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RESEARCH SUBMISSIONS

Tolerability and safety of galcanezumab in patients with chronic cluster headache with up to 15 months of galcanezumab treatment

Miguel J. A. Láinez MD, PhD, FAAN, FANA, FAHS[1] | Jean Schoenen MD, PhD[2] | Chad Stroud RPh[3] | Jennifer Bardos PharmD[3] | Mark Bangs MD[3] | Phebe Kemmer PhD[3] | Richard Wenzel PharmD[3] | Dulanji K. Kuruppu MD[3] | James Michael Martinez MD[3] | Tina M. Oakes PhD[3]

[1]Hospital Clinico Universitario, Universidad Católica de Valencia, Valencia, Spain

[2]Department of Neurology, Headache Research Unit, Citadelle Hospital, Liège University, Liège, Belgium

[3]Eli Lilly and Company, Indianapolis, Indiana, USA

Correspondence
Tina M. Oakes, Eli Lilly and Company, Indianapolis, IN 46285, USA.
Email: oakes_tina_marie_myers@lilly.com

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Abstract

Objective: The objective of the study was to assess the tolerability and safety of galcanezumab in patients with chronic cluster headache (CH) with up to 15 months of treatment.

Background: Chronic CH is a highly debilitating disease with a substantial and unmet medical need.

Methods: Patients were randomized to receive placebo or galcanezumab (300 mg) monthly for 12 weeks, followed by an optional 52-week open-label extension and 16-week posttreatment follow-up (washout). This is a secondary analysis and long-term follow-up of a previously conducted clinical trial. The safety analysis included patients who received galcanezumab at any time during the study. Outcomes included adverse events (AEs), discontinuations, laboratory values, vital signs, electrocardiograms (ECGs), and suicidality ratings.

Results: A total of 233 patients received at least one galcanezumab dose. The mean exposure was 341 days. Galcanezumab-treated patients were mostly male (n = 169/233; 72.5%) with a mean age of 44.9 (±10.9) years. Treatment-emergent adverse events (TEAEs) were reported by 185 patients (n = 185/233; 79.4%), 23 patients (n = 23/233; 9.9%) reported serious adverse events (SAEs), and 18 patients (n = 18/233; 7.7%) discontinued due to AEs. The SAE CH was reported by three patients. The most common TEAEs (>10%) were nasopharyngitis (n = 41/233; 17.6%) and injection site pain (n = 33/233; 14.2%). 27.5% of patients (n = 64/233) had TEAEs related to injection sites. Likely hypersensitivity events, including injection site rash, injection site urticaria, and injection site hypersensitivity were reported (n = 14/233;

Abbreviations: ADA, antidrug antibody; AE, adverse event; ALT, alanine aminotransferase; BP, blood pressure; CGRP, calcitonin gene-related peptide; CH, cluster headache; CI, confidence interval; EAIR, exposure-adjusted incidence rate; MedDRA, Medical Dictionary for Regulatory Activities; QTcF, Fridericia's corrected QT interval; SAE, serious adverse event; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

6.0%). There were past histories of suicidal ideation (n = 55/237; 23.2%) and suicidal behavior (n = 9/236; 3.8%). During the study, 15 patients (n = 15/230; 6.5%), seven with previous history, reported suicidal ideation. One patient had a nonfatal suicide attempt during the open-label extension and an aborted attempt during the washout. There were no new safety findings compared with the placebo-controlled treatment period in laboratory values, vital signs, or ECGs.

Conclusions: Galcanezumab 300 mg monthly had a favorable tolerability and safety profile in patients with chronic CH with up to 15 months of treatment.

KEYWORDS
adverse events, calcitonin gene-related peptide monoclonal antibody, long-term exposure

INTRODUCTION

Cluster headache (CH) is an uncommon (0.1% lifetime prevalence), highly debilitating, primary headache disorder with severe unilateral headache attacks lasting 15–180 min that can occur as frequently as eight times a day.[1] A CH attack must be accompanied by at least one ipsilateral trigeminal autonomic symptom and/or agitation or restlessness.[1] Chronic CH affects 10%–15% of patients and occurs without remission or with remission periods of <3 months, for at least 1 year.[1] The disease burden of CH is substantial, and includes suicidality, which increases during attacks, compared with between attacks.[2,3]

Verapamil and lithium are drugs of first choice in the preventive treatment of CH, and they can be associated with significant adverse effects and require monitoring, including electrocardiogram (ECG) for verapamil and monitoring of lithium plasma levels.[4–8] The prescribing information for verapamil contains warnings for potential heart failure, hypotension, elevated liver enzymes, and atrioventricular block.[7] Lithium toxicity can occur at close to therapeutic doses, and dosing of lithium is dependent on achieving serum concentrations within a narrow therapeutic range.[8] Regular monitoring is recommended for both of these medications.[7,8]

Calcitonin gene-related peptide (CGRP), highly expressed in the trigeminal neurovascular system, is implicated in the pathophysiology of migraine and CH.[9–11] It is a potent microvascular vasodilator that is also widely expressed in peripheral nerve fibers innervating the heart, coronary arteries, vascular beds, and myenteric systems.[12,13] Thus, CGRP may have a protective or compensatory role in cardiovascular (CV) disease.

Galcanezumab is a humanized monoclonal antibody that potently and selectively binds CGRP without blocking the receptor.[14] Clinical evidence showed galcanezumab treatment was not associated with clinically meaningful changes in blood pressure (BP), pulse, ECG, or increases in CV treatment-emergent adverse events (TEAEs) with up to 6 months of treatment, but longer term studies are still needed.[15] The safety of galcanezumab was evaluated in 2586 patients with migraine representing 1487 patient-years of exposure, including three placebo-controlled studies of 3–6 months and open-label treatment for up to 12 months. The most common adverse reaction in the three pivotal placebo-controlled studies was injection site reactions.[16] The overall safety profile of galcanezumab in the episodic CH clinical trial was consistent with that in migraine.[14,17] Galcanezumab is approved for the preventive treatment of migraine[18] and the treatment of episodic CH in the United States.[4,16]

Here, galcanezumab was studied in a 12-week, double-blind, placebo-controlled trial with a 52-week open-label extension to evaluate its efficacy, tolerability, and safety as a potential preventive treatment for patients with chronic CH.[9] Galcanezumab did not meet the primary endpoint and the efficacy and safety data for the double-blind phase of this trial have been published previously.[9] Herein, we present the tolerability and safety findings of subcutaneous galcanezumab in patients with chronic CH who received up to 15 months of treatment in this trial.

METHODS

Study design

This phase 3, multicenter, randomized, double-blind, placebo-controlled study (NCT02438826) of galcanezumab 300 mg for the prevention of chronic CH was comprised of the following periods (Figure 1) and published previously[9]: (1) screening/washout; (2) prospective baseline; (3) double-blind, placebo-controlled treatment; (4) optional open-label extension; and (5) posttreatment follow-up (washout).[9]

Patients entered Study period II after screening and washout, and when they experienced their next CH attack. Attack information and acute medication use were recorded daily in an electronic patient-reported outcome (ePRO) diary. Baseline ePRO entries for 14 consecutive days determined study eligibility, baseline attack frequency, and baseline acute medication use. Eligible patients were then randomized (1:1) to receive 12 weeks of double-blind treatment with either subcutaneous placebo or galcanezumab 300 mg given monthly (Study period III). On completion, patients could enter an optional 1-year open-label treatment period (Study period IV), in which all patients received up to 12 monthly injections of galcanezumab. On completion or early discontinuation, patients entered a

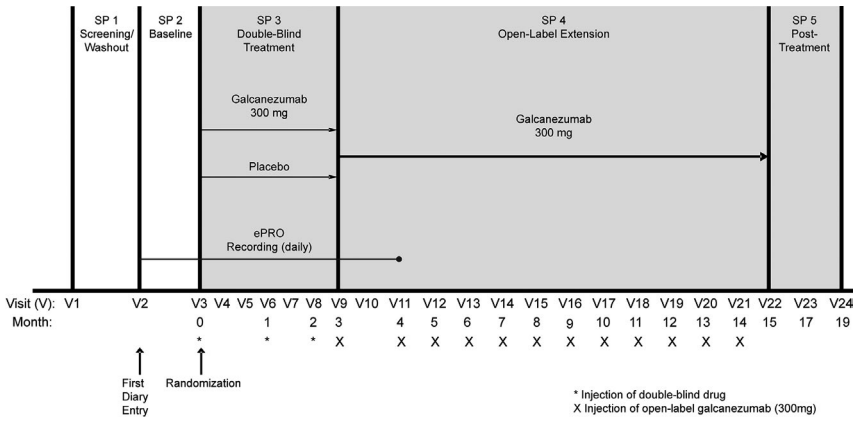

FIGURE 1 Depiction of the study design. SP 1 was the screening and washout period lasting 0–65 days. SP 2 was the prospective baseline period from 14 to 17 days. SP 3 was the double-blind treatment phase when patients received galcanezumab or placebo, and SP 4 was the open-label extension during which all patients received galcanezumab 300 mg monthly. SP 5 was the posttreatment follow-up (washout) phase. Month 0 started with Visit 3, when randomization to the treatment groups occurred and the first injections were given. Asterisks indicate blinded injection of galcanezumab 300 mg or placebo, and "x" indicates the open-label injection of galcanezumab. ePRO, electronic patient-reported outcome diary, SP, study period

16-week washout for safety follow-up (Study period V). Patients and investigators remained blind to the treatment patients received during Study period III.

Ethical approval and conduct

The study was conducted according to Good Clinical Practice and the Declaration of Helsinki guidelines. Patients provided written informed consent before undergoing study procedures.

Inclusion and exclusion criteria

The full inclusion and exclusion criteria were previously published.[9] The study included adult patients aged 18–65 years with a history of chronic CH.[19]

Patients were excluded if they had current or past exposure to an antibody to the CGRP ligand or receptor or to nerve growth factor. Patients who may have another trigeminal autonomic cephalalgia (TAC), or who were using indomethacin for a suspected TAC also were excluded. Patients were allowed the use of high-flow oxygen, triptans, acetaminophen, and nonsteroidal anti-inflammatory drugs for the acute treatment of CH attacks. Patients were allowed to use up to six prespecified preventive treatments (i.e., verapamil ≤480 mg/day, lithium, melatonin, valproate, gabapentin, and topiramate).

Exclusion criteria were published previously[9] and included any history of intracranial or carotid aneurysms, intracranial hemorrhage, or stroke, or risk for serious or acute CV events (myocardial infarction, unstable angina, coronary artery bypass graft, percutaneous coronary intervention, or pulmonary embolism/deep vein thrombosis within 6 months of screening). Patients who were considered by the investigator to be at significant risk for suicide were excluded as well.

Patient Global Impression of Improvement assessments

The Patient Global Impression of Improvement (PGI-I) scale was performed as previously described,[9] across double-blind (Month 3), open-label (Months 9 and 15), and posttreatment phases (Month 19). It is a patient-rated assessment, which measures the improvement of symptoms. In brief, the PGI is a 7-point scale where a score of 1 indicates that the patient is "very much better," a score of 4 indicates that the patient has experienced "no change," and a score of 7 indicates that the patient is "very much worse."

Safety assessments

Safety analyses were conducted for the galcanezumab-treated time (Study periods III/IV combined) and galcanezumab-treated time plus washout (Study periods III/IV/V combined). Assessments of tolerability and safety included adverse events (AEs), including TEAEs by preferred term, severity, relatedness, serious AEs (SAEs), and AEs leading to discontinuation (DCAEs). The TEAEs related to injection site were identified using the Medical Dictionary for Regulatory Activities version 20.1 (MedDRA®) high-level search term of "Injection site reactions." Potential hypersensitivity events were identified from three narrow standardized MedDRA® queries consisting of anaphylactic reaction, angioedema, and hypersensitivity. Each potential event was reviewed by a physician who was blinded to the study treatment to determine whether the identified events were likely hypersensitive in nature.

Triplicate measures of BP and pulse were collected monthly prior to blood draws and averaged for each visit. ECGs were performed at baseline and Months 3, 6, 15, and 19, and at early termination. Categorical vital sign changes and potentially clinically significant (PCS) changes are described in Table 1.

TABLE 1 Criteria for categorical changes in vital signs

Parameter	Direction	Criteria
Systolic BP (mm Hg)	High	≥140 and increase ≥20
	PCS high	≥180 and increase ≥20
	Sustained elevation	≥140 and increase ≥20 at two consecutive visits
Diastolic BP (mm Hg)	High	≥90 and increase ≥10
	PCS high	≥105 and increase ≥15
	Sustained elevation	≥90 and increase ≥10 at two consecutive visits
Systolic BP or diastolic BP (mm Hg)	Sustained elevation	Meeting criteria for systolic BP for two consecutive visits or meeting criteria for diastolic BP for two consecutive visits or both
Pulse (bpm)	High	>100 and increase ≥15
	Sustained elevation	>100 and increase ≥15 at two consecutive visits

Abbreviations: BP, blood pressure; bpm, beats per minute; PCS, potentially clinically significant.

Clinical laboratory blood samples were collected at baseline and Months 3, 6, 9, 15, and 19, and at early termination, and urine was collected at Months 6, 9, 15, and 19, and at early termination. Abnormally high hepatic laboratory results were defined as alanine aminotransferase (ALT) or aspartate aminotransferase ≥3X upper limit of normal (ULN), alkaline phosphatase ≥2X ULN, or total bilirubin ≥2X ULN.

Immunogenicity samples were assessed at baseline and Months 0.5, 1, 2, 3, 6, 12, 15, 17, and 19, and at early discontinuation. Antidrug antibody (ADA) status was determined with a validated, proprietary ELISA assay.[9] Treatment-emergent ADA (TE-ADA) was defined either by a baseline status of ADA not present and at least one postbaseline status of ADA present with a titer of ≥1:20 or, if a baseline titer was present, a postbaseline >4 times the baseline titer. Patients who had TE-ADA were further evaluated to determine whether the antibodies were neutralizing ADA (NAb).[20]

Suicidal ideation and suicidal behavior were assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS)[21] throughout the study.

Statistical analysis

Regarding sample size, described in detail previously,[9] the planned enrollment for the study was a minimum of 162 participants, with a later exercised opportunity to increase this after predefined sample size re-estimation at the first interim analysis. This provided power ranging between 73% and 89%, analysis that was performed using EAST software 6.2 assuming a 10% discontinuation rate. Safety analyses were conducted on all patients who received galcanezumab during either the double-blind treatment phase or the open-label extension and include measures obtained during the washout phase. Categorical safety analyses generally included both scheduled and unscheduled visits. Descriptive statistics only are presented for analyses with the galcanezumab-treated population. For all safety assessments of the galcanezumab-treated population, baseline was defined as Visits 1–3 before dosing at the start of the double-blind period for patients treated with galcanezumab during the double-blind period, and Visits 1–9 before dosing at the open-label period for patients treated with placebo during the double-blind phase.

In addition to frequencies and percentages, the exposure-adjusted incidence rate (EAIR; per 100 patient-years) was reported to account for differences in treatment durations and calculated for galcanezumab-treated time and galcanezumab-treated time plus washout, as well as for the double-blind treatment period, for comparison. The EAIR was defined as the total number of patients who experienced an event, divided by the total person-time at risk during the time interval. Person-time at risk was calculated as the sum of time to first occurrence of the event for patients who experienced the event, or the sum of time during the specified interval for patients who do not experience the event. AEs related to injection sites tended to occur on the day of injection and do not satisfy the constant hazard assumption of the EAIR calculation; thus, only unadjusted incidence was presented for this type of AE. 95% confidence intervals (CIs) were calculated based on a chi-squared distribution. All statistical analyses were conducted using SAS Enterprise Guide 7.1.

RESULTS

Patient disposition

Overall, 230 patients out of 237 patients that entered the study completed the double-blind treatment phase. From the 229 patients that entered the optional open-label period, 152 patients completed this phase (Figure 2). The most common reason for discontinuation during the open-label period was lack of efficacy (45 patients); 17 patients withdrew due to an AE, 13 withdrew from the study for other reasons, and two were lost to follow-up. There were 192 patients who entered the washout period, including 152 patients who completed the open-label extension, 34 who discontinued the open-label period early, and six patients who entered directly from the double-blind period. A total of 148 patients completed all study phases. Across the entire study, 78 patients received 15 doses of galcanezumab, and 158 patients received at least 12 doses.

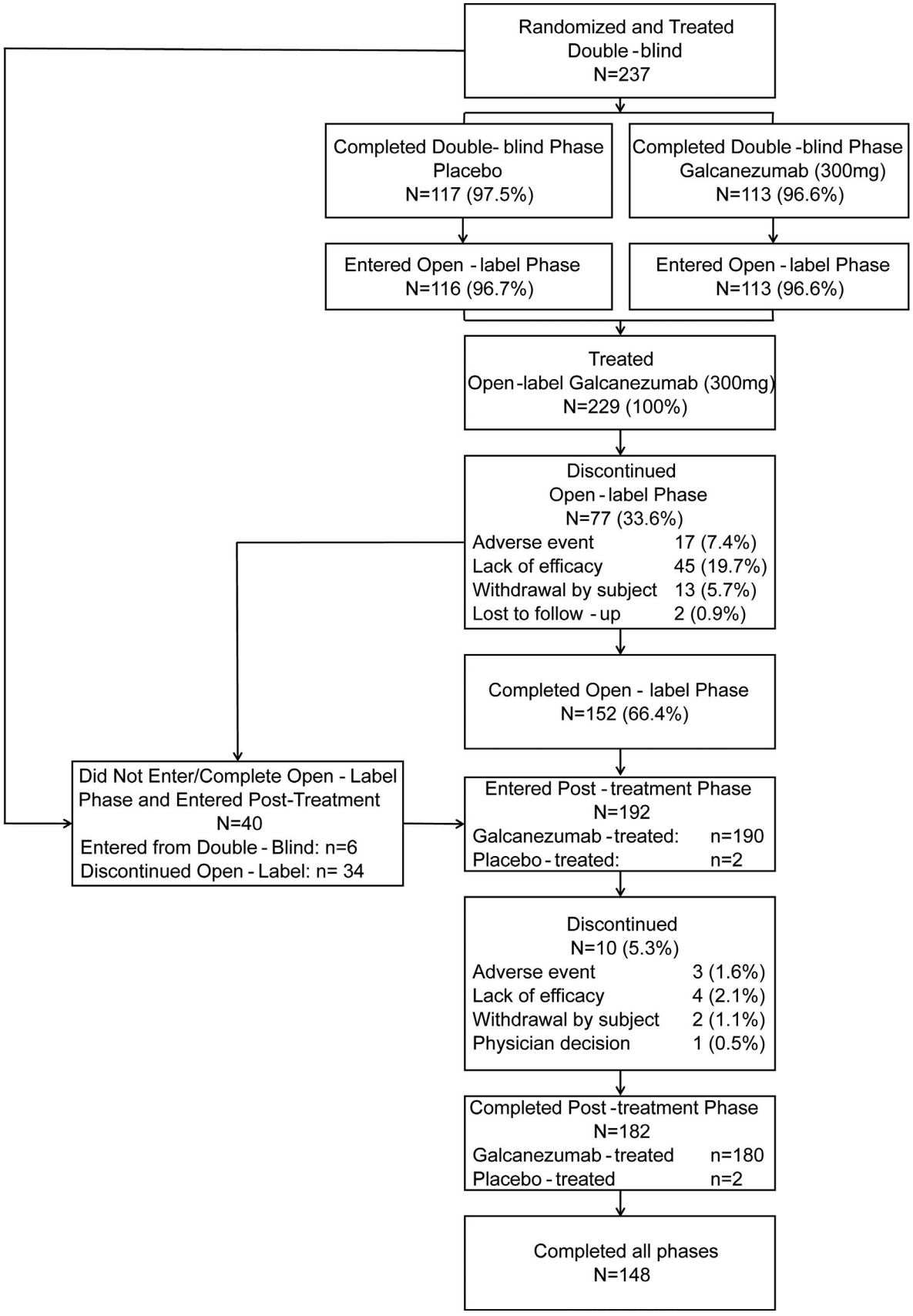

FIGURE 2 Patient disposition through the posttreatment phase. Where a patient discontinued treatment, they discontinued the study completely—and no more data were collected from them. *N*, total number of patients; *n*, number of patients in the category

TABLE 2 Baseline patient demographics and disease characteristics

	Galcanezumab (300 mg) *N* = 233 GMB-treated time
Mean (SD) age (years)	44.9 (10.9)
Mean (SD) BMI (kg/m^2)	26.4 (4.8)
Mean (SD) reported cluster headache attacks in the 7 days prior to Visit 1	17.9 (12.2)
Mean (SD) weekly cluster headache attacks	18.9 (10.2)
Mean (SD) duration of cluster headache illness (years)	8.0 (7.1)
Male sex; *n* (%)	169 (72.5)
Race	
White; *n* (%)	197 (84.6)
Black or African American; *n* (%)	2 (0.9)
Multiple; *n* (%)	34 (14.6)
Region	
Europe; *n* (%)	193 (82.8)
North America; *n* (%)	40 (17.2)
Verapamil use; *n* (%)	115 (49.4)
Daily cluster headache attack frequency	
≤4 attacks per day; *n* (%)	193 (82.8)
>4 attacks per day; *n* (%)	40 (17.2)
Lifetime suicidal ideation, prior to screening; *n* (%)	52 (22.3)
Lifetime suicidal behavior, prior to screening; *n* (%)	9 (3.9)

Abbreviations: GMB, galcanezumab; *N*, number of patients; *n*, numbers of patients in each category, SD, standard deviation.

There were 233 patients who received at least one dose of galcanezumab (Figure 2), with a mean exposure to galcanezumab of 341 days [±130 standard deviation (SD)]. The galcanezumab-treated population was predominantly male (72.5%) and White (84.6%), with a mean age of 44.9 years and a diagnosis of CH for an average of 8.0 years (Table 2). The discussion will focus primarily on galcanezumab-treated time, unless otherwise noted.

Patient-reported improvement in cluster headache

Although this report is focused primarily on the tolerability and safety of galcanezumab, a descriptive summary of the percentage of patients reporting individual PGI-I scores across double-blind (Month 3), open-label, and posttreatment phases is shown in Table S1. In brief, from Month 3 to Month 9, there were shifts to a higher percentage of patients having a score of 1 (very much better), 2 (much better), or 3 (a little better) at Month 9. This appears to be due to patients shifting from a score of 4 (no change) at Month 3 to a better score at Month 9. At Month 15, the majority of patients reported a score of 1 or 2. At Month 19, patients continued to report primarily scores of 1, 2, or 3. It should be noted that a limitation of subjective ratings is that during the open-label phase, all patients knew they were receiving active treatment with galcanezumab.

Serious adverse events

No deaths were reported during the galcanezumab-treated time or the washout. During the galcanezumab-treated time, 23 (9.9%) patients reported 25 SAEs, 12 of which led to discontinuation of treatment. An additional four SAEs were reported during the washout period, but none led to discontinuation (Table 3). All the SAEs, except for CH, were reported by one patient, and all were resolved. Three patients were hospitalized due to CH or worsening of CH following the eighth, ninth, and 12th dose of galcanezumab. The event of CH resolved, with one patient discontinuing treatment. Five SAEs were reported (each in one patient—amaurosis, cerebral ischemia, constipation, injection site urticaria, and reversible cerebral vasoconstriction syndrome) that were considered by the investigator to be possibly related to the investigational product. When adjusted for exposure, the incidence rate of SAEs did not increase with longer duration of treatment. The EAIR for the galcanezumab-treated population (10.9 [95% CI 6.9, 16.4]) was within the range of the EAIRs reported during double-blind treatment (placebo: 10.2 [95% CI 2.1, 29.8]; galcanezumab: 6.9 [95% CI 0.8, 25.1]).

Discontinuations due to adverse events

There were 18 (7.7%) patients with DCAEs, including the 12 SAEs mentioned above, during the galcanezumab-treated time, with no additional DCAEs occurring in the washout (Table 3). The EAIR increased during galcanezumab-treated time (8.3 [95% CI 4.9, 13.2]) compared with the EAIRs for the double-blind period (placebo: 3.4 [95% CI 0.1, 18.7]; galcanezumab: 3.5 [95% CI 0.1, 19.3]), driven primarily by patients discontinuing due to an SAE.

Treatment-emergent adverse events

There were 185 (79.4%) patients who reported one or more TEAEs during the galcanezumab-treated time and 192 (82.4%) during the galcanezumab-treated time plus the washout period. Overall, the EAIR for TEAEs did not increase with longer duration of treatment (Table 4). Nasopharyngitis and injection site pain were the most common TEAEs (>10%), and those with ≥5% frequency during galcanezumab-treated time are listed in Table 4. Most TEAEs were of mild (29.7%) or moderate (52.4%) intensity. Injection site pain and CH were the TEAEs reported most often as severe with a frequency of <2% ($n = 4$ patients each). All other severe TEAEs were reported in two or fewer patients.

TEAEs possibly related to study drug

There were 101 (43.4%) patients during the galcanezumab-treated time and 102 (43.8%) patients when including the washout period who had TEAEs that were possibly related to the investigational product by the investigator. The most common TEAEs considered possibly related (≥5%) were injection site events which are discussed in greater detail below.

Injection site reactions

A total of 64 (27.5%) patients reported one or more TEAEs related to injection sites (Table 5). The more commonly reported injection site reactions were injection site pain in 33 (14.2%) patients, injection site erythema in 15 (6.4%) patients, and injection site pruritus in 14 (6.0%) patients. One patient reported severe injection site pain after the second galcanezumab injection (Day 121; open-label extension period), that resolved the same day. That patient also experienced severe injection site urticaria the next day that was judged by the investigator as a serious adverse event for medical significance on Day 127. The patient discontinued treatment, and the injection site urticaria resolved on Day 133. There was no other SAE or DCAE related to the injection site. Most (90.2%) of the TEAEs related to injection site were judged to be mild or moderate. These TEAEs occurred on the same day as the injection, and the majority (i.e., 84.8%) of injection site pain TEAEs occurred within 60 min of administration.

Likely hypersensitivity events

Fourteen (6.0%) patients reported at least one hypersensitivity event during the galcanezumab-treated time; the events included injection site rash ($n = 3$), allergic rhinitis ($n = 2$), urticaria ($n = 2$), and injection site urticaria ($n = 2$). Allergic cough, allergic conjunctivitis, contact dermatitis, injection site hypersensitivity, and rash were reported by one patient each. Two additional patients had allergic rhinitis or skin reaction during the washout.

Vital signs and ECG

Patients whose BP and pulse values met the categorical criteria are summarized in Table 6. Twenty-nine (12.6%) patients met the categorical high systolic BP criteria, and six (2.6%) met the high criteria for sustained elevation. There were 52 (22.5%) patients who met categorical high diastolic BP criteria and 17 (7.5%) with sustained elevation. Seven (3.0%) patients had PCS diastolic BP increase (≥105 mm Hg and increase of ≥15 mm Hg). When adjusted for time at risk, the incidence rates for high systolic BP or high diastolic BP did not increase during galcanezumab-treated time or galcanezumab-treated time + washout (Table 6). The elevated BP values did not persist with continued exposure for most patients; there was considerable variability from visit to visit, and/or the increase in systolic BP or diastolic BP was confounded by other factors (as noted by the study investigator). A review of the mean observed BP values at baseline and endpoints for the double-blind period and galcanezumab-treated period is provided in Table S2. For systolic BP, no significant differences were observed between placebo and galcanezumab at baseline, or at endpoint of the double-blind period. Additionally, the mean SBP at endpoint of galcanezumab-treated time was similar to the mean SBP for galcanezumab at the endpoint of the double-blind period. For diastolic BP, no significant differences were observed between placebo and galcanezumab at baseline, whereas a statistically significant increase in mean observed value was seen for diastolic BP in galcanezumab-treated patients relative to placebo at the end of the double-blind period (GMB: 81.3 mm Hg vs. PBO: 79.7 mm Hg; +1.6 mm Hg, $p = 0.04$) (Table S2). The mean observed value for diastolic BP at the end of galcanezumab-treated time was similar to the value at the end of the double-blind period. Nine patients during the galcanezumab-treated time had primarily mild to moderate hypertension-related TEAEs and a total of 10 patients when including the washout period. The hypertension TEAE was resolved in eight of the 10 events. Two events were considered to be possibly related to the study drug by the investigator. Eight of the 10 patients reporting a TEAE of hypertension had elevated BP values before starting treatment with galcanezumab.

There were 16 (6.9%) patients who met high pulse criteria, with four (1.8%) patients meeting sustained criteria. Among the four patients meeting the sustained criteria, one patient reported mild tachycardia and mild dizziness, both of which resolved.

Few patients had treatment-emergent ECG abnormalities at any time during galcanezumab-treated time. Three patients (1.4%) had high PR intervals, two patients (0.9%) had a low PR interval, two patients (0.9%) had high Fridericia's corrected QT interval (QTcF), and five patients (2.3%) had QTcF increase >30 ms. During the washout period only, one patient had a low PR interval, one patient had a high QRS interval, and two patients had QTcF increase >30 ms, although no patient met QTcF high criteria. No patient met QTcF >480 ms at any time, either during galcanezumab-treated time or during the washout period.

Clinical laboratory evaluation

Overall, changes in clinical laboratory results were not sustained, and there were no clinical laboratory SAEs or DCAEs during either the galcanezumab-treated time or the washout period. No patient had an abnormally high hepatic laboratory result. One patient with an increased ALT at baseline (1.4X ULN) had a TEAE, judged not related to galcanezumab by the study physician, of high ALT of moderate severity (2.1X ULN) during the open-label period. The ALT level dropped to baseline levels at a subsequent laboratory assessment.

A TEAE of increased blood creatine phosphokinase (CPK), mild severity, during galcanezumab-treated time was judged by the study investigator to be related to galcanezumab. This patient had elevated

TABLE 3 SAEs and DCAEs

	Galcanezumab (300 mg) $N = 233$	
	GMB-treated time *n* (%)	GMB-treated time + washout *n* (%)
Patients with ≥1 SAE	23 (9.9)	27 (11.6)
Appendicitis	1 (0.4)	1 (0.4)
Amaurosis[a]	1 (0.4)	1 (0.4)
Anxiety[a]	1 (0.4)	1 (0.4)
Arthrodesis	1 (0.4)	1 (0.4)
Atrial fibrillation[a]	1 (0.4)	1 (0.4)
Breast cancer stage III[a]	1 (0.4)	1 (0.4)
Cerebral ischemia[a]	1 (0.4)	1 (0.4)
Chest pain	1 (0.4)	1 (0.4)
Cluster headache[a,b]	3 (1.3)	3 (1.3)
Colon neoplasm[a]	1 (0.4)	1 (0.4)
Constipation	1 (0.4)	1 (0.4)
Diverticulitis	1 (0.4)	1 (0.4)
Extradural hematoma[a]	1 (0.4)	1 (0.4)
Gastroenteritis	1 (0.4)	1 (0.4)
Helicobacter gastritis	1 (0.4)	1 (0.4)
Injection site urticaria[a]	1 (0.4)	1 (0.4)
Kidney rupture	0 (0.0)	1 (0.4)
Metastasis[a]	1 (0.4)	1 (0.4)
Palpitations[a]	1 (0.4)	1 (0.4)
Pituitary tumor	0 (0.0)	1 (0.4)
Rectal abscess	1 (0.4)	1 (0.4)
Reversible cerebral vasoconstriction syndrome[a]	1 (0.4)	1 (0.4)
Rhabdomyolysis	1 (0.4)	1 (0.4)
Road traffic accident	1 (0.4)	1 (0.4)
Small intestinal obstruction	0 (0.0)	1 (0.4)
Ureterolithiasis	0 (0.0)	1 (0.4)
Urinary tract infection bacterial	1 (0.4)	1 (0.4)
Nonserious AEs leading to discontinuation		
Depression	1 (0.4)	1 (0.4)
Dermatitis	1 (0.4)	1 (0.4)
Dyspnea exertional	1 (0.4)	1 (0.4)
Electrocardiogram PR prolongation	1 (0.4)	1 (0.4)
Insomnia	1 (0.4)	1 (0.4)
Transient ischemic attack	1 (0.4)	1 (0.4)

Abbreviations: AE, adverse event; DCAEs, discontinuations due to adverse events; GMB, galcanezumab; *N*, number of patients; *n*, numbers of patients in each category; SAEs, serious adverse events.

[a]SAEs that led to discontinuation.

[b]One of the three patients discontinued due to the SAE of cluster headache.

CPK levels at baseline and a maximum increase postbaseline of 1.5X ULN. This TEAE resolved after 1 month, and the CPK levels returned to baseline while on galcanezumab.

Treatment-emergent antidrug antibodies

Among the 220 patients who were evaluable for TE-ADA during galcanezumab-treated time, there were 14 (6.4%) patients who were ADA-positive at baseline prior to receiving galcanezumab, 10 of whom had NAb present. During galcanezumab-treated time, eight (3.6%) patients were TE-ADA-positive, and seven of these patients had NAb present. Of the patients with ADA present at baseline, none had a fourfold increase in titer or met TE-ADA criteria during the study. During galcanezumab-treated time plus the washout period, there were 20 (10.9%) patients who were TE-ADA positive, and 19 of these patients had NAb present.

The majority (84.6%) of patients had no detectable ADA during the galcanezumab-treated time, and among those who did, the majority of titers were 1:10. The highest titer was 1:1280 in one patient. No reasonable causal association or temporal relationship between TE-ADA positive and the occurrence of SAEs, DCAEs, or AEs related to injection sites or hypersensitivity was found.

Suicide-related thoughts and behaviors

There were 15 (6.5%) patients in the galcanezumab-treated time and an additional three, or 18 (7.8%) total patients, during washout with suicidal ideation. A total of 12 (5.2%) patients during the galcanezumab-treated time and an additional two patients during the washout period reported suicidal ideation compared with the month prior to study screening. There were eight (3.6%) patients in the galcanezumab-treated time and 10 (4.4%) patients when including the washout period who reported suicidal ideation compared with all prior history. Fourteen (6.1%) of the 15 patients in the galcanezumab-treated time and 17 (7.4%) of 18 when including the washout period reported a "wish to be dead" on the C-SSRS.

There was one patient with a nonfatal suicide attempt and aborted suicide attempt. The patient had a previous history of ongoing depression and suicidal ideation and behavior and reported a suicide attempt following the last dose of the open-label period. This patient also reported an aborted suicide attempt during the washout period. The investigator considered the AEs of suicide attempt and suicidal ideation as not related to study drug. The patient was under treatment for depression with a primary care physician and completed the washout period.

DISCUSSION

The overall safety profile of galcanezumab in chronic CH was consistent with that shown in the migraine[14] and episodic CH studies.[17]

TABLE 4 Exposure-adjusted AEs with ≥5% incidence in the galcanezumab-treated time

	Double-blind period						All galcanezumab exposures					
	Placebo (*N* = 120)			Galcanezumab (*N* = 117)			GMB-treated time (*N* = 233)			GMB-treated time + washout (*N* = 233)		
Preferred term	***n* (%)**	**TPY**	**EAIR (95% CI)**	***n* (%)**	**TPY**	**EAIR (95% CI)**	***n* (%)**	**TPY**	**EAIR (95% CI)**	***n* (%)**	**TPY**	**EAIR (95% CI)**
Patients with ≥1 TEAE	75 (62.5)	15.3	489.0 (384.6, 613.0)	84 (71.8)	14.3	589.7 (470.4, 730.1)	185 (79.4)	71.2	259.8 (223.7, 300.0)	192 (82.4)	81.3	236.1 (203.9, 272.0)
Nasopharyngitis	15 (12.5)	27.0	55.5 (31.1, 91.5)	12 (10.3)	27.6	43.5 (22.5, 76.0)	41 (17.6)	194.3	21.1 (15.1, 28.6)	46 (19.7)	244.2	18.8 (13.8, 25.1)
Injection site pain[a]	11 (9.2)	27.5	[a]	13 (11.1)	26.2	[a]	33 (14.2)	195.2	[a]	33 (14.2)	248.1	[a]
Back pain	1 (0.8)	29.7	3.4 (0.1, 18.8)	5 (4.3)	28.3	17.7 (5.7, 41.3)	19 (8.2)	206.4	9.2 (5.5, 14.4)	21 (9.0)	263.5	8.0 (4.9, 12.2)
Injection site erythema[a]	1 (0.8)	29.5	[a]	8 (6.8)	27.6	[a]	15 (6.4)	207.3	[a]	15 (6.4)	265.5	[a]
Influenza	3 (2.5)	29.5	10.2 (2.1, 29.8)	2 (1.7)	28.7	7.0 (0.8, 25.2)	15 (6.4)	208.3	7.2 (4.0, 11.9)	18 (7.7)	266.1	6.8 (4.0, 10.7)
Injection site pruritus[a]	1 (0.8)	29.5	[a]	5 (4.3)	28.4	[a]	14 (6.0)	206.2	[a]	14 (6.0)	264.8	[a]
Fatigue	7 (5.8)	29.0	24.2 (9.7, 49.8)	5 (4.3)	28.1	17.8 (5.8, 41.5)	14 (6.0)	206.9	6.8 (3.7, 11.4)	14 (6.0)	266.3	5.3 (2.9, 8.8)
Influenza-like illness	1 (0.8)	29.5	3.4 (0.1, 18.9)	5 (4.3)	28.2	17.7 (5.8, 41.3)	12 (5.2)	207.1	5.8 (3.0, 10.1)	13 (5.6)	266.1	4.9 (2.6, 8.4)
Dizziness	5 (4.2)	29.1	17.2 (5.6, 40.1)	5 (4.3)	28.0	17.8 (5.8, 41.6)	12 (5.2)	208.3	5.8 (3.0, 10.1)	13 (5.6)	267.2	4.9 (2.6, 8.3)
Constipation	2 (1.7)	29.3	6.8 (0.8, 24.7)	2 (1.7)	28.7	7.0 (0.8, 25.2)	12 (5.2)	209.9	5.7 (3.0, 10.0)	15 (6.4)	268.5	5.6 (3.1, 9.2)
Nausea	6 (5.0)	29.0	20.7 (7.6, 45.0)	6 (5.1)	28.0	21.4 (7.9, 46.6)	11 (4.7)	207.6	5.3 (2.7, 9.5)	12 (5.2)	266.6	4.5 (2.3, 7.9)
Arthralgia	4 (3.3)	29.1	13.8 (3.8, 35.2)	0 (0.0)	29.0	0.00 (NA, 12.8)	11 (4.7)	211.6	5.2 (2.6, 9.3)	13 (5.6)	271.9	4.8 (2.6, 8.2)

Abbreviations: CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 patient-years); GMB, galcanezumab; *N*, number of patients in the analysis population; *n*, number of patients within each specific category; TEAE, treatment-emergent adverse event; TPY, total patient-year-at-risk.

[a]Adverse events related to injection sites tend to occur on the day of injection and do not satisfy the constant hazard assumption of the EAIR calculation. Therefore, EAIRs are not calculated for adverse events related to injection sites, and only the unadjusted *n* and % are presented for these events.

TABLE 5 TEAEs related to injection sites

	Galcanezumab (300 mg) *N* = 233
	GMB-treated time *n* (%)
Injection site pain	33 (14.2)
Injection site erythema	15 (6.4)
Injection site pruritus	14 (6.0)
Injection site reaction	9 (3.9)
Injection site swelling	5 (2.2)
Injection site induration	4 (1.7)
Injection site bruising	3 (1.3)
Injection site rash	3 (1.3)
Injection site discoloration	2 (0.9)
Injection site paresthesia	2 (0.9)
Injection site urticaria	2 (0.9)
Injection site hematoma	1 (0.4)
Injection site hemorrhage	1 (0.4)
Injection site hypersensitivity	1 (0.4)
Injection site edema	1 (0.4)

Abbreviations: GMB, galcanezumab; *N*, number of patients; *n*, numbers of patients in each category; TEAE, treatment-emergent adverse event.

For migraine, patients received 120 or 240 mg of galcanezumab monthly for up to 12 months.[14] This study extended the safety data of galcanezumab to 300 mg given monthly for up to 15 months in patients with chronic CH. The most commonly reported TEAEs were related to injection site and were not observed to increase in frequency with increased treatment duration. The TEAE profile in chronic CH is consistent with those summarized from five clinical studies of galcanezumab in patients with migraine.[14]

Constipation, pruritus (not associated with injection site), and vertigo were also identified as adverse drug reactions in the integrated study of patients with migraine receiving galcanezumab for up to 12 months.[14] In the present study, pruritus (not associated with injection site) and vertigo were each reported by <2% of patients, and were of mild or moderate severity. Mostly mild to moderate constipation was reported by 5% of patients. The one SAE of constipation event resolved with no change to treatment. The incidence of pruritus, vertigo, and constipation did not increase with longer exposure to galcanezumab, most events resolved, and none led to discontinuation.[4]

Hypersensitivity reactions are a possibility with monoclonal antibody treatments.[14] There were no anaphylactic reactions. The one case of severe injection site urticaria was reported the day after the patient experienced severe injection site pain and resolved 12 days later. Overall, hypersensitivity reactions were generally consistent with those reported with migraine.[14] Due to cases reported after galcanezumab was approved for the treatment of migraine, hypersensitivity reactions were added to the Warnings and Precautions section of the US prescribing information.[16]

Preclinical and clinical studies have shown that CGRP is a potent vasodilator, acting either directly relaxing vascular smooth muscle or by enhancing production of the potent vasodilator nitric oxide.[12,22] However, clinical data have not supported that CGRP is involved in homeostasis or compensatory regulation of BP. Results from preclinical studies suggested that endogenous CGRP was not instrumental in regulating systemic and regional hemodynamics.[12,23,24] This was reflected in the results of the present study. Fewer than 5% of patients met criteria for sustained elevation in systolic BP, and <10% of patients met criteria for sustained elevated diastolic BP with up to 15 months of exposure to galcanezumab. Overall, the increases in BP were not observed to persist and were noted to be associated with significant variability, and the incidence rates did not increase with longer exposure to galcanezumab. Hypertension was one of the most common preexisting diagnoses, with a frequency of 12% among patients treated with galcanezumab and 11% overall. Most patients in the study were current users of tobacco (62.9% of patients) and the mean daily consumption of different tobacco types suggests that smoking (rather than the use of smokeless tobacco) constituted the majority of tobacco use (99.4% of tobacco use). Since smoking can transiently increase BP, it may have contributed to the variability observed in BP measurements.[25] The observation that few (i.e., ≤2.5%) patients had any ECG abnormalities is also consistent with an absence of effect on hemodynamic function.

In an integrated analysis with up to 6 months of double-blind treatment of GMB in migraine, GMB-treated patients reported three vascular SAEs, namely myocardial infarction, pulmonary embolism, and transient ischemic attack.[15] Here, four vascular SAEs including atrial fibrillation, amaurosis of the right eye, cerebral ischemia, and reversible cerebral vasoconstriction syndrome were reported. Of these events, there was no apparent relationship between galcanezumab dosing and onset, where onset ranged from following the second monthly dose to following the 11th monthly dose, as well as throughout the posttreatment washout phase. The four SAE cases had associated risk factors such as heavy smoking, comorbid medical conditions, and use of certain concomitant medications. One mild (nonserious) event of transient ischemic attack that led to discontinuation occurred approximately 1 month after the 14th dose of GMB, was judged related to the treatment by the investigator, and resolved on the same day. According to the investigator, the symptoms suggesting (or resembling) a transient ischemic attack were possibly related to the patient's anxiety and panic attack. Diagnostic testing showed a patent foramen ovale, no acute intracranial abnormality, and a mild old cerebellar infarct.

Therapeutic antibodies can potentially be recognized by the body as foreign and cause production of ADAs.[26–28] Among 220 patients, TE-ADAs were detected in 3.6% of patients in the galcanezumab treatment time and in 10.9% of patients when the washout is included. Although TE-ADAs were observed in the present study, and had NAb in vitro, there did not appear to be a clinical impact on safety in this study. This is consistent with results from patients with migraine, where 12% and 7% of patients treated with 120 and 240 mg of galcanezumab during a 12-month treatment phase developed TE-ADAs, respectively.[29]

CH has earned the moniker of "suicide headache" due to its high rate of suicidal ideation.[2,3] Data from the US Cluster Headache

TABLE 6 Exposure-adjusted categorical changes in blood pressure and pulse

	Double-blind period								GMB-treated time				GMB-treated time +washout			
	Placebo				Galcanezumab (300 mg)				Galcanezumab (300 mg)							
Category	*N*	*n* (%)	TPY	EAIR (95% CI)	*N*	*n* (%)	TPY	EAIR (95% CI)	*N*	*n* (%)	TPY	EAIR (95% CI)	*N*	*n* (%)	TPY	EAIR (95% CI)
SBP																
High	119	5 (4.2)	29.0	17.2 (5.6, 40.2)	117	2 (1.7)	28.9	6.9 (0.8, 25.0)	231	29 (12.6)	201.8	14.4(9.6, 20.6)	231	32 (13.9)	255.7	12.5 (8.6, 17.7)
PCS	119	0	29.7	0 (NA, 12.4)	117	0	28.9	0 (NA, 12.8)	231	0	216.9	0 (NA, 1.7)	231	0	279.7	0 (NA, 1.3)
Sustained	119	0	29.7	0 (NA, 12.4)	116	0	28.8	0 (NA, 12.8)	227	6 (2.6)	212.3	2.8 (1.0, 6.2)	229	9 (3.9)	273.2	3.3 (1.5, 6.3)
DBP																
High	119	7 (5.9)	28.8	24.3 (9.8, 50.1)	117	12 (10.3)	28.3	42.4 (21.9, 74.1)	231	52 (22.5)	182.1	28.6 (21.3, 37.5)	231	57 (24.7)	230.4	24.7 (18.7, 32.1)
PCS	119	0	29.7	0 (NA, 12.4)	117	0	28.9	0 (NA, 12.8)	231	7 (3.0)	213.9	3.3 (1.3, 6.7)	231	10 (4.3)	274.4	3.6 (1.8, 6.7)
Sustained	119	0	29.7	0 (NA, 12.4)	116	3 (2.6)	28.5	10.6 (2.2, 30.8)	227	17 (7.5)	203.6	8.4 (4.9, 13.4)	229	18 (7.9)	261.2	6.9 (4.1, 10.9)
SBP or DBP																
Sustained	119	0	29.7	0 (NA, 12.4)	116	3(2.6)	28.5	10.6 (2.2, 30.8)	227	21 (9.3)	201.2	10.4 (6.5, 16.0)	229	24 (10.5)	257.2	9.3 (6.0, 13.9)
Pulse																
High	119	1 (0.8)	29.7	3.4 (0.1, 18.8)	117	3 (2.6)	28.5	10.6 (2.2, 30.8)	231	16 (6.9)	209.4	7.6 (4.4, 12.4)	231	18 (7.8)	267.7	6.7 (4.0, 10.6)
Sustained	119	0	29.7	0 (NA, 12.4)	116	1 (0.9)	28.6	3.5 (0.1, 19.5)	227	4 (1.8)	215.2	1.9 (0.5, 4.8)	229	4 (1.8)	277.0	1.4 (0.4, 3.7)

Note: Categorical change definitions: for systolic BP: high: ≥140 mm Hg and increase from baseline ≥20 mm Hg. PCS high: ≥180 mm Hg and increase from baseline ≥20 mm Hg. Sustained high: ≥140 mm Hg and increase from baseline ≥20 for two consecutive visits. For diastolic BP: high: ≥90 mm Hg and increase from baseline ≥10. PCS high: ≥105 mm Hg and increase from baseline ≥15 mm Hg. Sustained high: ≥90 mm Hg and increase from baseline ≥10 for two consecutive visits. For pulse: high: >100 beats per minute and increase from baseline ≥15. Sustained high: >100 beats per minute and increase from baseline ≥15 for two consecutive visits.

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; EAIR, exposure-adjusted incidence rate (per 100 patient-years); GMB, galcanezumab; *N*, number of patients with normal BP and pulse at baseline; *n*, number of patients with treatment-emergent change in BP and pulse; PCS, potentially clinically significant; SBP, systolic blood pressure; TPY, total patient-year-at-risk.

Survey found that 55% of patients with CH who responded have had suicidal thoughts, and 2% attempted suicide.[3] Moreover, 50% of responders reported self-injurious behavior during a CH attack.[3] In a study of 193 patients, primarily with episodic CH, that was part of the Korean Cluster Headache Registry Study, 64% had passive suicidal ideation, and 36% had active suicidal ideation, 6% had a suicidal plan, and 2% attempted suicide, during the ictal phase.[2] These numbers were markedly reduced during the interictal phase, with 4% having passive and active suicidal ideation and 3% and 1% having suicidal planning or an attempt, respectively.[2] In the present study of chronic CH, the assessment of suicidality using the C-SSRS was likely completed outside of an attack (i.e., interictal), and the frequency of suicidal ideation appears to be more aligned with the reported interictal frequency in a primarily episodic CH population.[2]

A limitation of the study is that longer exposures than what were used in this study are needed to assess rare or less frequent AEs. Another limitation is that patients with serious or unstable conditions were excluded from the clinical trial and may limit the generalizability of the study results.

CONCLUSIONS

The safety profile of galcanezumab in the present study was consistent with that shown in the migraine population and in the episodic CH study. This study extended the observations made in migraine trials to a higher dose (300 mg) and a slightly longer (15 months) duration.

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CONFLICT OF INTEREST

Chad Stroud, Jennifer Bardos, Mark Bangs, Phebe Kemmer, Richard Wenzel, Dulanji K. Kuruppu, James Michael Martinez, and Tina M. Oakes are employees and minor stockholders of Eli Lilly and Company. Miguel J. A. Láinez has received honoraria, consultation fees, and research grants from Allergan, Amgen, Bayer, Bial, Boehringher, Chiesi, ElectroCore, Eli Lily, Medtronic, Novartis, Otsuka, PRIM, Roche, Teva, and UCB. Jean Schoenen has received honoraria and speaker's fees from Teva, Novartis, Eli Lilly, Allergan, Amgen, Electrocore, Cefaly Technology, and Man & Science.

AUTHOR CONTRIBUTIONS

Study concept and design: Phebe Kemmer, James Michael Martinez, Tina M. Oakes. *Acquisition of data*: Miguel J. A. Láinez, Jean Schoenen. *Analysis and interpretation of data*: Mark Bangs, Jennifer Bardos, Phebe Kemmer, Dulanji K. Kuruppu, Miguel J. A. Láinez, James Michael Martinez, Tina M. Oakes, Jean Schoenen, Chad Stroud. *Drafting of the manuscript*: Chad Stroud. *Revising it for intellectual content*: Mark Bangs, Jennifer Bardos, Phebe Kemmer, Dulanji K. Kuruppu, Miguel J. A. Láinez, James Michael Martinez, Tina M. Oakes, Jean Schoenen. *Final approval of the completed manuscript*: Mark Bangs, Jennifer Bardos, Phebe Kemmer, Dulanji K. Kuruppu, Miguel J. A. Láinez, James Michael Martinez, Tina M. Oakes, Jean Schoenen, Chad Stroud.

INSTITUTIONAL REVIEW BOARD APPROVAL

The study protocol was reviewed and approved by the appropriate institutional or ethical review board for each site.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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