.5% (placebo) of patients. Treatment-emergent adverse events reported by ≥2% of eptinezumab-treated patients at an incidence greater than placebo included: upper respiratory tract infection (30 mg, 11.4%; 100 mg, 9.9%; 300 mg, 10.3%; placebo, 7.2%), and fatigue (30 mg, 2.3%; 100 mg, 3.6%; 300 mg, 3.6%; placebo, <1%).

Conclusion: Eptinezumab (100 mg or 300 mg) significantly reduced migraine frequency, was well tolerated, and had an acceptable safety profile when used for the preventive treatment of migraine in adults with episodic migraine.

ClinicalTrials.gov identifier: NCT02559895

Keywords

Eptinezumab, ALD403, episodic migraine, efficacy, safety

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Introduction

Migraine affects over 1 billion individuals worldwide, resulting in over 45 million person-years lived with disability, making migraine the second leading cause of disability worldwide (1). Migraine symptoms interfere with family, education, and work, and contribute to the development of comorbidities such as cardiovascular disease, depression, and anxiety (2–8). Migraine can be defined as episodic or chronic based on the number of headache days per month. Episodic migraine is described as migraine with or without aura occurring in a headache pattern of <14 days per month.

Calcitonin gene-related peptide (CGRP) plays a key role in mediating and initiating migraine (9–11).

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Monoclonal antibodies blocking the CGRP ligand or receptor have demonstrated efficacy in episodic and chronic migraine (12–21). Eptinezumab (ALD403) is a humanized monoclonal antibody that selectively inhibits both α-CGRP and β-CGRP (22,23). It has a half-life ($t_{1/2}$) of 27 days (24) and was efficacious and well tolerated in randomized, double-blind, placebo-controlled, phase 2 trials conducted in adults with episodic migraine (24) or chronic migraine (25).

The PRevention Of Migraine via Intravenous ALD403 Safety and Efficacy (PROMISE) phase 3 studies evaluate the efficacy, safety, and pharmacokinetics of intravenous (IV) eptinezumab every 12 weeks in patients with episodic (PROMISE-1) or chronic migraine (PROMISE-2). This report presents the primary results of the PROMISE-1 study.

Materials and 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 guideline E6, local regulatory requirements, and the principles of the Declaration of Helsinki. All patients provided written informed consent prior to their participation. *ClinicalTrials.gov*: NCT02559895.

Study design and patients

PROMISE-1 was a parallel-group, double-blind, randomized, placebo-controlled efficacy and safety study performed at 84 sites in the USA and the Republic of Georgia from 30 September 2015 to 14 December 2017.

Adults aged 18–75 years (inclusive) with a diagnosis of migraine per ICHD criteria (26) at or before the age of 50 years were eligible for participation if they had a history of migraine for ≥12 months with ≤14 headache days per month, including ≥4 migraine days, in the 3 months prior to screening. Eligible patients were also required to have completed an electronic diary (eDiary) on ≥25 of the 28 days between the screening visit and randomization (i.e. the screening period), documenting ≤14 headache days, including ≥4 migraine days. Patients using acute migraine medications were eligible if use was limited to ≤14 days per 28-day period in the 3 months before screening and during the 28-day screening period; triptan use was limited to ≤10 days per 28-day period in the 3 months prior to screening and the 28-day screening period. Eligible patients could not regularly use (>7 days) prophylactic headache medication within 2 months prior to screening and during the 28-day period prior to randomization; short-term (<7 days/month) prophylactic treatment for menstrual migraine was allowed. Patients using barbiturates or prescription opiates ≤4 days/month were eligible if use was stable for ≥2 months prior to screening. Patients using non-prescription codeine preparations containing ≤16 mg codeine were eligible, as well as those using stable hormonal therapy (e.g. contraceptives, hormone replacement therapy).

Individuals were excluded if they had confounding pain syndromes or any pain syndrome requiring regular analgesia; uncontrolled or untreated psychiatric conditions; temporomandibular disorders; headache or migraine disorders that did not meet the ICHD-III beta version (2013) section 1.3 criteria for migraine with or without aura; present or previous malignancies; or other specified medical conditions (see Supplemental material 1 for more detail on exclusion criteria). Also excluded were patients who received any experimental unregistered therapy within 30 days or five plasma half-lives before screening; any monoclonal antibody treatment within 6 months of screening; botulinum toxin (any type) for any other reason requiring injections in the head, face, or neck within 4 months prior to screening or during the 28-day screening period; or who used approved devices, neuromodulation, neurostimulation, or injectable therapy for headache prophylaxis within 2 months prior to screening or during the 28-day screening period. Individuals were also excluded from participation if they were unable to differentiate migraine from other headaches.

Study procedures

An eDiary was provided to each patient to record information regarding migraine/headache characteristics, severity, duration, and acute migraine medication use. Patients used the eDiary for 4 weeks following the screening visit to confirm eligibility criteria and establish baseline values. Patients were instructed to complete the eDiary each trial day whether or not they had a headache. Eligible patients were randomly assigned to receive eptinezumab 30 mg, 100 mg, 300 mg, or placebo in a 1:1:1:1 ratio. Randomization was stratified by the number of migraine days recorded during the screening period (≤9 days vs. >9 days).

The total duration of the study was 60 weeks, with 12 scheduled visits (screening, day 0 [randomization], and weeks 4, 8, 12, 16, 20, 24, 28, 36, 48, and 56 [five half-lives following the final dose]). The 56 weeks were divided into two periods: a fully blinded primary

efficacy and safety period (through week 24) and a long-term safety period (through week 56). After the last patient completed the week 24 visit, study data were analyzed and unblinded results were provided to the sponsor. The study sites and patients remained blinded to individual treatment assignments until study completion. The primary efficacy analysis was based on data captured through week 12.

Patients received up to four treatments of eptinezumab or placebo (administered IV day 0, week 12, week 24, and week 36). Assignment was concealed. Upon first patient screened, study sites were provided with appropriate investigational product for each individual patient to be dosed, with subsequent treatment packs shipped automatically prior to the next scheduled treatment visit. Treatments were reconstituted in a total volume of 100 mL 0.9% saline and administered over a period of 1 hour (±15 minutes, per protocol, if required). Patients were monitored for 4 hours following treatment.

Outcome measures. Patients completed the eDiary from the time of screening through week 48; 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). A migraine day was defined as any day on which the patient had a migraine or probable migraine. A migraine was classified by the following characteristics: lasted 4–72 hours; with at least two of the following: unilateral location, pulsating quality, moderate or severe pain intensity, or aggravation by or causing avoidance of routine physical activity; and had one or more of the following: nausea and/or vomiting and photophobia and phonophobia (26). A probable migraine was a qualifying headache with two of the three preceding criteria.

The primary efficacy endpoint was the change from baseline in monthly migraine days (MMDs) over weeks 1–12, assessed using eDiary data. The key secondary efficacy endpoints were ≥75% migraine responder rate over weeks 1–4, ≥75% migraine responder rate over weeks 1–12, ≥50% migraine responder rate over weeks 1–12, and percentage of patients with a migraine on the day after dosing. Other secondary endpoints using the eDiary included change in acute migraine medication days (weeks 1–12), 100% migraine responder rates, and headache endpoints.

During the scheduled visits, patients completed several patient-reported outcome measures, including the Short-Form 36 Health Survey, EuroQol 5-Dimensions 5-Levels, and Allodynia Symptom Checklist-12 – the results of which will be published separately.

Safety was assessed via adverse event (AE) monitoring, clinical laboratory tests, vital signs measurements, physical examinations, 12-lead ECGs, and concomitant medication use. The Columbia-Suicide Severity Rating Scale (C-SSRS) (27) was administered to prospectively assess suicidal ideation and behavior. AEs of special interest (AESIs) were monitored and included hypersensitivity and anaphylaxis AEs, AEs associated with C-SSRS, cardiovascular AEs, hepatic AEs, and AEs associated with study drug administration.

Blood samples were collected on scheduled visits for analysis of immunogenicity, including monitoring the development of anti-eptinezumab antibodies and assaying for neutralizing potential.

Statistical methods. A total of 200 patients per group were required to provide at least 95% power for the primary endpoint for each comparison, assuming a treatment effect of ≥1 day and a common standard deviation of ≤2.7. These sample size calculations were performed using PASS 2008 and were based on *t*-tests that approximated the analysis of covariance (ANCOVA) used for the primary endpoint.

All randomized patients who received study medication were included in the safety and efficacy populations. For the safety analyses, patients were summarized within the treatment group for which they received treatment. For the efficacy analyses, patients were summarized within the treatment group to which they were randomly assigned.

A serial procedure was used to account for multiplicity associated with more than one dose level and for primary and secondary endpoints (Figure 1), in line with the industry guidance issued by the US Food and Drug Administration on *Multiple endpoints in clinical trials* (28); this procedure maintained a study-wide two-sided 5% alpha level. This procedure started with eptinezumab 300 mg versus placebo comparison for the primary endpoint. If this was significant, testing continued in the series for a subset of key secondary endpoints for eptinezumab 300 mg versus placebo. If all *p*-values were significant in this first series, the procedure moved on to the primary endpoint for eptinezumab 100 mg and subsequently to the same subset of key secondary endpoints as tested for the 300 mg group. If all *p*-values were significant in the second series, the procedure moved on to the remaining key secondary endpoint for eptinezumab 300 mg and 100 mg. Eptinezumab 30 mg was tested only if all the preceding primary and key secondary endpoints had reached statistical significance for eptinezumab 300 mg and 100 mg. The term "unadjusted" will be used to indicate tests with observed *p*-values <0.05 that failed to be statistically significant due to a failed test earlier in the testing algorithm (see Supplemental material 2 for more detail).

For the primary endpoint, an ANCOVA model with change from baseline as the response variable and

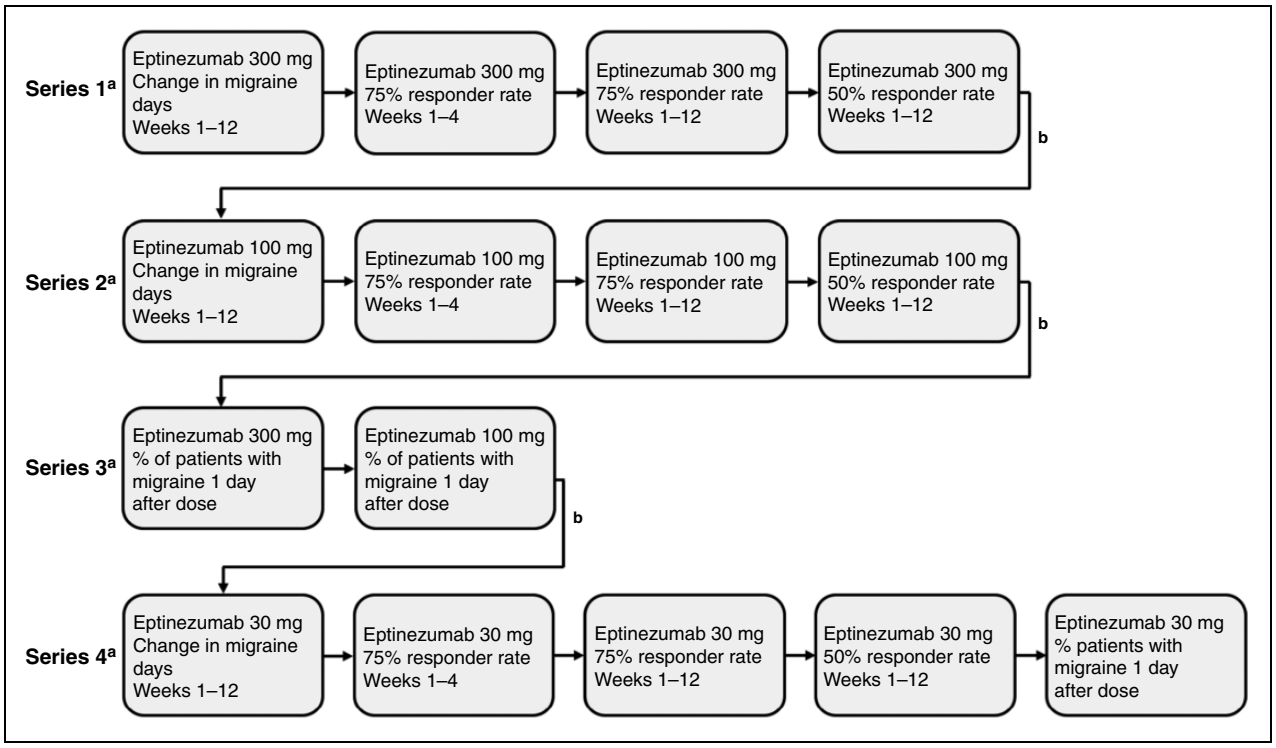

Figure 1. Decision rule for dose levels (primary and key secondary endpoints).
[a]Statistical significance must have been met to proceed to the next test within each series.
[b]To proceed to the next series, all tests in the previous series must have shown a statistically significant difference from placebo.

treatment and baseline migraine days as independent variables was used to test for a difference between treatment arms. Model-based estimates, including confidence intervals for the treatment differences, were used to summarize the results. Normalization was used to address missing migraine data in the primary efficacy analysis. If the eDiary was completed for $\geq$21 days of a 4-week interval, the observed frequency was normalized to 28 days by multiplying by the inverse of the completion rate. If the eDiary 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 eDiary had been completed.

For the key secondary endpoints, testing was based on Cochran-Mantel-Haenszel (CMH)/extended CMH tests. The tests were stratified by the randomization stratification factor. Exploratory and safety endpoints were summarized using descriptive statistics. All analyses were conducted using SAS software (SAS Institute, Inc., Cary, NC, USA) v9.2 or higher.

Results

A total of 2413 patients provided informed consent and were screened for study inclusion. Of these patients, 1515 patients were not randomized to treatment primarily due to reasons related to inclusion criteria (n = 1210, 79.9%), specifically inability to accurately complete the headache eDiary (n = 653/1210, 43.1%), ineligible migraine history (n = 222/1210, 14.7%), and unwilling to comply with study protocol (n = 196/1210, 12.9%). A total of 898 patients were randomized to receive treatment; 888 received treatment and were included in the efficacy population (Figure 2). A total of 193 patients (21.7%) across the full duration of the study (eptinezumab 30 mg, n = 52 [33.9%]; eptinezumab 100 mg, n = 45 [20.4%]; eptinezumab 300 mg, n = 43 [19.4%]; placebo, n = 54 [24.3%]) discontinued treatment early; the incidence of patients who discontinued treatment early was generally balanced across the treatment groups. The most frequently reported reasons for early treatment discontinuation were withdrawal of consent (total population, n = 98, [10.9%]; 30 mg, n = 23 [10.3%]; 100 mg, n = 20 [8.9%]; 300 mg, n = 23 [10.3%]; placebo, n = 32 [14.2]) and loss to follow-up (total population, n = 43 [4.8%]; 30 mg, n = 7 [3.1%]; 100 mg, n = 12 [5.3%]; 300 mg, n = 11 [4.9%]; placebo, n = 13 [5.8%]). There were 212 patients (23.9%) who discontinued the study early, and the most frequently reported reasons were withdrawal by patient (133 patients [15.0%]) and loss to follow-up (67 patients [7.5%]). Overall, 835 of 888

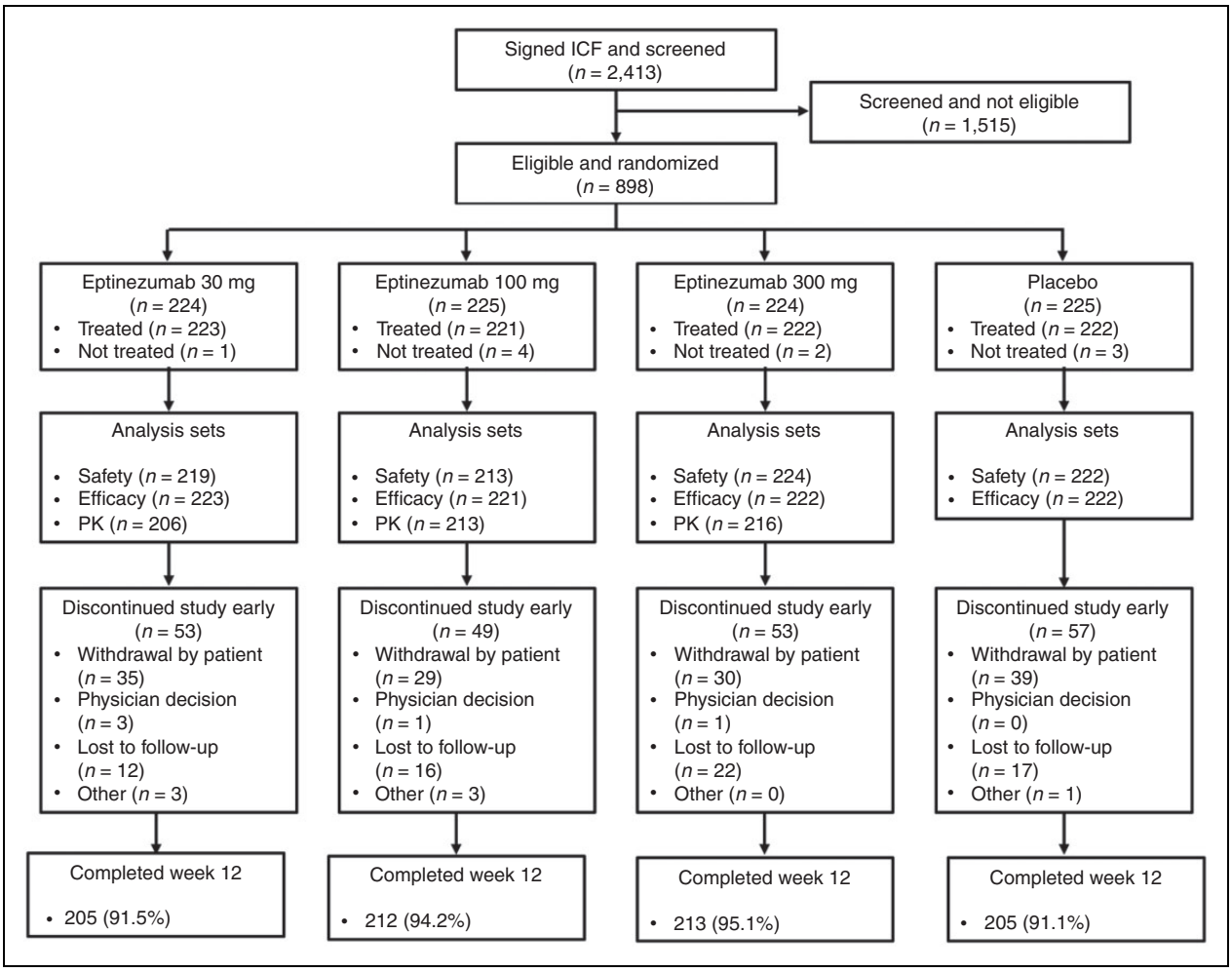

Figure 2. Patient disposition.
ICF: informed consent form; PK: pharmacokinetics.

patients (94.0%) remained in the study until week 12 (the end of the primary efficacy time period) with a total of 694 patients (78.2%) attending the week 48 visit.

Demographic and baseline clinical characteristics are summarized in Table 1. The mean patient age was 39.8 years, with 61.4% of patients >35 years of age. The majority of patients were female (84.3%), white (83.8%), and not Hispanic or Latino (81.9%).

Migraine history was well balanced across treatment groups. The mean number of MMDs during the 28-day screening period was ~8.6 across treatment groups; approximately one-fourth of patients used at least one headache medication during this time period. At baseline, the mean percentage of days with ergotamine, triptan, and opioid usage was 0.1%, 5.4%, and 0.4%, respectively. Medical and surgical history (including menstrual medical history) also was generally well balanced, with no clinically relevant differences identified across treatment groups.

Nearly all patients (98.8%) reported using at least one concomitant medication 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 (86.0%), musculoskeletal system medications (56.5%), alimentary tract and metabolism medications (32.3%), and respiratory system medications (31.1%).

Efficacy findings

Primary efficacy endpoint

Eptinezumab 100 mg and 300 mg demonstrated statistically significant reduction from baseline in the frequency of migraine days during weeks 1–12 compared to placebo (eptinezumab 30 mg, −0.82 [95% confidence interval (CI) −1.39, −0.25], $p = 0.0046$ vs. placebo

Table 1. Demographics and baseline characteristics (safety population).

	Eptinezumab				
	30 mg n = 219	100 mg n = 223	300 mg n = 224	Placebo n = 222	Total n = 888
Mean (SD) age, y	39.1 (11.54)	40.0 (10.66)	40.2 (11.72)	39.9 (11.67)	39.8 (11.39)
Sex, n (%)					
Male	34 (15.5)	44 (19.7)	25 (11.2)	36 (16.2)	139 (15.7)
Female	185 (84.5)	179 (80.3)	199 (88.8)	186 (83.8)	749 (84.3)
Ethnicity, n (%)					
Hispanic or Latino	45 (20.5)	42 (18.8)	40 (17.9)	34 (15.3)	161 (18.1)
Not Hispanic or Latino	174 (79.5)	181 (81.2)	184 (82.1)	188 (84.7)	727 (81.9)
Race, n (%)					
White	180 (82.2)	196 (87.9)	187 (83.5)	181 (81.5)	744 (83.8)
Black or African American	31 (14.2)	17 (7.6)	27 (12.1)	30 (13.5)	105 (11.8)
Asian	1 (<1)	1 (<1)	1 (<1)	2 (<1)	5 (<1)
American Indian or Alaska Native	0	0	2 (<1)	1 (<1)	3 (<1)
Native Hawaiian or other Pacific Islander	0	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Multiple races	5 (2.3)	7 (3.1)	5 (2.2)	5 (2.3)	22 (2.5)
Other	2 (<1)	1 (<1)	1 (<1)	2 (<1)	6 (<1)
Mean (SD) weight, kg	82.0 (23.27)	82.4 (23.38)	80.2 (20.88)	82.4 (21.73)	81.8 (22.32)
Mean (SD) height, cm	165.6 (8.40)	167.3 (9.13)	166.4 (8.09)	166.7 (9.16)	166.5 (8.72)
Mean (SD) BMI, kg/m^2	29.9 (8.32)	29.4 (7.66)	28.9 (7.14)	29.6 (7.28)	29.4 (7.60)
Mean (SD) age at migraine diagnosis, y	22.2 (10.31)	22.5 (10.77)	22.0 (9.87)	23.1 (10.87)	22.4 (10.45)
Mean (SD) duration of migraine diagnosis at baseline, y	17.0 (10.93)	17.4 (11.18)	18.2 (11.75)	16.9 (11.23)	17.4 (11.27)
Mean (SD) number of headache days[a]	10.2 (3.35)	10.0 (3.02)	10.1 (3.06)	9.9 (2.83)	
Mean (SD) number of migraine days[a]	8.7 (3.05)	8.7 (2.85)	8.6 (2.87)	8.4 (2.68)	
Mean (SD) % days with headache medication usage[b]					
N	219	221	223	221	884
Any	24.9 (18.65)	24.7 (17.44)	26.1 (19.40)	24.7 (19.14)	25.1 (18.65)
Ergotamine	0.2 (1.95)	0.2 (2.35)	0.1 (0.80)	0	0.1 (1.58)
Triptan	5.2 (9.00)	5.3 (9.48)	5.8 (9.96)	5.5 (9.09)	5.4 (9.38)
Opioid	0.5 (2.83)	0.2 (0.86)	0.5 (2.86)	0.6 (3.02)	0.4 (2.55)

[a]Full analysis population; mean eDiary-reported migraine and headache characteristics during the 28-day screening period.
[b]eDiary-reported medications (for each patient, the denominator for the percentage was the number of days with a non-missing evening report for the selected interval; only patients who completed the evening report at least half the time for the selected interval were included).
BMI: body mass index; SD: standard deviation.

[unadjusted]; eptinezumab 100 mg, −0.69 [−1.25, −0.12], $p = 0.0182$ vs. placebo; eptinezumab 300 mg, −1.11 [−1.68, −0.54], $p = 0.0001$ vs. placebo; Figure 3, Table 2). Mean MMDs at baseline (during the 28-day screening period) were 8.7 (standard deviation [SD], 3.05) in the eptinezumab 30 mg group, 8.7 (2.85) in the eptinezumab 100 mg group, 8.6 (2.87) in the eptinezumab 300 mg group, and 8.4 (2.68) in the placebo group; during weeks 1–12, mean MMDs were 4.6 (4.2, 5.0), 4.7 (4.3, 5.1), 4.3 (3.9, 4.7), and 5.4 (5.0, 5.8), respectively.

Key secondary efficacy endpoints

The ≥75% migraine responder rates (weeks 1–4 and weeks 1–12) and ≥50% migraine responder rates (weeks 1–12) are summarized in Figure 4 and Table 2. The ≥75% migraine responder rates for weeks 1–4 were 30.0% for eptinezumab 30 mg, 30.8% for eptinezumab 100 mg, 31.5% for eptinezumab 300 mg, and 20.3% for placebo (Figure 4, Table 2). Patients treated with eptinezumab were more likely to achieve ≥75% migraine response during weeks 1–4

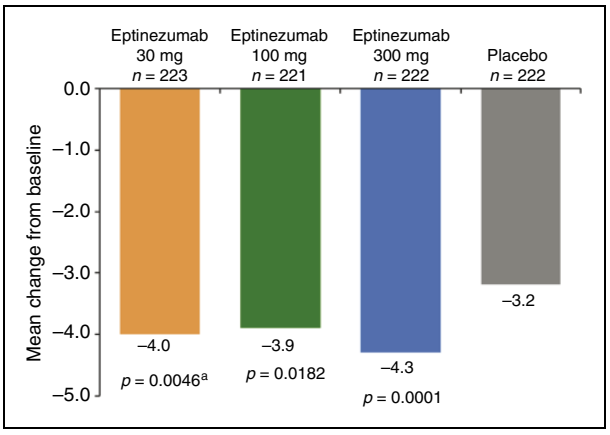

Figure 3. Primary endpoint: Change from baseline to week 12 in mean monthly migraine days (full analysis population).
[a]Not statistically significant per the testing hierarchy; unadjusted *p*-value presented.

than were patients in the placebo group (difference from placebo [95% CI] of 9.8% [1.7, 17.8; $p = 0.0170$] for eptinezumab 30 mg; 10.5% [2.5, 18.6; $p = 0.0112$] for eptinezumab 100 mg; and 11.3% [3.2, 19.3; $p = 0.0066$] for eptinezumab 300 mg). For weeks 1–12, corresponding ≥75% responder rates were 24.7%, 22.2%, 29.7%, and 16.2%, respectively. The ≥50% migraine responder rates for weeks 1–12 were 50.2% for eptinezumab 30 mg, 49.8% for eptinezumab 100 mg, 56.3% for eptinezumab 300 mg, and 37.4% for placebo. Data from the eptinezumab 300 mg treatment group demonstrated that monthly ≥75% migraine responder rates were sustained throughout the 12-week interval (31.5% during weeks 1–4 and 29.7% during weeks 1–12). Patients in all eptinezumab groups were more likely to achieve ≥50% or ≥75% migraine reduction during weeks 1–12 than were patients in the placebo group. Odds ratios versus placebo for ≥75% migraine response during this time period were 1.7 (95% CI: 1.1, 2.7) for eptinezumab 30 mg, 1.5 (0.9, 2.4) for eptinezumab 100 mg, and 2.2 (1.4, 3.4) for eptinezumab 300 mg; those for ≥50% migraine response were 1.7 (1.2, 2.5), 1.7 (1.1, 2.4), and 2.2 (1.5, 3.2), respectively.

An observed migraine preventive effect of eptinezumab was observed on the first day after dosing. At baseline (28-day screening period), the average percentage of patients with a migraine on any given day was 30.7%. On the first day after dosing, the percentage of patients with a migraine was 17.3% in the eptinezumab 30 mg group, 14.8% in the eptinezumab 100 mg group, and 13.9% in the eptinezumab 300 mg group versus 22.5% in the placebo group ($p = 0.1539$, $p = 0.0312$, and $p = 0.0159$ vs. placebo [all unadjusted], respectively).

Safety findings. A total of 888 patients received at least one dose of study medication. The majority of patients (n = 691 [77.8%]) received all four doses, including 76.3% of patients in the eptinezumab 30 mg group, 79.4% of patients in the eptinezumab 100 mg group, 80.4% of patients in the eptinezumab 300 mg group, and 75.2% of patients in the placebo group. There were no deaths reported in this study.

Adverse events

Across the study, 530 patients (59.7%) experienced at least one treatment-emergent adverse event (TEAE). The incidence of TEAEs was generally balanced among treatment groups; no dose-related trends in TEAE incidence were observed (Table 3). For most patients, these events were mild or moderate. Twenty-five patients (2.8%) had severe TEAEs. One patient in the placebo group had a life-threatening serious adverse event (SAE) of chronic obstructive pulmonary disease (COPD) and apnea related to COPD. The SAE of COPD led to study drug discontinuation.

A total of 84 (12.6%) patients who received eptinezumab and 19 (8.6%) patients who received placebo had at least one study-drug-related TEAE, as determined by the investigator. The most frequently reported study-drug-related TEAEs were nausea (n = 14 [1.6%]) and fatigue (n = 12 [1.4%]); the remaining study-drug-related TEAEs were reported in <1% of patients.

In total, 17 patients (1.9%) experienced a serious TEAE, 11 of whom (1.7%) received eptinezumab and 6 (2.7%) received placebo. The most frequently reported serious TEAEs by system organ class were injury, poisoning, and procedural complications (n = 3 [<1%]) and neoplasms benign, malignant, and unspecified, including cysts and polyps (n = 3 [<1%]). None were considered related to study drug.

A total of 29 patients (3.3%) experienced a TEAE that led to study drug withdrawal: 12 (5.5%) in the eptinezumab 30 mg group, six (2.7%) in the eptinezumab 100 mg group, five (2.2%) in the eptinezumab 300 mg group, and six (2.7%) in the placebo group. Six of these events were serious (acute kidney injury, stomal hernia, and rhabdomyolysis, all with eptinezumab 30 mg, and intervertebral disc protrusion, COPD, and stage II breast cancer with placebo); no SAEs were considered related to study treatment and all except for stage II breast cancer were resolved at study completion. Seven (1.1%) patients who received eptinezumab had study drug withdrawn due to hypersensitivity: n = 4 (1.8%) in the eptinezumab 30 mg group, n = 1 (<1%) in the eptinezumab 100 mg group, and n = 2 (<1%) in the eptinezumab 300 mg group. All incidences of

Table 2. Summary of efficacy (full analysis population).

	Eptinezumab			
	30 mg n = 223	100 mg n = 221	300 mg n = 222	Placebo n = 222
Mean MMDs, weeks 1–12				
Actual				
Mean	4.6	4.7	4.3	5.4
(95% CI)	(4.18, 5.00)	(4.32, 5.12)	(3.89, 4.70)	(5.00, 5.81)
Change from baseline				
Mean	−4.0	−3.9	−4.3	−3.2
(95% CI)	(−4.41, −3.61)	(−4.28, −3.47)	(−4.70, −3.90)	(−3.60, −2.79)
Difference from placebo (95% CI)	−0.82 (−1.39, −0.25)	−0.69 (−1.25, −0.12)	−1.11 (−1.68, −0.54)	
p-value vs. placebo	0.0046[a]	0.0182	0.0001	
75% migraine responder rate, weeks 1–4				
Patients, n (%)	67 (30.0%)	68 (30.8%)	70 (31.5%)	45 (20.3%)
Difference from placebo (95% CI)	9.8% (1.8%, 17.8%)	10.5% (2.4%, 18.6%)	11.3% (3.2%, 19.3%)	
p-value vs. placebo	0.0170[a]	0.0112	0.0066	
Odds ratio vs. placebo	1.694	1.752	1.817	
75% migraine responder rate, weeks 1–12				
Patients, n (%)	55 (24.7)	49 (22.2%)	66 (29.7%)	36 (16.2%)
Difference from placebo (95% CI)	8.4 (1.0, 15.9)	6.0% (−1.4%, 13.3%)	13.5% (5.8%, 21.2%)	
p-value vs. placebo	0.0272[a]	0.1126	0.0007	
Odds ratio vs. placebo	1.686	1.470	2.179	
50% migraine responder rate, weeks 1–12				
Patients, n (%)	112 (50.2)	110 (49.8)	125 (56.3)	83 (37.4)
Difference from placebo (95% CI)	12.8% (3.7%, 22.0%)	12.4% (3.2%, 21.5%)	18.9% (9.8%, 28.0%)	
p-value vs. placebo	0.0064[a]	0.0085[a]	0.0001	
Odds ratio vs. placebo	1.691	1.662	2.158	
Patients with migraine 1 day after dosing				
Baseline percentage[b]	31.0%	31.0%	30.8%	29.8%
Day 1 percentage	17.3%	14.8%	13.9%	22.5%
p-value vs. placebo	0.1539	0.0312[a]	0.0159[a]	

[a]Not statistically significant per the testing hierarchy; unadjusted *p*-value presented.
[b]Baseline is the daily average over the 28-day screening period prior to receiving treatment.
CI: confidence interval; MMDs: monthly migraine days.

hypersensitivity were mild to moderate in severity, considered related to study drug, and resolved the same day.

Anti-drug antibodies

The incidence of anti-eptinezumab antibodies was maximal at 24 weeks (eptinezumab 30 mg, 18/185 [9.7%]; eptinezumab 100 mg, 35/189 [18.5%]; eptinezumab 300 mg, 34/194 [17.5%]) and then markedly declined by week 56 (30 mg, 10/169 [5.9%]; 100 mg, 12/173 [6.9%]; 300 mg, 7/170 [4.1%]). A dose-response trend in the number of patients with anti-drug antibodies (ADAs) was observed after week 8. Among ADA-positive patients, 14 patients in the 30 mg group, 22 patients in the 100 mg group, and 16 patients in the 300 mg group had ADAs with neutralizing potential (NAb). The incidence of NAbs generally increased over time from week 8 to week 24 (except at week 16), and then decreased after week 24. Of the 87 ADA-positive patients at week 24, 39 patients were NAb positive. There was no dose-response trend related to NAb-positive observations. Overall NAb-positive incidence was 7.8% (52 of 666 treated). Importantly, formation of ADAs with or without NAb did not affect efficacy (change in MMDs over weeks 1–12 for ADA-positive vs. ADA-negative patients: 30 mg, −4.3 vs. −4.0; 100 mg, −4.3 vs. −3.8; 300 mg, −3.9 vs. −4.4). Similarly, the development of ADAs, including NAbs, had no impact on the safety profile of eptinezumab.

Discussion

These results demonstrate a statistically significant and clinically meaningful migraine preventive effect of

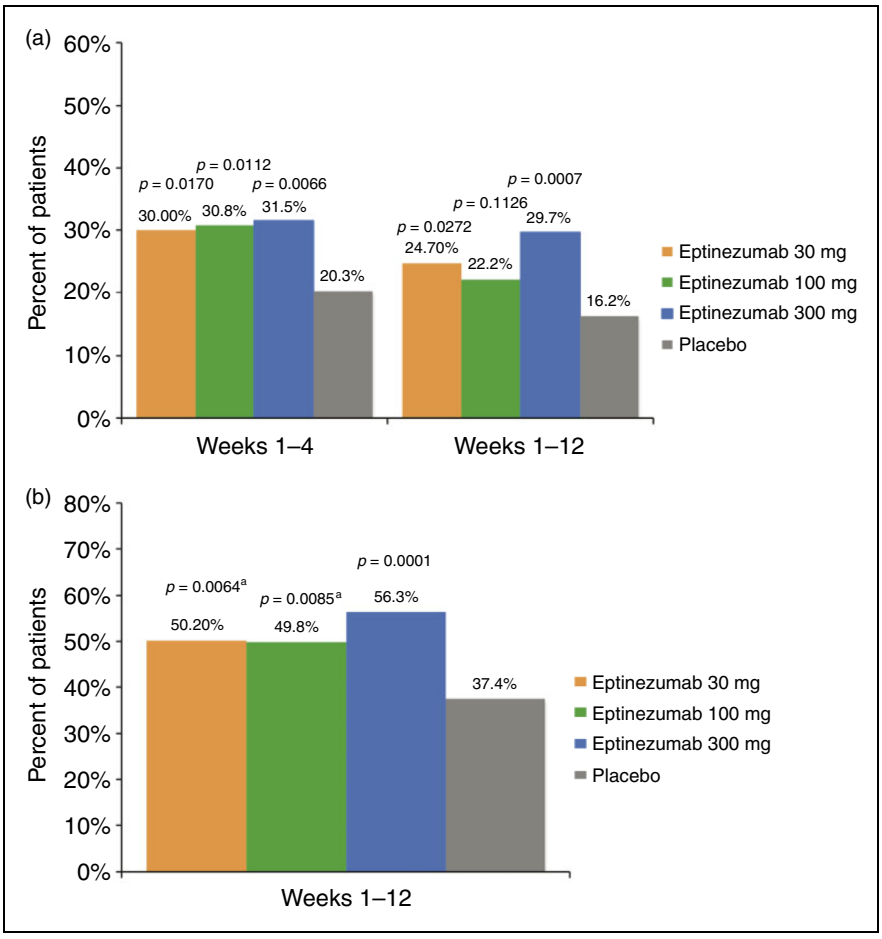

Figure 4. Key secondary endpoints: (a) ≥75% migraine responder rates and (b) ≥50% migraine responder rates (full analysis population).
[a]Not statistically significant per the testing hierarchy; unadjusted *p*-value presented.

Table 3. Treatment-emergent adverse events reported in ≥ 2% of patients (safety population).

	Eptinezumab				
	30 mg n = 219	100 mg n = 223	300 mg n = 224	Placebo n = 222	Total n = 888
Any event, n (%)	128 (58.4)	141 (63.2)	129 (57.6)	132 (59.5)	530 (59.7)
Upper respiratory tract infection	25 (11.4)	22 (9.9)	23 (10.3)	16 (7.2)	86 (9.7)
Nasopharyngitis	14 (6.4)	17 (7.6)	14 (6.3)	12 (5.4)	57 (6.4)
Sinusitis	7 (3.2)	6 (2.7)	11 (4.9)	14 (6.3)	38 (4.3)
Dizziness	8 (3.7)	10 (4.5)	4 (1.8)	8 (3.6)	30 (3.4)
Nausea	9 (4.1)	5 (2.2)	5 (2.2)	8 (3.6)	27 (3.0)
Bronchitis	5 (2.3)	6 (2.7)	7 (3.1)	8 (3.6)	26 (2.9)
Cough	1 (<1)	8 (3.6)	6 (2.7)	7 (3.2)	22 (2.5)
Fatigue	5 (2.3)	8 (3.6)	8 (3.6)	1 (<1)	22 (2.5)
Back pain	4 (1.8)	7 (3.1)	3 (1.3)	7 (3.2)	21 (2.4)
Influenza	3 (1.4)	4 (1.8)	8 (3.6)	5 (2.3)	20 (2.3)
Diarrhea	4 (1.8)	3 (1.3)	8 (3.6)	3 (1.4)	18 (2.0)

eptinezumab in patients with episodic migraine over weeks 1–12 following the first IV administration. The ≥75% migraine responder rates were 24.7% for patients treated with eptinezumab 30 mg, 22.2% for 100 mg, and 29.7% for 300 mg, compared with 16.2% for placebo, with ≥50% responder rates of 50.2%, 49.8%, 56.3%, and 37.4%, respectively. These findings are consistent with previous phase 2 results in patients with episodic migraine, where 33% of patients treated with eptinezumab 1000 mg experienced a ≥75% reduction in monthly migraine days over 12 weeks compared with 9% in the placebo group (24). Similarly, 51% of patients receiving eptinezumab 1000 mg demonstrated a ≥50% reduction in MMDs compared to 33% in those patients receiving placebo (24).

The preventive effects of eptinezumab in patients with episodic migraine were observed as early as the first day after administration (day 1), with a >50% reduction in the percentage of patients with a migraine on day 1 compared to baseline in the 100 mg and 300 mg treatment groups. The results seen on the first day following the administration, if normalized to a 28-day period, are reflective of the prevalence observed over weeks 1–12. During the first month following administration, nearly a third of patients treated with eptinezumab 100 mg (30.8%) and 300 mg (31.5%) experienced a ≥75% reduction in migraine days. The migraine preventive effect of eptinezumab was maintained over the full 12-week dosing interval, with patients receiving eptinezumab experiencing significantly greater reductions from baseline in mean migraine days during weeks 1–12 relative to placebo (the primary endpoint). Within the statistical testing hierarchy, eptinezumab 30 mg did not achieve significance for any of the prespecified primary and key secondary endpoints; thus, formal statistical testing of the remaining endpoints was not performed (for more information, please see Supplemental material 3).

Eptinezumab treatment demonstrated acceptable safety and tolerability across doses compared to placebo, with no apparent dose-related trend in the nature, frequency, or severity of TEAEs. Study-drug–related TEAEs were low (eptinezumab, all doses, 12.6%; placebo, 8.6%), in line with previously reported studies for eptinezumab (24,29,30) and the anti-CGRP class (16,19,21). The percentage of patients with any TEAE was similar across the eptinezumab and placebo groups, with most events being mild or moderate in severity.

All anti-drug antibodies (ADAs) bind to the therapeutic and, as such, are considered binding antibodies (31,32). Binding antibodies may or may not have clinical impact. Neutralizing antibodies (NAbs) are a subset of binding antibodies that, from an *in vitro* assessment, show the potential to inhibit biological activity by interfering with interactions between the therapeutic and its target (31,32). The key term is neutralizing "potential". The ability to neutralize eptinezumab activity *in vivo* should not be automatically assumed based on the presence of NAbs that were determined using an *in vitro* assay. It is important to recognize that the assessment of NAb is qualitative. This means that the number of NAb antibodies may be low in concentration compared to the concentration of the therapeutic agent, or they may have low binding affinity and, as such, do not result in a loss of therapeutic activity. For these reasons, immunogenicity data must be correlated with clinical safety and efficacy to determine if the ADA/NAb observations are clinically meaningful. For the PROMISE-1 study, the ADA/NAb observations were not clinically impactful.

The ADA profile observed in the PROMISE-1 study showed a clear time-related trend, exhibiting a maximal response in ADA incidence and amplitude (titer) at week 24 followed by a steady decline through week 48. Because the maximum ADA response was detected at week 24, this time point and the values at end of study week 56 were used to demonstrate the peak and the declining nature of the ADA response to eptinezumab. The ADA and NAb response profiles for eptinezumab were consistent with other studies where the maximal frequency and titer of ADA was observed at the week-24 treatment time point, regardless of dose level or number of doses administered at 12-week intervals. Neither ADA- nor NAb-positive status was associated with reduced efficacy, and there was no trend for diminishing efficacy with increasing ADA titer. These data suggest immunogenicity is unlikely to influence either induction or sustainability of the treatment response to eptinezumab. Overall, the immunogenicity results showed no evidence of an impact on the safety or efficacy profile of eptinezumab.

In the management of patients with migraine, the requirement for daily dosing and occurrences of intolerable AEs frequently complicate patient adherence to traditional migraine preventive medications and ultimately interfere with medication effectiveness. It has been estimated that up to 80% of patients suspend preventive treatment because of AEs and poor tolerance, and long-term compliance is poor even among those who do tolerate therapy (only one of five patients are compliant for up to a year) (33). Certain characteristics of eptinezumab (i.e. need for dosing only once quarterly, an acceptable tolerability profile) may help overcome these obstacles to improve patient adherence with preventive therapy. The 12-week dosing interval for eptinezumab is among the longest of the current FDA-approved CGRP monoclonal antibodies (erenumab and galcanezumab are administered monthly;

fremanezumab is administered monthly or as three simultaneous injections once per quarter) (34–36).

Study limitations

PROMISE-1 was designed utilizing guidelines for controlled trials of drugs in migraine put forth by the International Headache Society Clinical Trials subcommittee (37). Study sites were in only two countries, limiting geographic diversity. The study also enrolled low numbers of non-Caucasians and men.

The overall response to placebo was high in this trial. High rates of placebo response are common and have been attributed to a number of factors, including the novelty of treatment, number of active treatment arms increasing patient expectations, and the number of patients previously naïve to preventive therapy (38–44). The amount of patient contact with migraine care experts throughout the trial may also have contributed to the higher than expected placebo response.

These results demonstrate that eptinezumab (100 mg, as the lowest effective dose, or 300 mg) is associated with a clinically meaningful preventive effect over multiple efficacy measures, is well tolerated, and has an acceptable safety profile for the prevention of migraine in adult patients with episodic migraine. The migraine preventive effect was observed as early as the first day after IV administration (day 1), with a >50% reduction in the percentage of patients with a migraine on day 1 compared to baseline for eptinezumab 100 mg and 300 mg. Clinical results with eptinezumab 30 mg were less consistent over the same 12-week treatment period. During the first month following administration, nearly a third of patients in the eptinezumab 100 mg and 300 mg groups experienced a ≥75% reduction in migraine days. The migraine preventive effect of eptinezumab was maintained over 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 1–12 relative to placebo.

Key findings

- PROMISE-1 was a phase 3, randomized, double-blind, placebo-controlled, study evaluating intravenous eptinezumab 30 mg, 100 mg, 300 mg, or placebo for the prevention of episodic migraine.
- Results demonstrate a statistically significant and clinically meaningful migraine preventive effect of eptinezumab in patients with episodic migraine over weeks 1–12 following the first IV administration.
- The preventive effects of eptinezumab in patients with episodic migraine were observed as early as the first day after administration (day 1).
- Eptinezumab treatment demonstrated acceptable safety and tolerability across doses compared to placebo, with no apparent dose-related trend in the nature, frequency, or severity of TEAEs.

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(continued)

Continued.

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Data availability

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

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: At the time of study design, conduct, or reporting, the following disclosures were reported. MA: Consultant and/or scientific advisor, Alder BioPharmaceuticals, Allergan, Amgen, Eli Lilly, Novartis, Teva Pharmaceuticals; principal investigator, Amgen 20120178 (phase II), 20120295 (phase II), 20130255 (open-label extension), 20120297 (phase III), 20150308 (phase II), ElectroCore GM-11 gamma-Core-R, TEVA TV48125-CNS-30068 (phase III), Novartis CAMG334A2301 (phase III), Alder BioPharmaceuticals PROMISE-2 (phase III); associate editor, *Cephalalgia*, *Headache*; co-editor, *Journal of Headache and Pain*. JS: Advisory board and/or speaker, Alder BioPharmaceuticals, Autonomic Technologies, Biohaven Pharmaceuticals, Eli Lilly, Teva Pharmaceuticals; research support, Alder BioPharmaceuticals, Allergan, Amgen, Autonomic Technologies, Avanir Pharmaceuticals, Biohaven Pharmaceuticals, Colucid Pharmaceuticals, Dr. Reddy's Laboratories, Eli Lilly, Impax Pharmaceuticals, Scion NeuroStim, Teva Pharmaceuticals, Zosano Pharma. RC, BS, SP, JS: Full-time employee, Lundbeck Seattle BioPharmaceuticals, Inc. (previously known as Alder BioPharmaceuticals, Inc.); stockholder: Alder BioPharmaceuticals, Inc. DMB: Full-time employee at the time of study and manuscript development, Alder BioPharmaceuticals, Inc. (currently known as Lundbeck Seattle BioPharmaceuticals, Inc.). BA: Contracted service provider, Lundbeck Seattle BioPharmaceuticals, Inc. (previously known as Alder BioPharmaceuticals, Inc.); stockholder, Alder BioPharmaceuticals, Inc. JH: Contracted service provider, Biostatistical Resources, Lundbeck Seattle BioPharmaceuticals, Inc. (previously known as Alder BioPharmaceuticals, Inc.).

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