ORIGINAL ARTICLE

Trial of Galcanezumab in Prevention of Episodic Cluster Headache

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ABSTRACT

BACKGROUND

Episodic cluster headache is a disabling neurologic disorder that is characterized by daily headache attacks that occur over periods of weeks or months. Galcanezumab, a humanized monoclonal antibody to calcitonin gene–related peptide, may be a preventive treatment for cluster headache.

METHODS

We enrolled patients who had at least one attack every other day, at least four total attacks, and no more than eight attacks per day during a baseline assessment, as well as a history of cluster headache periods lasting at least 6 weeks, and randomly assigned them to receive galcanezumab (at a dose of 300 mg) or placebo, administered subcutaneously at baseline and at 1 month. The primary end point was the mean change from baseline in the weekly frequency of cluster headache attacks across weeks 1 through 3 after receipt of the first dose. The key secondary end point was the percentage of patients who had a reduction from baseline of at least 50% in the weekly frequency of cluster headache attacks at week 3. Safety was also assessed.

RESULTS

Recruitment was halted before the trial reached the planned sample size of 162 because too few volunteers met the eligibility criteria. Of 106 enrolled patients, 49 were randomly assigned to receive galcanezumab and 57 to receive placebo. The mean (±SD) number of cluster headache attacks per week in the baseline period was 17.8±10.1 in the galcanezumab group and 17.3±10.1 in the placebo group. The mean reduction in the weekly frequency of cluster headache attacks across weeks 1 through 3 was 8.7 attacks in the galcanezumab group, as compared with 5.2 in the placebo group (difference, 3.5 attacks per week; 95% confidence interval, 0.2 to 6.7; P=0.04). The percentage of patients who had a reduction of at least 50% in headache frequency at week 3 was 71% in the galcanezumab group and 53% in the placebo group. There were no substantial between-group differences in the incidence of adverse events, except that 8% of the patients in the galcanezumab group had injection-site pain.

CONCLUSIONS

Galcanezumab administered subcutaneously at a dose of 300 mg once monthly reduced the weekly frequency of attacks of episodic cluster headache across weeks 1 through 3 after the initial injection, as compared with placebo. (Funded by Eli Lilly; ClinicalTrials.gov number, NCT02397473.)

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Cluster headache is a disabling primary headache disorder that is characterized by attacks of intense headache on one side of the head, with associated agitation or restlessness, as well as by cranial autonomic symptoms, such as lacrimation, conjunctival injection, and nasal congestion.[1] Attacks last 15 to 180 minutes when untreated and can occur once or several times per day during cluster headache periods that can last for weeks to months. Cluster headache periods are separated by attack-free remissions of variable duration, depending on whether the patient has episodic cluster headache or chronic cluster headache.[2] Episodic cluster headache is more common than the chronic variety, affecting 75 to 90% of persons with this disorder, and is characterized by attacks occurring in cluster headache periods (or bouts) separated by pain-free remission periods.[3,4] Cluster headache has a negative effect on quality of life, day-to-day functioning, and ability to work.[5,6] Patients may describe cluster headache as the worst pain they have known,[7] and suicide and suicidal ideation have been reported during periods of cluster headache.[8]

Treatment of cluster headache is aimed at terminating attacks and is also used preventively to reduce the frequency of attacks. Commonly used treatments for cluster headache attacks include high-flow oxygen[9] and triptans — selective agonists of serotonin (5-hydroxytryptamine [HT]) receptors that activate 5-HT_{1B} and 5-HT_{1D} (5-$HT_{1B/1D}$) receptors, such as sumatriptan, administered either subcutaneously[10,11] or intranasally,[12] and zolmitriptan, administered intranasally.[13,14] At present, there are no approved preventive medications for cluster headache in the United States. Off-label treatments include high-dose verapamil[15] and lithium,[16] each of which has been associated with side effects.[17] The severity of attacks in some patients has led to the development of invasive treatments such as deep-brain stimulation,[18] trigeminal nerve-root section,[19] and occipital-nerve stimulation.[20]

Galcanezumab, a humanized monoclonal antibody that selectively binds to calcitonin gene–related peptide (CGRP) and inhibits its activity, has been shown to be effective as a preventive treatment for migraine.[21,22] The role of CGRP in cluster headache[23-26] provided the rationale for the evaluation of galcanezumab for the prevention of cluster headache. The aim of this trial was to assess the safety and efficacy of galcanezumab, administered subcutaneously at a dose of 300 mg at baseline and at 1 month, for the prevention of episodic cluster headache.

A Quick Take is available at NEJM.org

METHODS

TRIAL POPULATION

Eligible participants were 18 to 65 years of age, had a history of episodic cluster headache as defined according to the *International Classification of Headache Disorders, 3rd edition (beta version)*,[27] and were able to distinguish cluster headache attacks from other headache disorders, such as migraine. To be eligible for randomization, patients were required to have a cluster headache attack frequency of at least one attack every other day, at least four total attacks, and no more than eight attacks per day during 7 consecutive days of the prospective baseline period. To minimize the possibility of early spontaneous remission owing to the natural course of the disease, patients were also required to have had a cluster headache period that had lasted at least 6 weeks.[28]

Key exclusion criteria were recent participation in a clinical trial of an investigational drug or device, current or any previous use of any CGRP antibody, antibody to the CGRP receptor or antibody to nerve growth factor, concurrent use of other therapeutic monoclonal antibodies, and status of having another distinct trigeminal autonomic cephalalgia (suspected on the basis of clinical history and examination)[27] or a history of migraine variants that could have been due to cerebral ischemia. Additional inclusion and exclusion criteria are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Patients were allowed to use only the following medications to treat their cluster headache attacks: subcutaneous, intranasal, or oral triptans; high-flow oxygen; acetaminophen (paracetamol); and nonsteroidal antiinflammatory drugs. No concomitant preventive medications for cluster headache were permitted.

TRIAL OVERSIGHT

The protocol (available at NEJM.org) was approved by the ethics review board for each investigative site. All the patients provided written informed consent in accordance with the principles of the Declaration of Helsinki. Eli Lilly funded this trial, provided galcanezumab, and conducted the analyses. The initial draft of the

manuscript was written by two of the authors, one of whom was an employee of the sponsor. There was no commercial writing support. Confidentiality agreements were in place between the authors and the sponsor. All the authors vouch for the accuracy and completeness of the data, for the adherence of the trial to the protocol, and for the reporting of adverse events.

TRIAL DESIGN

This international, randomized, blinded trial was conducted at 35 sites in Europe and North America. The trial compared galcanezumab (at a dose of 300 mg) with placebo, both of which were administered subcutaneously at baseline and at 1 month. The trial comprised a screening period, a prospective baseline period, and an 8-week double-blind, placebo-controlled period. Patients were also observed in a subsequent 4-month washout period, the data from which have not yet been analyzed. Patients who met the initial screening criteria were given an electronic diary in which to record their daily information regarding cluster headache attacks during the prospective baseline and double-blind periods.

Patients could enter the screening phase either during an active cluster headache period or while they were in remission. Patients who entered the screening phase during an active cluster headache period could directly enter the prospective baseline period after any necessary washout period for excluded medications, and those who entered screening during remission transitioned into the prospective baseline period when they entered an active cluster headache period and began to record information about the cluster headache attacks in their electronic diary. Patients who entered the screening phase while they were in remission were withdrawn from the trial after 12 months if they had not entered a cluster headache period or had a cluster headache attack; they could be rescreened and reenter the trial once. The prospective baseline period lasted 10 to 15 days, of which 7 consecutive days were used to determine eligibility. Eligible participants were then enrolled in the 8-week double-blind, placebo-controlled period.

Patients who met all the eligibility criteria were randomly assigned in a 1:1 ratio to receive galcanezumab or placebo in a double-blind manner. Randomization was performed by means of a computer-generated random sequence and an interactive Web-response system. Assignments were balanced according to the mean daily frequency of cluster headache attacks (≤4 or >4 attacks per day), sex, and trial site on the basis of a minimization algorithm.[29] Galcanezumab or placebo was administered subcutaneously by trained staff at the start of the double-blind period (month 0) and at month 1. Galcanezumab was supplied as a lyophilized formulation in glass vials and reconstituted by designated personnel who were aware of the trial-group assignments but did not have contact with patients and were not involved in any clinical aspects of the study, including administration of galcanezumab or placebo, clinical evaluations, and assessments of adverse events.

Patients entered the following information in their electronic diaries daily during the prospective baseline and double-blind periods: the number of cluster headache attacks regardless of attack duration, the average attack severity and duration over a 24-hour period, and the use of treatments for attacks. The data regarding the frequency of cluster headache attacks were converted into nine intervals of approximately 7 calendar days each: the baseline 7-day interval, week 1 (starting from the day of the first injection and lasting 7 days), week 2 (7 days), week 3 (7 days), week 4 (from the end of week 3 to the day before the second injection), week 5 (starting from the day of the second injection and lasting 7 days), week 6 (7 days), week 7 (7 days), and week 8 (from the end of week 7 to the end of the double-blind period). Weeks 4 and 8 could have been shorter or longer than a calendar week, and if a patient was withdrawn early, the last week of the patient's trial participation may not have been a full 7 days. The total number of cluster headache attacks for each interval was calculated; subsequently, the weekly totals were adjusted to a 7-day cluster headache attack frequency, and changes from baseline to each of the weeks 1 through 8 were calculated.

EFFICACY END POINTS

The primary end point was the overall mean change from baseline in the weekly frequency of cluster headache attacks across weeks 1 through 3 after the receipt of the first dose of galcanezumab. The key secondary end point was the percentage of patients with a reduction from baseline of at least 50% in the weekly frequency of cluster headache attacks at week 3. The primary and key secondary end points were evalu-

ated after the initial dose, and the trial included secondary end-point assessments of efficacy and safety after the second dose. The other secondary end points were the following: the mean change in the weekly frequency of cluster headache attacks from baseline to each weekly interval through week 8; the percentage of patients with reduction of at least 50% in the weekly frequency of cluster headache attacks from baseline at each weekly interval through week 8; the percentage of patients with reduction of at least 30% in the weekly frequency of cluster headache attacks through week 8; and the percentage of patients reporting that their condition was "very much better" or "much better" on the Patient Global Impression of Improvement scale (patients' responses were rated on a scale from 1 [very much better] to 7 [very much worse]) at weeks 4 and 8.

SAFETY

The safety evaluation included the assessment of spontaneously reported adverse events (adverse events that first occurred or worsened during the postbaseline period and serious adverse events), vital signs, electrocardiograms, and laboratory measures. Suicidal ideation and behaviors were assessed with the use of the Columbia–Suicide Severity Rating Scale (C-SSRS).[30] The C-SSRS captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine whether a suicide-related thought or behavior occurred.

Immunogenicity of the antibody was assessed by a validated assay that was designed to detect antidrug antibodies to galcanezumab. During the double-blind period, a patient was classified as having a positive result for antidrug antibody if antibodies were present at baseline and at least one postbaseline antibody titer during the double-blind period was at least 4 times as high as the baseline measurement or if antibodies were not present at baseline and at least one postbaseline result of antibody titer during the double-blind period was at least 1:20.

STATISTICAL ANALYSIS

We planned for the trial to include a minimum of 162 participants and allowed for the opportunity to increase the maximum sample size to 222 at an interim analysis on the basis of a prespecified sample-size reestimation process to mitigate the uncertainty with the expected effect size. The sample-size reestimation approach provided the trial with 73 to 89% power for assumed effect sizes of 0.4 to 0.5 to detect a significant difference between the galcanezumab and placebo groups at a one-sided alpha level of 0.025, assuming that 10% of the participants discontinued and with a futility assessment at an interim analysis. We planned to conduct the interim analysis when approximately 114 participants (70% of the planned minimum sample size) had completed the first 3 weeks of the double-blind period. However, no interim analysis was performed because enrollment was halted before reaching 114 participants.

All efficacy and safety analyses were conducted in the modified intention-to-treat population, which consisted of all patients who had been randomly assigned to a trial group and received at least one dose of galcanezumab or placebo.[31] The primary end point of the change from baseline in the weekly frequency of cluster headache attacks was analyzed with the use of a mixed-effects–model, repeated-measures analysis that used data from week 1 through week 3. The model included the fixed, categorical effects of trial-group assignment, sex, pooled investigative site, week, and trial group–by–week interaction, as well as the continuous, fixed covariate of baseline value of weekly frequency of cluster headache attacks.

For the key secondary efficacy end point, the between-group difference in the percentage of patients who had a reduction from baseline of at least 50% in the weekly frequency of cluster headache attacks at week 3 was determined with the use of Koch's nonparametric randomization-based analysis of covariance method.[32] Adjustments were made for pooled investigative site by including it as a stratification variable and for the continuous baseline value of weekly frequency of cluster headache attacks and sex as covariates. A SAS/IML software macro (NParCov3)[33] was used for the calculation. A post hoc mixed-effects–model analysis that was conducted for the percentage change from baseline in the weekly frequency of cluster headache attacks across weeks 1 through 3 used a model similar to that used for the primary end point.

To maintain the overall type I error rate at a two-sided alpha level of 0.05 for the primary and key secondary end points, a gatekeeping strategy was used in which significance of the key sec-

ondary end point would be evaluated only if a significant treatment effect in the primary efficacy end point was achieved. There was no adjustment for multiple comparisons for other secondary end points, and only point estimates with 95% confidence intervals, unadjusted for multiple comparisons, are presented. These analyses should be considered to be exploratory.

Missing data were handled as follows: For the primary and secondary efficacy end points, for which data were captured with the use of the electronic diary, if there were 4 or more days with nonmissing diary data and the adherence to using the diary was more than 50% in the weekly interval, the mean number of cluster headache attacks across the nonmissing days was used to impute the missing days. Otherwise, the data for the weekly interval were considered to be missing and were not imputed in the analyses. For the key secondary efficacy end point, patients with missing data at week 3 were considered not to have had a response. Sensitivity analyses were conducted under a missing-not-at-random assumption to assess the robustness of the primary analysis.

RESULTS

POPULATION OF PATIENTS

Enrollment was halted by the sponsor before the trial reached the planned sample size owing to a lower-than-anticipated number of patients entering into an active cluster headache period during the screening period. The first patient visit was in May 2015, and the last patient visit was in June 2018.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=57)	Galcanezumab (N=49)
Age — yr	45±11	47±11
Male sex — no. (%)	47 (82)	41 (84)
Geographic region — no. (%)		
North America	19 (33)	17 (35)
Europe	38 (67)	32 (65)
Race — no. (%)†		
White	47 (82)	43 (88)
Black	4 (7)	2 (4)
Asian	1 (2)	1 (2)
Multiple	5 (9)	3 (6)
Hispanic ethnic group — no. (%)†	4 (7)	3 (6)
Tobacco use — no./total no. (%)‡		
Former smoking	8/57 (14)	12/48 (25)
Current smoking	29/57 (51)	26/48 (54)
No. of cluster headache attacks per week in the baseline period	17.3±10.0	17.8±10.1
Duration of cluster headache disease — yr§	17.6±11.5	15.8±11.1
History of suicidality before screening — no. (%)¶		
Lifetime suicidal ideation before screening	5 (9)	9 (18)
Lifetime suicidal behavior before screening	0	1 (2)

* Plus–minus values are means ±SD. There were no significant between-group differences in the characteristics of the patients at baseline.
† Race and ethnic group were reported by the patient. No patient reported being American Indian, Alaska Native, or Native Hawaiian or other Pacific Islander.
‡ Data were missing for one patient in the galcanezumab group.
§ Data were missing for one patient in the placebo group and for two in the galcanezumab group.
¶ History of suicidality before screening was based on answers to the Columbia–Suicide Severity Rating Scale. Suicidal ideation was defined as a "yes" answer to any of the five suicidal ideation questions (categories 1 through 5), and suicidal behavior as a "yes" answer to any of the five suicidal behavior questions (categories 6 through 10).[30]

Of 314 patients screened, 106 underwent randomization and received at least one dose of galcanezumab or placebo (modified intention-to-treat population for the primary analysis); 49 patients were assigned to receive galcanezumab, and 57 to receive placebo. Of the 106 patients, 74 (35 in the galcanezumab group and 39 in the placebo group) entered screening while they were in an active period of cluster headaches; the remaining 32 patients (14 in the galcanezumab group and 18 in the placebo group) entered screening while they were in remission and had the onset of an active cluster headache period during screening.

The trial groups were balanced with respect to demographic and clinical characteristics (Table 1). The mean age of the patients was 47 years in the galcanezumab group and 45 years in the placebo group, and the majority of patients were men (84% and 82%, respectively); approximately two thirds of the patients were enrolled in Europe. The mean (±SD) number of cluster headache attacks per week in the baseline period was 17.8±10.1 in the galcanezumab group and 17.3±10.1 in the placebo group. A total of 46 patients (94%) in the galcanezumab group and 47 (82%) in the placebo group received both doses as assigned. The double-blind phase of the trial was completed by 92% of the patients assigned to receive galcanezumab and by 79% of those assigned to receive placebo (P=0.10 for the between-group difference in the percentage of patients completing the trial) (Fig. 1). In the placebo group, 14% of the patients discontinued the trial during the double-blind phase owing to lack of efficacy, as compared with 2% in the galcanezumab group.

EFFICACY END POINTS

The mean (±SE) reduction in the weekly frequency of cluster headache attacks across weeks 1 through 3 was 8.7±1.4 in the galcanezumab group, as compared with 5.2±1.3 in the placebo group (between-group difference in mean change, 3.5 attacks per week; 95% confidence interval, 0.2 to 6.7; P=0.04) (Table 2). The mean percentage reduction from baseline in the weekly frequency of cluster headache attacks across weeks 1 through 3 was 52% in the galcanezumab group, as compared with 27% in the placebo group. Results of the sensitivity analysis that accounts for missing data are shown in Table S1 in the Supplementary Appendix.

The key secondary end point of the percentage of patients having a reduction of at least

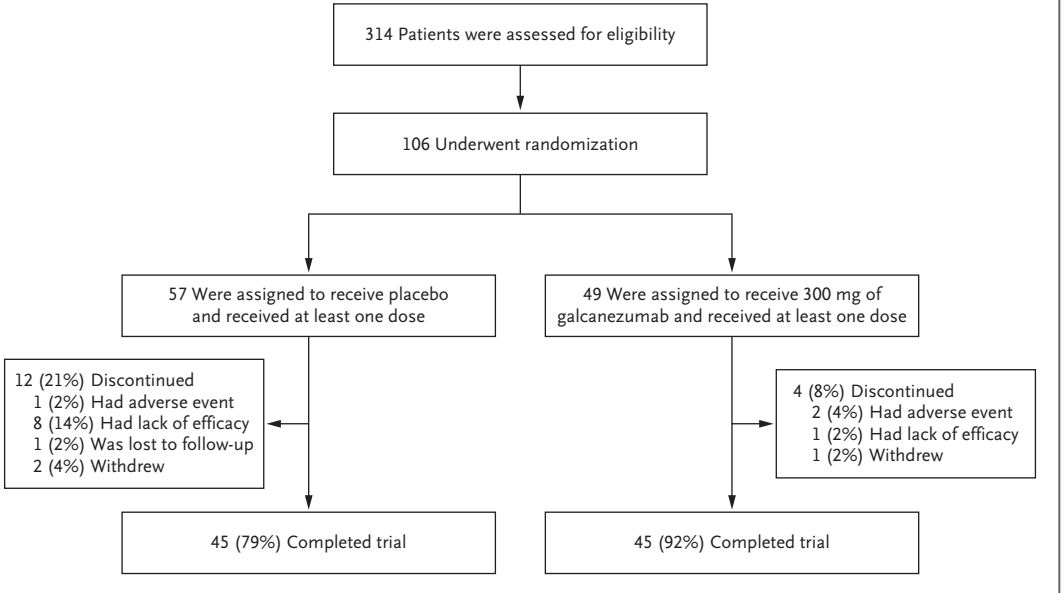

Figure 1. Enrollment, Randomization, and Follow-up during the 8-Week Double-Blind, Placebo-Controlled Period.
The modified intention-to-treat population that was used for the primary analysis comprised patients who underwent randomization and received at least one dose of galcanezumab or placebo. Fewer patients in the galcanezumab group than in the placebo group discontinued owing to lack of efficacy.

Table 2. Primary and Key Secondary End Points.*

End Point	Placebo (N=57)	Galcanezumab (N=49)	P Value
Least-squares mean change from baseline in weekly frequency of cluster headache attacks across wk 1–3	−5.2±1.3	−8.7±1.4	0.04
Percentage of patients with a response at wk 3†	53	71	0.046

* Plus–minus values are means ±SE.
† Response was defined as a reduction of at least 50% in the weekly frequency of cluster headache attacks. Patients with missing data at week 3 were considered not to have had a response.

50% in the weekly frequency of cluster headache attacks at week 3 was 71% in the galcanezumab group, as compared with 53% in the placebo group (P=0.046) (Table 2). Other secondary end-point results are presented in Table 3, and in Figures S1 through S4 in the Supplementary Appendix. For the eight 1-week epochs, the difference between active treatment and placebo tended to be larger in the initial weeks than in the later weeks (Table 3). Convergence after week 4 in the mean change in weekly frequency of attacks between the trial groups is shown in Figure S1 in the Supplementary Appendix.

SAFETY

No deaths or serious adverse events occurred during the double-blind phase of the trial. There was a higher frequency of adverse events in the galcanezumab group than in the placebo group (43% vs. 33%) (Table 4), with a majority of the events being rated mild to moderate in severity. Adverse events leading to discontinuation occurred in 4% of the patients in the galcanezumab group and 2% of those in the placebo group. Injection-site pain occurred in 8% of the patients in the galcanezumab group, as compared with none in the placebo group (P=0.04) (Table 4). No patient in either group reported suicidal ideation or behavior.

No clinically meaningful differences between the trial groups were observed with regard to laboratory analyses (including liver-function tests), vital signs, or electrocardiographic variables. Abnormally elevated liver-function test findings are shown in Table 4. No patient in either group had elevations of 3 or more times the upper limit of the normal range in the alanine aminotransferase or aspartate aminotransferase levels or elevations of 2 or more times the upper limit of the normal range in the alkaline phosphatase or total bilirubin levels.

At baseline, six patients who had been assigned to the galcanezumab group and two who had been assigned to the placebo group had antidrug antibodies present. No patient had a positive result for antidrug antibodies during the double-blind phase of the trial.

DISCUSSION

Preventive treatment of episodic cluster headache with galcanezumab resulted in a greater reduction in the weekly frequency of cluster headache attacks than did the use of placebo across weeks 1 through 3. A greater percentage of patients who received galcanezumab had a reduction of at least 50% in the weekly frequency of cluster headache attacks at week 3 than those receiving placebo. Beginning at week 4 and through the remainder of the 8-week double-blind period, the mean changes in the weekly frequency of cluster headache attacks in the galcanezumab group and the placebo group converged. This suggests that spontaneous improvement or remission may have occurred during the second half of the double-blind phase, reflecting the typical course of a bout of cluster headache,[1,28] or that the treatment effect with galcanezumab no longer differed substantially from that with placebo at those time points. For other secondary end points, the findings were consistent with the direction of the treatment effect for the primary end-point measure, with a larger galcanezumab treatment effect in the initial weeks of the double-blind phase. A total of 8% of the patients who received galcanezumab had injection-site pain.

Spontaneous remission is expected and has been reported in clinical trials of cluster headache, such as a finding that 64% of patients with episodic cluster headache in the placebo group had a response in a trial of suboccipital injections of glucocorticoid.[34] The design of the current trial

Table 3. Other Secondary End Points.*

Week	Weekly Frequency of Cluster Headache Attacks			≥50% Reduction in Weekly Frequency of Cluster Headache Attacks			≥30% Reduction in Weekly Frequency of Cluster Headache Attacks			Condition Very Much or Much Better†		
	Placebo	Galcanezumab	Difference (95% CI)	Placebo	Galcanezumab	Odds Ratio (95% CI)	Placebo	Galcanezumab	Odds Ratio (95% CI)	Placebo	Galcanezumab	Odds Ratio (95% CI)
	least-squares mean change from baseline in no. of events			*% of patients*			*% of patients*			*% of patients*		
1	−3.5±1.3	−5.1±1.4	−1.5 (−5.0 to 2.0)	25±6	39±8	1.9 (0.8 to 4.5)	41±7	59±8	2.1 (0.9 to 4.8)	—	—	—
2	−4.5±1.5	−8.8±1.6	−4.4 (−8.6 to −0.1)	36±7	58±8	2.5 (1.1 to 5.7)	48±8	64±8	1.9 (0.8 to 4.5)	—	—	—
3	−7.5±1.4	−11.3±1.5	−3.8 (−7.6 to 0)	52±8	72±7	2.4 (1.0 to 5.7)	67±7	73±7	1.3 (0.5 to 3.4)	—	—	—
4	−11.0±1.1	−11.5±1.2	−0.5 (−3.4 to 2.5)	73±7	77±7	1.2 (0.5 to 3.2)	77±6	75±7	0.9 (0.3 to 2.5)	46±10	72±8	3.0 (1.2 to 7.5)
5	−13.0±1.1	−11.3±1.2	1.7 (−1.2 to 4.6)	90±5	71±7	0.3 (0.1 to 0.9)	86±5	79±6	0.6 (0.2 to 1.8)	—	—	—
6	−12.1±1.4	−12.3±1.4	−0.2 (−3.9 to 3.4)	81±6	78±7	0.8 (0.3 to 2.4)	88±5	87±5	0.9 (0.2 to 3.5)	—	—	—
7	−13.7±1.1	−12.9±1.2	0.8 (−2.2 to 3.7)	88±5	80±6	0.6 (0.2 to 1.9)	92±4	89±5	0.7 (0.2 to 3.1)	—	—	—
8	−14.4±1.0	−13.1±1.0	1.3 (−1.2 to 3.8)	88±5	74±7	0.4 (0.1 to 1.3)	95±4	84±6	0.3 (0.1 to 1.5)	66±9	72±9	1.3 (0.5 to 3.4)

* Plus–minus values are least-squares means ±SE. Analyses were conducted in the modified intention-to-treat population, which included patients who had been randomly assigned to a trial group, received at least one dose of galcanezumab or placebo, and had a nonmissing baseline value (there was no baseline value for the Patient Global Impression of Improvement [PGI-I] score) and at least one nonmissing postbaseline value for the weeks included in the analysis. Percentages are estimates. Confidence intervals (CIs) were not adjusted for multiple comparisons.

† The determination regarding a condition that was very much better or much better was made on the basis of the PGI-I score (patients' responses were rated on a scale from 1 [very much better] to 7 [very much worse]). Analyses were conducted at weeks 4 and 8.

Table 4. Safety Analyses.

Variable	Placebo (N=57)	Galcanezumab (N=49)
Death — no. (%)	0	0
Serious adverse event — no. (%)	0	0
Discontinuation due to adverse event — no. (%)	1 (2)	2 (4)
Vertigo	0	1 (2)
Cluster headache	1 (2)	0
Asthma	0	1 (2)
≥1 Adverse event during the trial — no. (%)	19 (33)	21 (43)
Common adverse events*		
Injection-site pain	0	4 (8)†
Nasopharyngitis	1 (2)	3 (6)
Injection-site swelling	0	2 (4)
Pyrexia	1 (2)	2 (4)
Abnormal liver-function test finding — no./total no. (%)‡		
Alanine aminotransferase	1/49 (2)	2/43 (5)
Aspartate aminotransferase	0/49	1/45 (2)
Total bilirubin	1/50 (2)	0/47

* Common adverse events were those with an incidence of 3% or more in the galcanezumab group.
† P=0.04 for the comparison with placebo.
‡ Patients were considered to have a high value if they had a normal value at baseline, followed by a value above the upper limit of the normal range at any postbaseline visit. These patients had a value that was less than 1.5 times the upper limit of the normal range.

conformed to guidelines for clinical trials in cluster headache, including a minimum length of the double-blind observation period of 2 weeks,[28] which is designed to address the natural history of the disorder, in which cluster headache periods typically terminate spontaneously. The incidence of discontinuation of the trial regimen was higher in the placebo group (21%) than in the galcanezumab group (8%), whereas the incidence of discontinuation due to an adverse event did not differ substantially between the groups.

Cluster headache is a disorder of the brain, as shown by imaging findings,[35] results of treatment by deep-brain stimulation,[36,37] and the cyclic nature of the disorder.[1] The data from this trial provide some evidence of a role of CGRP in cluster headache[38]; however, the site of action of galcanezumab is unknown. Antibodies of the IgG class enter into the cerebrospinal fluid at only 0.1% of the plasma concentration.[39] This finding may suggest a peripheral site of action, such as the trigeminal ganglion.[40]

We planned that the trial would have a minimum of 162 patients undergoing randomization, but enrollment was halted before the trial reached the planned sample size owing to a low number of patients entering an active cluster bout during the screening period. Nevertheless, the data were sufficient for analysis of the primary and key secondary end points.[28]

In conclusion, in this trial involving patients with episodic cluster headache in which recruitment was stopped before the anticipated number of patients were enrolled, a single injection of galcanezumab at a dose of 300 mg reduced the weekly frequency of cluster headache attacks across weeks 1 through 3, as compared with placebo. Longer and larger trials are required in order to determine the durability and safety of this medication.

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