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# Phase 3 randomized, placebo-controlled study of galcanezumab in patients with chronic cluster headache: Results from 3-month double-blind treatment

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## Abstract

**Objective:** To report efficacy and safety of galcanezumab in adults with chronic cluster headache.

**Background:** Galcanezumab is a humanized monoclonal antibody that binds to calcitonin gene-related peptide and inhibits its biological activity.

**Methods:** This study comprised a prospective baseline period, a 12-week double-blind, placebo-controlled treatment period, and a 52-week open-label period. Up to six protocol-specified concomitant preventive medications were allowed if patients were on a stable dose for 2 months prior to the prospective baseline period. Patients were randomized 1:1 to monthly subcutaneous galcanezumab (300 mg) or placebo. The primary endpoint was overall mean change from baseline in weekly attack frequency with galcanezumab compared to placebo. Key secondary endpoints were $\geq$50% response rate and percentage of patients meeting sustained response. Results from the double-blind treatment period are reported.

**Results:** A total of 237 patients were randomized and treated (120 placebo; 117 galcanezumab). At baseline, the mean age was 45 years and 63% were using $\geq$1 preventive drug. The primary endpoint was not met; mean change in weekly attack frequency was $-4.6$ placebo versus $-5.4$ galcanezumab ($p = 0.334$). Key secondary endpoints also were not met. Injection site-related treatment-emergent adverse events were more common in the galcanezumab than the placebo group, with significantly more injection site erythema.

**Conclusion:** Treatment with galcanezumab 300 mg did not achieve its primary and key secondary endpoints. This study underscores the potential distinct biology of cCH as well as the significant unmet need for safe, effective, and well-tolerated preventive treatment. The safety profile of galcanezumab in cCH is consistent with that observed in trials of episodic CH and migraine.

**Trial registration:** NCT02438826; https://www.clinicaltrials.gov/ct2/show/NCT02438826.

## Keywords

Galcanezumab, chronic cluster headache, LY2951742, CGRP, humanized monoclonal antibody

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## Introduction

Cluster headache (CH) is a primary headache disorder characterized by attacks of intense unilateral headache, restlessness or agitation, and ipsilateral cranial autonomic symptoms (1,2). Attacks occur near daily to multiple times daily during cluster periods. The two subtypes, episodic CH (eCH) and chronic CH (cCH), are differentiated by the presence and duration of attack-free remission periods. Chronic cluster headache, affecting up to 20% of patients (3), is associated with cluster periods lasting 1 year or longer without remission or with remission periods lasting less than 3 months (4). The disease burden of cCH is substantial (5). Current guidelines for CH prevention (6,7) are based on a small body of evidence and few controlled trials. Additional evidence-based preventive treatments are needed.

Calcitonin gene-related peptide (CGRP) is implicated in the pathophysiology of CH and migraine (8). CGRP is highly expressed in anatomical locations activated during cluster headache and migraine, such as the trigeminal ganglion neurons and peripheral projections of the trigeminal nerve (9,10). Similar to migraine (11,12), CGRP levels were elevated during CH attacks in patients with eCH and normalized after spontaneous resolution or acute treatment with oxygen or subcutaneous sumatriptan (13,14). More recently, infusion of CGRP was shown to induce cluster headache attacks in patients with episodic and less predictably in chronic CH (15).

Galcanezumab is a humanized monoclonal antibody that binds CGRP and prevents its biological activity (16). In Phase 3 trials in patients with episodic and chronic migraine, galcanezumab treatment demonstrated clinically meaningful changes in migraine headache days, and a favorable safety profile (17–19). Galcanezumab also demonstrated efficacy in reducing CH attack frequency in a Phase 3, randomized, double-blind, placebo-controlled study in patients with eCH (20). Here we report results from the 12-week double-blind period of a Phase 3 trial of galcanezumab in patients with cCH that have been reported in abstract form previously (21,22).

## Methods

### Study design

This Phase 3, multi-center, randomized, double-blind, placebo-controlled study of galcanezumab 300 mg for the prevention of cCH comprised periods (Figure 1): a) Screening/washout (0–65 days); b) prospective baseline (14–17 days); c) double-blind, placebo-controlled treatment (12 weeks); d) optional open-label extension (52 weeks); and e) post-treatment follow-up (washout) (16 weeks).

The prospective baseline period began after the patient completed screening and washout of excluded medications, and upon experiencing a CH attack (hereafter "attack") and beginning to record their attack information and acute medication use in an electronic patient reported outcome (ePRO) diary. Fourteen consecutive days from the ePRO diary were used to determine eligibility, establish baseline attack frequency and baseline use of acute medications; hereafter, this 14-day eligibility period is referred to as the baseline period. Patients meeting entry criteria were then randomized (1:1) to 12 weeks of double-blind treatment with monthly subcutaneous injections of placebo or galcanezumab 300 mg. Treatment was assigned using a computer-generated random sequence generated by an interactive web response system, programmed using the dynamic allocation method (23) to balance treatment arms for gender, average daily attack frequency ($\leq 4$ attacks per day/$> 4$ attacks per day), verapamil use (yes/no), and investigative site.

Investigational product was administered by blinded trained staff. Galcanezumab was supplied as a lyophilized formulation in glass vials, and placebo was administered as 0.9% sodium chloride for injection. Galcanezumab and placebo were administered by blinded personnel using single dose, disposable syringes that were visibly indistinguishable from each other, with blinded labels containing subject number and study name. Patients in both groups received three injections at each dosing visit. Syringe preparation was completed by designated unblinded site personnel, not involved in clinical aspects of the study, including investigational product administration, clinical evaluations, and adverse event assessments.

### Inclusion and exclusion criteria

This study enrolled males and females, aged 18 to 65 years with a history of cCH, without a remission period, or with remissions lasting <1 month, for at least 1 year as defined by ICHD-3 beta (24), the criteria that were in effect until enrollment was completed. The diagnostic criteria for cCH have since been updated and the duration of the remission periods changed to <3 months (4). During the baseline period, patients must have had at least eight total attacks, at least one attack every other day, and a maximum of eight attacks/day (24).

Patients were excluded from the study if they had any current or past exposure to any CGRP antibody, any antibody to the CGRP receptor, or nerve growth factor antibodies. Patients suspected of having another distinct trigeminal autonomic cephalalgia (TAC) or using

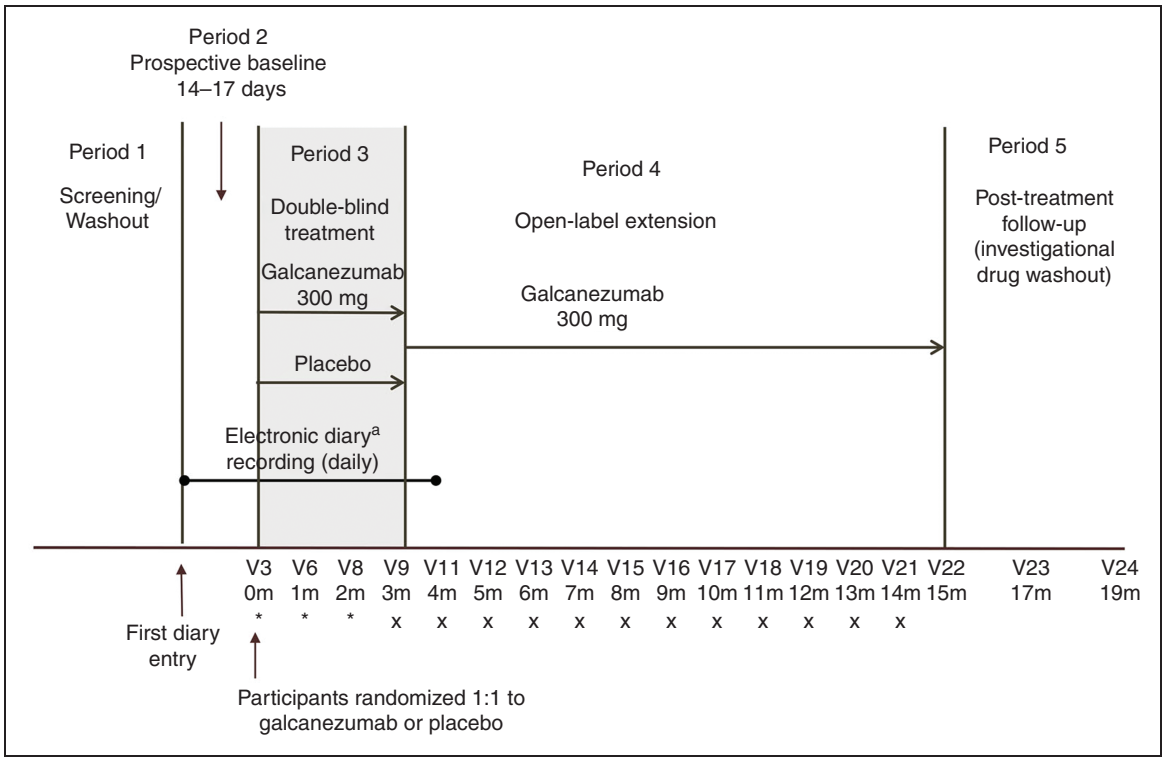


**Figure 1.** Study diagram.
ePRO: electronic patient reported outcome.
*injection of blinded investigational drug; X, injection of open-label galcanezumab 300 mg.
[a]ePRO diary reporting was completed daily during period 2, period 3, and the first month of period 4.

indomethacin to treat another suspected TAC were also excluded. If indomethacin was used to treat another condition, patients had to complete a washout period prior to the prospective baseline period. Additionally, patients who had used botulinum toxin type A or type B in the head or neck area within 4 months of the prospective baseline period were declared a screen fail and discontinued; however, these patients were allowed to rescreen for the study once, after they had completed the 4-month washout period for botulinum toxin type A or type B. Patients with a serious or unstable medical condition that precluded study participation, including (but not limited to) patients with a significant risk for suicide, history of substance abuse or dependence in the past year, history of stroke or intracranial aneurysm, or at risk for serious or acute cardiovascular events based on history or electrocardiogram findings, were also excluded. Supplemental material 1 shows the complete details of all inclusion and exclusion criteria.

The following acute treatments for attacks were allowed: High-flow oxygen, oral triptans, subcutaneous and intranasal sumatriptan, intranasal zolmitriptan, acetaminophen/ paracetamol, and non-steroidal anti-inflammatory drugs. Patients could use up to six prespecified preventive treatments for cCH (verapamil $\leq$ 480 mg/day, lithium, valproate, gabapentin, melatonin, and topiramate) provided they were on a stable dose for at least 2 months prior to the prospective baseline period and the dose remained stable throughout double-blind treatment. No other acute or preventive treatments for cCH were allowed.

## *Efficacy assessments*

Patients recorded attack-related information in an ePRO diary daily during the prospective baseline period, double-blind treatment period, and the first month of the open-label period. Patients recorded the number of attacks, average attack duration, average attack pain severity, and acute medication use for cCH. Pain severity was rated as: 0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe (25). The daily diary data were converted into biweekly intervals for analysis (weeks 1/2, 3/4, 5/6, 7/8, 9/10, and 11/12 for the double-blind period).

The primary endpoint was the overall mean change from baseline in weekly attack frequency across weeks 1–12 of the double-blind treatment period with galcanezumab compared with placebo. Key secondary endpoints were a) estimated mean percentage of patients with a $\geq$50% reduction from baseline in weekly attack frequency across weeks 1–12 and b) percentage of

patients meeting sustained response through week 12. Sustained response was defined as a ≥50% reduction in the weekly attack frequency from baseline to weeks 3/4 and maintained at weeks 5/6, weeks 7/8, weeks 9/10, and weeks 11/12. Patients discontinuing study treatment prior to weeks 11/12 were not considered sustained responders.

Other secondary assessments were: Mean change in weekly attack frequency from baseline to each 2-week interval through week 12; percentage of patients with a ≥50% reduction in weekly attack frequency from baseline at each 2-week interval through week 12; percentage of patients with a ≥30% reduction in weekly attack frequency from baseline at each 2-week interval through week 12; and percentage of patients reporting a score of 1 (''very much better'') or 2 (''much better'') on the Patient Global Impression of Improvement (PGI-I) scale at week 4, week 8, and week 12.

Pre-specified subgroup analyses for the primary efficacy measure included these variables: Sex, race, ethnicity, age, baseline average number of attacks, baseline verapamil use, and region. Overall baseline preventive use was a post-hoc subgroup analysis.

### *Clinical safety assessments*

Treatment-emergent adverse events were defined as adverse events (AEs) first occurring or worsening during the double-blind period compared with baseline. Treatment-emergent AEs, serious AEs (SAEs), AEs leading to discontinuation, vital signs and weight, electrocardiograms, and laboratory measurements are reported. Suicidal ideation and behavior were assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) (26).

Anti-drug antibody (ADA) status was determined using a proprietary validated assay that was based on an affinity capture elution ELISA, with an additional up-front acid pretreatment step (27,28). The assay was validated according to Food and Drug Administration guidance (29,30). This included validation of a minimal required dilution of 1:10 with a sensitivity of 2.9 ng/mL and a drug tolerance of galcanezumab 298.9 µg/mL at 125 ng/mL of surrogate material. Among patients evaluated for treatment-emergent-ADA, treatment emergent-ADA-positive was defined as having a baseline status of ADA not present and at least one post-baseline status of ADA-present with a titer ≥1:20 or having a baseline and post-baseline status of ADA-present, with the post-baseline titer being fourfold greater than the baseline titer.

### *Statistical analyses*

Efficacy and safety analyses were conducted on intent-to-treat patients who were randomized and received at least one dose of investigational product. The primary endpoint of change from baseline in weekly attack frequency across weeks 1–12 was analyzed using a mixed-effects model repeated measures analysis with longitudinal observations at weeks 1/2, 3/4, 5/6, 7/8, 9/10, and 11/12. The model included fixed, categorical effects of treatment, sex, verapamil use, pooled investigative site, week, and treatment-by-week interaction, as well as the continuous, fixed covariate of baseline value. Sensitivity analyses were performed for the primary endpoint.

For the key secondary outcome of the estimated mean percentage of patients with a ≥50% reduction from baseline in the weekly attack frequency during the double-blind treatment period, a categorical, pseudo-likelihood-based repeated measures analysis was used. This analysis included fixed, categorical effects of treatment, sex, verapamil use, week, and treatment-by-week interaction, as well as the continuous, fixed covariate of baseline value.

For the key secondary outcome of sustained response, treatment differences in the percentage of patients meeting the sustained response definition were determined using Koch's nonparametric randomization-based analysis of covariance method (31), which adjusted for continuous baseline value, sex, and verapamil use.

To maintain the overall type I error rate at a two-sided alpha level of 0.05 for the primary and key secondary endpoints, the Cui-Hung-Wang test statistic (32) was calculated for each due to sample size re-estimation at the interim analysis. A gate-keeping strategy was employed whereby significance of the treatment comparison for primary and key secondary endpoints was tested in a pre-specified order.

For other secondary efficacy outcomes and safety, treatment effects were evaluated based on a two-sided significance level of 0.05 without adjustment for multiplicity. A categorical, pseudo-likelihood-based repeated measures analysis was used to analyze the categorical longitudinal secondary efficacy outcomes, including at least 50% and at least 30% reduction in weekly attack frequency from baseline at each 2-week interval through week 12, and PGI-I at weeks 4, 8, and 12. Categorical comparisons between treatment groups for safety measures were performed using Fisher's exact tests, where appropriate.

For the primary and secondary efficacy endpoints, for which data were captured with electronic diary use, if there were 8 or more days with non-missing diary data and the adherence to using the diary was more than 50% in the biweekly interval, the average number of cluster headache attacks across the non-missing days was used to impute the missing days. Otherwise, data for the biweekly interval were considered to be missing and were not imputed in the analyses.

*Sample size.* The protocol included a sample size re-estimation approach. Study sites were blinded to the details. The planned enrollment was a minimum of 162 participants with the opportunity to increase to a maximum of 222 at the first interim analysis based on a pre-defined sample size re-estimation, which provided power ranging between 73% and 89% for assumed effect sizes between 0.40 and 0.50 to detect a significant difference between placebo and galcanezumab 300 mg at a one-sided $\alpha = 0.025$. The power analysis was performed using EAST software version 6.2 assuming a 10% discontinuation rate.

*Interim analyses.* Two planned interim analyses were conducted. Safety analysis, futility analysis, and sample size re-estimation were conducted at the first interim analysis. For the first interim analysis, an independent data monitoring committee conducted an unblinded review of efficacy and safety data. The review included 106 randomized patients who received at least one dose, who had baseline and at least one post-baseline value of weekly attack frequency, and who completed the week 4 visit for sample size re-estimation and futility evaluation. The review also included 110 randomized patients with at least one dose for safety evaluation. Based on pre-specified criteria, the committee recommended a sample size increase to 222. No further study modifications were recommended.

The second interim analysis was performed on the final set of all randomized patients through the end of the double-blind period. The results from this second interim analysis are reported here.

## Results

### Patient disposition

This study was conducted at 39 study sites in 12 countries (Belgium, Canada, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Spain, United Kingdom, and United States). The first patient was enrolled on 29 July 2015; the last patient completed double-blind treatment on 27 March 2018.

Overall, 387 patients were screened and 147 patients did not meet screening criteria (Figure 2). Of 240 patients who were randomized to double-blind treatment, three patients in the placebo group did not receive treatment; thus, 237 patients (120 placebo; 117 galcanezumab) were included in the intent-to-treat population (Figure 2). Overall, 230 (97%) patients completed double-blind treatment. Three patients discontinued from placebo treatment (AE [n = 1]; lack of efficacy [n = 1]; subject withdrawal [n = 1]) and four patients discontinued from galcanezumab treatment (AE [n = 1]; protocol deviation [n = 2]; subject withdrawal [n = 1]). The two protocol deviations that led to discontinuation were having met a cardiovascular exclusion criterion (high Bazett's QT interval prior to starting treatment) and taking an excluded medication (prednisone). The placebo- and galcanezumab-treated patients discontinued due to an AE of palpitations and an SAE of atrial fibrillation (lasting 1 day; patient diagnosed with thyroid nodules 3 weeks later), respectively (both resolved).

### Baseline demographics

The patient population was predominately male (72.6%) and white (84.4%), with a mean age of 45.0 years (Table 1). Most patients were from Europe (82.7%). Overall, 63.3% of patients were taking at least one preventive medication and among these patients, 72%, 24%, 3%, and 1% were taking 1, 2, 3, and 4 preventatives, respectively. Approximately 50% of all patients were taking verapamil. Oxygen and subcutaneous sumatriptan were the most frequently used acute treatments (oxygen: 53.3% placebo; 65.0% galcanezumab; subcutaneous sumatriptan: 62.5% placebo; 63.3% galcanezumab). Most patients (83.1%) had $\leq 4$ daily attacks during the baseline period (mean weekly attacks $18.8 \pm 10.2$; average pain severity $2.7 \pm 0.7$ [moderate-to-severe]). Before screening, 23.2% of patients reported lifetime suicidal ideation and 3.8% reported lifetime suicidal behavior.

### Efficacy

The primary endpoint was not met. The mean reduction from baseline in weekly attack frequency across weeks 1–12 was −4.6 attacks with placebo versus −5.4 attacks with galcanezumab ($p = 0.334$) (Figure 3(a)). At weeks 1/2, there was a significantly greater mean change from baseline in weekly attack frequency with galcanezumab compared to placebo (−4.0 attacks vs −1.8 attacks, respectively; $p = 0.006$) (Figure 3(a); Table 2). No significant treatment group differences were observed at other biweekly intervals. Sensitivity analyses (data not shown) were performed and results were consistent with that of the primary efficacy analysis.

Key secondary endpoints were not met. The mean percentage of patients with a $\geq 50\%$ reduction in weekly attack frequency from baseline across weeks 1 to 12 was 27.1% with placebo and 32.6% with galcanezumab ($p = 0.170$) (Figure 3(b); Table 2). A similar percentage of patients in each treatment group met the definition of sustained response (17.5% placebo; 16.2% galcanezumab; $p = 0.946$) (Figure 3(c)). Other secondary outcomes were also not met (Table 2).

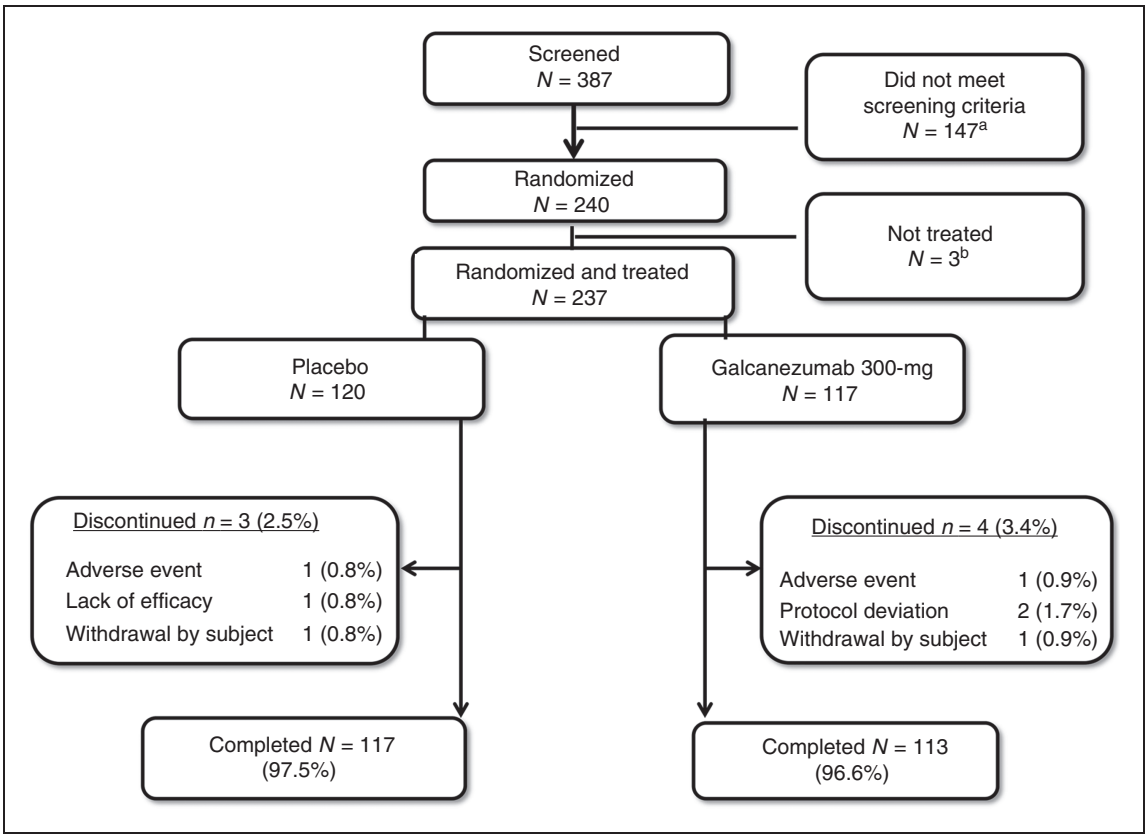


**Figure 2.** Patient disposition during the double-blind period.
N: population size; n: number in group.
[a]The most common reasons for screen failure were not meeting cluster headache attack frequency criteria during the prospective baseline period or having a cardiovascular or a drug- or alcohol-related exclusion criterion.
[b]Three patients who were randomized to placebo did not receive treatment.

Pre-specified subgroup analyses for the primary efficacy measure included sex, race, ethnicity, age, baseline average number of attacks, baseline verapamil use, and region. The treatment effect differed in North America versus Europe, with a greater overall mean reduction in weekly cluster headache attack frequency observed in Europe compared with North America (region-by-treatment interaction; $p = 0.007$). Subgroup-by-treatment interactions for sex, race, ethnicity, age, baseline average number of attacks, and baseline verapamil or preventive use were not statistically significant (Supplemental material 2; Table A). *Post-hoc* analyses were conducted to further understand the regional difference by searching for potential confounders or effect modifiers. An imbalance was observed in the following variables in North America: Baseline weekly attack frequency, baseline subcutaneous sumatriptan use, and lifetime suicidal ideation/behavior prior to screening (Supplemental material 2, Table B). There was also evidence of treatment-by-baseline subcutaneous sumatriptan use interaction (Supplemental material 2, Table C) with a greater reduction in attack frequency with galcanezumab compared to placebo in high-frequency users of subcutaneous sumatriptan (defined as ( > 7.031 times of baseline sumatriptan use per week) compared to the low-frequency users.

### *Concomitant medication*

Acute medication including oxygen was used in 93.3% and 94.9% of patients in the placebo and galcanezumab groups, respectively, during the double-blind period. Subcutaneous sumatriptan (67.5% in each treatment group) and oxygen (53.3% placebo; 65.0% galcanezumab) were the most common. The percentages of patients using an allowed preventive medication were verapamil (53.3% placebo; 47.0% galcanezumab); lithium (15.0% placebo; 11.1% galcanezumab), topiramate (10.8% placebo; 7.7% galcanezumab), valproate (5.8% placebo; 6.8% galcanezumab), melatonin (1.7% placebo; 5.1% galcanezumab), and gabapentin (2.5% placebo; 2.6% galcanezumab). There were no significant differences between treatment groups for any acute or preventive medication.

**Table 1.** Baseline characteristics of the intent-to-treat population.

| Characteristic | Placebo N = 120 | Galcanezumab N = 117 | Total N = 237 |
|---|---|---|---|
| Age, mean (±SD) | | | |
| Mean age | 44.4 (±10.8) | 45.6 (±11.0) | 45.0 (±10.9) |
| Gender, n (%) | | | |
| Male | 86 (71.7) | 86 (73.5) | 172 (72.6) |
| Race, n (%) | | | |
| Black or African American | 1 (0.8) | 1 (0.9) | 2 (0.8) |
| White | 101 (84.2) | 99 (84.6) | 200 (84.4) |
| Multiple | 18 (15.0) | 17 (14.5) | 35 (14.8) |
| Region, n (%) | | | |
| Europe | 101 (84.2) | 95 (81.2) | 196 (82.7) |
| North America | 19 (15.8) | 22 (18.8) | 41 (17.3) |
| Verapamil use, *n* (%) | 63 (52.5) | 55 (47.0) | 118 (49.8) |
| Body mass index (kg/m$^2$), mean (±SD) | 26.3 (±4.8) | 26.4 (±4.8) | 26.4 (±4.8) |
| Lifetime suicidal ideation prior to screening, *n* (%) | 30 (25.0) | 25 (21.4) | 55 (23.2) |
| Lifetime suicidal behavior prior to screening, *n* (%)[a] | 5 (4.2) | 4 (3.4) | 9 (3.8) |
| Duration of cluster headache illness, years, mean (±SD)[b] | 8.4 (±7.5) | 7.7 (±6.6) | 8.0 (±7.1) |
| Prospective baseline period | | | |
| Weekly attacks, mean (±SD) | 18.5 (±10.7) | 19.2 (±9.8) | 18.8 (±10.2) |
| Severity of pain, mean (±SD)[c] | 2.6 (±0.7) | 2.8 (±0.7) | 2.7 (±0.7) |
| Daily cluster attack category, ≤4 per day, n (%) | 100 (83.3) | 97 (82.9) | 197 (83.1) |

N: number of intent-to-treat patients with non-missing demographic measures; n: number of patients within each specific category; SD: standard deviation.

[a]N = 119 and N = 236 in placebo group and total groups, respectively.

[b]Duration of cluster headache illness (years) was defined using (informed consent date – first cluster headache medical history start date + 1) /365.25. N = 119, N = 116, and N = 235 for placebo, galcanezumab, and total, respectively.

[c]Pain severity rated using a 5-point pain scale: 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain, and 4 = very severe pain (33).

## *Safety*

The mean exposure duration during the double-blind period was 90.6 and 90.3 days for placebo and galcanezumab, respectively. Most patients (97.5%) received all three doses of study drug. Adverse events reported during the double-blind treatment period are summarized in Table 3. No deaths were reported. Three placebo-treated patients reported SAEs of melena, non-cardiac chest pain, and depression, respectively, all of which resolved. Two galcanezumab-treated patients each reported one SAE (atrial fibrillation [discontinued treatment] and constipation [no change to study treatment]) with both AEs noted as resolved. Constipation was judged by the investigator as treatment related.

A higher percentage of galcanezumab-treated patients reported treatment-emergent AEs (62.5% placebo; 71.8% galcanezumab), with the majority of patients (92.5%) reporting treatment-emergent AEs as mild or moderate. Injection site pain, nasopharyngitis, injection site erythema, and nausea were reported by ≥5% of galcanezumab-treated patients (Table 3), with injection site erythema reported by significantly more galcanezumab- than placebo-treated patients (0.8% placebo; 6.8% galcanezumab, $p = 0.018$). During double-blind treatment, no patient reported suicidal behavior; similar numbers of placebo- (n = 6) and galcanezumab-treated (n = 5) patients reported suicidal ideation.

There were no clinically meaningful differences in laboratory parameters between treatment groups, and no patient met abnormal hepatic laboratory criteria (i.e. alanine aminotransferase or aspartate aminotransferase ≥3 × the upper limit of normal, alkaline phosphatase or total bilirubin ≥2 × the upper limit of normal). A statistically significant mean difference was observed for diastolic blood pressure (−1.7 mmHg placebo; 0.2 mmHg galcanezumab, least squares mean change difference: 1.9 mmHg; $p = 0.044$) (Table 4); however, this was not associated with increases in reported hypertension AEs (2.5% placebo;

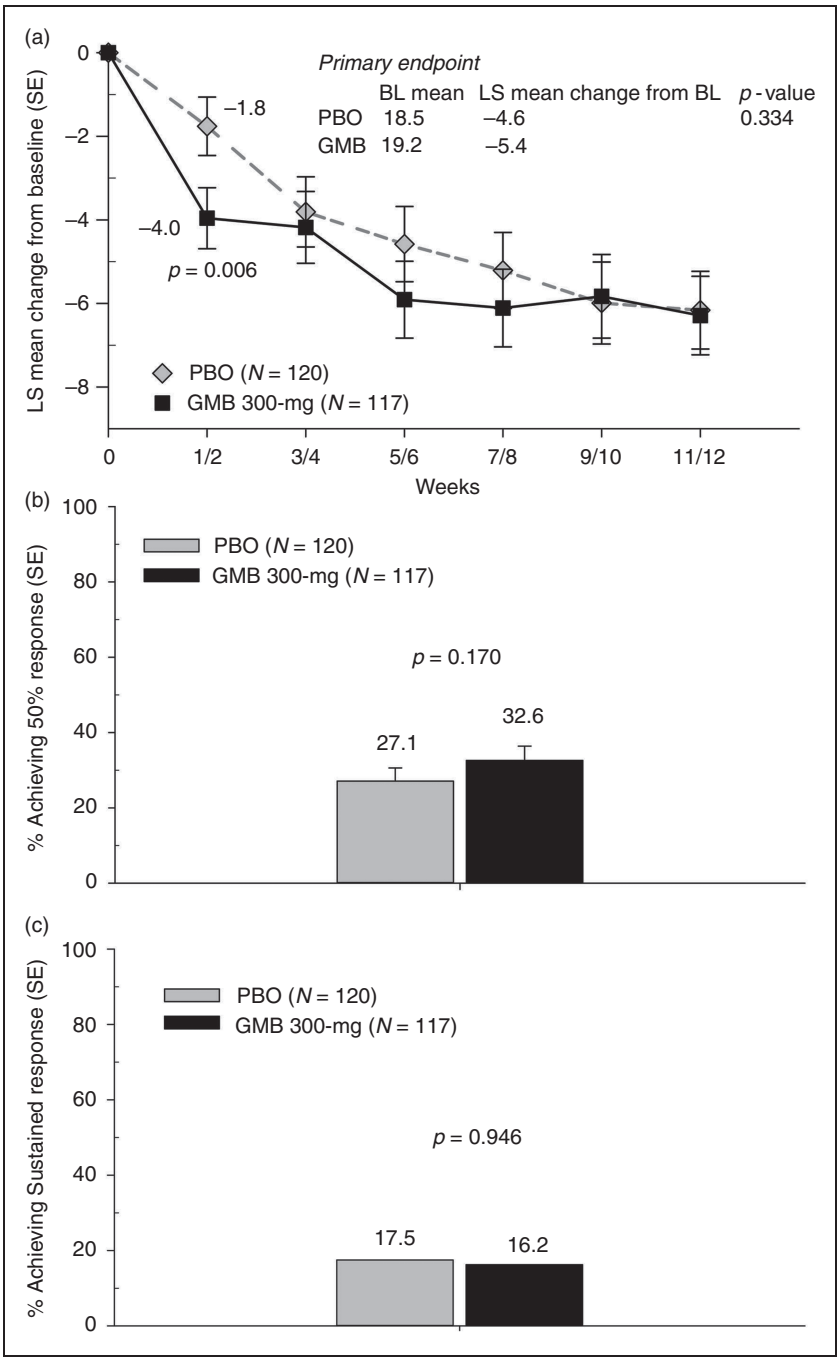


**Figure 3.** Primary endpoint and key secondary endpoints. a) Least squares mean change from baseline in weekly cluster headache attack frequency. The primary endpoint is overall mean change from baseline in weekly cluster headache attack frequency across weeks 1–12. b) Mean percentage of patients achieving a response of $\geq$ 50% reduction in weekly cluster headache frequency across weeks 1–12 (first key secondary endpoint). c) Percentage of patients achieving a sustained response through week 12. A sustained response was defined as $\geq$ 50% reduction in the weekly cluster attack frequency from baseline to weeks 3/4 and maintained at weeks 5/6, 7/8, 9/10, and 11/12 (second key secondary endpoint). CHW adjusted *p*-values are shown.
BL: baseline; CHW: Cui, Hung, and Wang; GMB: galcanezumab; LS: least squares; N: population size; PBO: placebo; SE: standard error.

2.6% galcanezumab), or initiation of, or dose increases in antihypertensive medication (1.7% placebo; 1.7% galcanezumab). There were no statistically significant or clinically meaningful differences between placebo and galcanezumab in the percentage of patients with categorical increases in blood pressure, pulse, or weight or in quantitative or qualitative electrocardiograms.

**Table 2.** Secondary efficacy outcomes.

| | Week 1/2 | Week 3/4 | Week 5/6 | Week 7/8 | Week 9/10 | Week 11/12 | Overall |
|---|---|---|---|---|---|---|---|
| Change from baseline in weekly cluster headache attack frequency[a] | | | | | | | |
| Placebo, least squares mean change from baseline (SE) | −1.8 (0.7) | −3.8 (0.8) | −4.6 (0.9) | −5.2 (0.9) | −6.0 (1.0) | −6.2 (0.9) | −4.6 (0.8) |
| Galcanezumab 300 mg, least squares mean change from baseline (SE) | −4.0 (0.7)* | −4.2 (0.9) | −5.9 (0.9) | −6.1 (0.9) | −5.8 (1.0) | −6.3 (0.9) | −5.4 (0.8) |
| Estimated percentage of 50% responders for weekly cluster headache attack frequency[a] | | | | | | | |
| Placebo, model estimated rate (SE), % | 13.3 (3.1) | 25.7 (4.2) | 29.4 (4.4) | 31.1 (4.5) | 30.2 (4.4) | 38.3 (4.7) | 27.1 (3.5) |
| Galcanezumab 300 mg, model estimated rate (SE) | 19.9 (3.8) | 27.1 (4.3) | 38.7 (4.8) | 34.6 (4.7) | 39.7 (4.9) | 38.6 (4.8) | 32.6 (3.8) |
| Estimated percentage of 30% responders for weekly cluster headache attack frequency[a] | | | | | | | |
| Placebo, model estimated rate (SE) | 23.0 (3.9) | 39.1 (4.7) | 39.5 (4.7) | 42.9 (4.8) | 44.7 (4.8) | 47.2 (4.9) | 39.0 (3.9) |
| Galcanezumab 300 mg, model estimated rate (SE) | 35.2 (4.6)** | 45.5 (4.9) | 52.3 (5.0) | 53.8 (5.0) | 54.4 (5.0) | 53.7 (5.0) | 49.1 (4.1) |
| PGI-I[b] Percentage of patients with score 1 or 2 at each of weeks 4, 8, 12 | Week 4 | | Week 8 | | Week 12 | | Overall |
| Placebo, model estimated rate (SE) | 19.4 (4.5) | | 32.0 (5.5) | | 35.6 (5.7) | | 28.4 (4.7) |
| Galcanezumab 300 mg, model estimated rate (SE) | 21.5 (4.8) | | 32.1 (5.7) | | 30.4 (5.5) | | 27.7 (4.7) |

*$p = 0.006$, CHW adjusted.
**$p = 0.037$.
[a]N=120 placebo and N=117 galcanezumab intent-to-treat patients with baseline and at least one post-baseline measurement.
[b]N=103 placebo and N=102 galcanezumab intent-to-treat patients with at least one post-baseline measurement.
CHW: Cui, Hung, and Wang; N: population size; PGI-I: Patient Global Impression of Improvement; SE: standard error.

**Table 3.** Summary of adverse events during the double-blind treatment period.[a]

| Category | Placebo (N = 120) | GMB 300 mg (N = 117) |
|---|---|---|
| Deaths, n (%) | 0 | 0 |
| Serious adverse events, n (%) | 3 (2.5) | 2 (1.7) |
| Atrial fibrillation | 0 | 1 (0.9) |
| Constipation | 0 | 1 (0.9) |
| Melena | 1 (0.8) | 0 |
| Non-cardiac chest pain | 1 (0.8) | 0 |
| Depression | 1 (0.8) | 0 |
| Discontinuation due to adverse events, n (%) | 1 (0.8) | 1 (0.9) |
| Atrial fibrillation | 0 | 1 (0.9) |
| Palpitations | 1 (0.8) | 0 |
| Patients with ≥ 1 treatment-emergent adverse event, n (%)[b] | 75 (62.5) | 84 (71.8) |
| Injection site pain | 11 (9.2) | 13 (11.1) |
| Nasopharyngitis | 15 (12.5) | 12 (10.3) |
| Injection site erythema | 1 (0.8) | 8 (6.8)[c] |
| Nausea | 6 (5.0) | 6 (5.1) |
| Back pain | 1 (0.8) | 5 (4.3) |
| Dizziness | 5 (4.2) | 5 (4.3) |
| Fatigue | 7 (5.8) | 5 (4.3) |
| Influenza-like illness | 1 (0.8) | 5 (4.3) |
| Injection site pruritus | 1 (0.8) | 5 (4.3) |
| Pain in extremity | 1 (0.8) | 4 (3.4) |
| Dysmenorrhea[d] | 0 | 1 (3.2) |
| Menstrual disorder[d] | 0 | 1 (3.2) |
| Gastroenteritis | 1 (0.8) | 3 (2.6) |
| Myalgia | 3 (2.5) | 3 (2.6) |
| Pruritus | 0 | 3 (2.6) |
| Pyrexia | 1 (0.8) | 3 (2.6) |
| Tinnitus | 1 (0.8) | 3 (2.6) |
| Vomiting | 3 (2.5) | 3 (2.6) |

GMB: galcanezumab; N: number of patients in the population; n: number of participants within each specific category.
[a]Adverse events were coded using terms from Medical Dictionary for Regulatory Activities version 20.1.
[b]Treatment-emergent adverse events occurring with a frequency of ≥ 2% (before rounding) in the galcanezumab group are shown.
[c]$p = 0.018$.
[d]Denominator adjusted for female-specific event.

Concomitant use of galcanezumab and verapamil did not lead to increases in treatment-emergent cardiovascular events, including bradycardia, first degree atrioventricular block, dizziness, or dyspnea events during double-blind treatment. There were no reports of treatment-emergent heart failure, congestive heart failure, pulmonary edema, rapid ventricular response, or second- or third-degree atrioventricular block.

There were 14 patients with ADA present at baseline, and one galcanezumab-treated patient with treatment-emergent ADA during the double-blind period, with no TEAEs reported.

## Discussion

To our knowledge this is one of the largest completed randomized, placebo-controlled trials to investigate the efficacy and safety of a preventive treatment for cCH. Similar to the eCH study (20), this study in patients with cCH evaluated whether galcanezumab reduced the frequency of weekly attacks, an endpoint consistent with the 1995 IHS guideline (25). In this cCH study, the primary endpoint, reduction in attack frequency across weeks 1–12, and key secondary objectives were not met. This is in contrast to the eCH study, which demonstrated that galcanezumab significantly reduced the number of weekly CH attacks across weeks 1–3 (20). In the eCH study, the early primary endpoint (across weeks 1–3) was necessary to ensure an adequate test prior to spontaneous remission as noted in the IHS guideline (25); however, for cCH, a durable effect measured across weeks 1–12 was chosen due to the largely unremitting nature of the disorder. While not observed at any other biweekly interval, a significantly greater reduction in the weekly attack frequency was observed with galcanezumab compared to placebo at weeks 1/2.

With regard to the regional difference between Europe and North America on the primary endpoint, the results of the *post hoc* analyses provide evidence that the observed interaction by region could be partially induced by both imbalance of the confounders (baseline weekly attack frequency; baseline subcutaneous sumatriptan use; and lifetime suicidal ideation and behavior prior to screening) between treatment groups within region, and the difference in the distribution of effect modifier (baseline subcutaneous sumatriptan use). Given the small sample size in North America, the interaction of region by treatment could also be a spurious finding.

The patient populations in the chronic and episodic studies had a similar mean age, and were predominantly male, Caucasian, and from Europe. The numbers of weekly attacks at baseline were similar ($17.5 \pm 10.0$ episodic (20); $18.8 \pm 10.2$ chronic). One between-study difference was that preventive medications were allowed in the cCH trial, but not in the eCH trial. In the cCH trial, 63% of patients used at least one preventive medication, with 49.8% of all patients using verapamil; however, a subgroup analysis by baseline

**Table 4.** Summary of least squares mean changes from baseline to endpoint in blood pressure, pulse, and weight.

| | Placebo N = 119 | Galcanezumab N = 117 | Least squares mean difference[b] |
|---|---|---|---|
| Systolic blood pressure, Least squares mean change from baseline, mm Hg[a] | −1.33 | 0.11 | 1.44 |
| Diastolic blood pressure, Least squares mean change from baseline, mmHg[a] | −1.74 | 0.18 | 1.92[c] |
| Pulse, least squares mean change from baseline, beats/minute[a] | −0.85 | 0.60 | 1.45 |
| Weight, least squares mean change from baseline, kg[a] | 0.26 | −0.00 | −0.26 |

[a]From baseline to the final post-baseline value during the double-blind treatment period.
[b]Least squares mean treatment differences are derived relative to placebo using analysis of covariance model: Change from baseline = treatment, pooled investigative site, and baseline value.
[c]$p = 0.044$ for between treatment comparison for change from baseline.

verapamil or preventive drug use did not show a treatment interaction.

Other studies have also shown differential treatment effects between chronic and episodic CH. For instance, lithium demonstrated efficacy in a comparator trial in cCH, but not in a placebo-controlled trial in eCH (34,35). In the ACT-1 and -2 randomized, double-blind clinical trials, non-invasive vagus nerve stimulation versus sham for the acute treatment of CH showed efficacy in patients with eCH, but not in patients with cCH (36,37). Potential differences between eCH and cCH are supported by research suggesting the brain anatomy (38) and the chronobiology of patients with cCH differ from those of patients with eCH and healthy controls (39).

It is conceivable that differences exist between episodic and chronic CH related to the role (or degree of influence) of CGRP. Studies to date that have reported CGRP elevations during CH attacks that normalized after successful treatment of the attack with subcutaneous sumatriptan or oxygen were in patients with eCH (13,14). However, in a recent study, CGRP infusion provoked an attack in 50% of patients with cCH compared to 89% of patients with eCH during an active cluster period (15), suggesting possible pathophysiological differences between the chronic and episodic subtypes and a different role of CGRP in cCH than in eCH.

It is also possible that cCH is more treatment-resistant than eCH. Based on reported clinical observations, a subset of patients with cCH who do not respond adequately to existing treatment options may be refractory to preventive treatments (36,40). These observations have resulted in a recommendation to establish diagnostic criteria for refractory cCH (40). In this study, patients who had inadequate responses to prior and current preventive treatments were not excluded, and 63% were on preventive treatments at baseline, suggesting an inadequate response to those preventives. Additionally, the percentage of patients reporting lifetime suicidal ideation and behavior at baseline was higher in the cCH study compared to the eCH study (ideation: 23% vs. 13%; behavior: 4% vs. 1%, respectively), also suggesting a more severely affected patient population. However, as approximately 30% of patients in the eCH study were not in an active cluster period at the time of the baseline assessment of lifetime suicidality, this may have contributed to the lower reported frequency in the eCH study compared to the cCH study.

Galcanezumab-treated patients had a high completion rate (96.6%) and low rate of discontinuation due to AEs ( <1%). There was a higher frequency of treatment-emergent AEs in the galcanezumab group compared with the placebo group, which was due primarily to injection site-related treatment-emergent AEs. Overall, the safety of galcanezumab in patients with cCH was consistent with that seen with patients in the eCH and episodic and chronic migraine trials (17–20).

This study does have limitations. The patient population was predominantly European, which may limit generalizability of these results to patients in other geographies. Restrictions in the inclusion criteria of this study may also limit the generalizability of the results. The number of failed preventive drugs prior to study entry was not collected, and this information may have contributed to an understanding of the extent to which patients were treatment resistant. It is possible that patients with cCH may take longer to respond adequately to preventive CGRP antibody therapy, though conducting a longer placebo-controlled study in such a severely affected patient population would be challenging. This study includes a 52-week open-label extension; however, the results are not yet available.

## Conclusion

The primary and key secondary endpoints were not met in this cCH prevention trial. The safety of galcanezumab in patients with cCH was consistent with that of patients with eCH and migraine.

### Clinical implications

- The disease burden of chronic cluster headache is substantial and there is a significant unmet need for new treatment.
- Treatment with galcanezumab 300 mg did not achieve its primary endpoint (overall mean change from baseline in weekly attack frequency across weeks 1–12) in patients with chronic cluster headache.
- Galcanezumab safety was consistent with that of patients with episodic cluster headache and migraine.

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## Ethical approval and conduct

The study protocol was reviewed and approved by the appropriate institutional or ethical review board for each site. The study was conducted according to Good Clinical Practice and the Declaration of Helsinki guidelines. Patients provided written informed consent before undergoing study procedures.

## Data sharing

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available on request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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