Research Submission

Treatment Outcomes in Patients Treated With Galcanezumab vs Placebo: Post Hoc Analyses From a Phase 3 Randomized Study in Patients With Episodic Cluster Headache

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Background.—Cluster headache (CH) is a highly disabling primary headache disorder. To date, characterization of outcomes in the preventive treatment of episodic CH, including precise definitions of clinically meaningful attack frequency reduction and impact on acute treatment management, is lacking.

Methods.—This was a Phase 3, randomized, double-blind, placebo-controlled study in patients (men or women aged 18-65 years) diagnosed with episodic CH as defined by the International Classification of Headache Disorders-3 beta criteria. In this post hoc analysis, we evaluated the median time-to-first occurrence of ≥50, ≥75, or 100% reduction from baseline in CH attack frequency, and impact on acute medication use. An anchor-based assessment of clinically relevant attack frequency reduction using the Patient Global Impression of Improvement (PGI-I) scores at Week 4 was also assessed.

Results.—The median time-to-first occurrence of ≥50, ≥75, or 100% reduction from baseline in CH attacks was consistently shorter (9-10 days sooner) with galcanezumab vs placebo (median [95% confidence interval, 95% CI]: ≥50%, 5 days [4.0 to 7.0] vs 14 days [6.0 to 19.0]; ≥75%, 11 days [7.0 to 16.0] vs 21 days [13.0 to 26.0]; 100%, 22 days [16.0 to 37.0] vs 32 days [23.0 to 34.0]). Mean reduction from baseline in the overall frequency of weekly pooled acute medication use across Weeks 1-3 was significantly greater with galcanezumab vs placebo (11.0 vs 5.5; odds ratio, OR [95% CI]: 5.52 [1.02, 10.01]; P value = .017). Patients reporting "much better" on the PGI-I experienced a median weekly CH attack reduction of approximately 43% from baseline across Weeks 1-3. The overall odds of achieving an attack reduction threshold of 43% across Weeks 1-3 was significantly higher with galcanezumab vs placebo (Weeks 1-3: OR [95% CI], 2.60 [1.3 to 5.3]).

Conclusions.—Faster median time-to-first occurrence of response rates, lower frequency of pooled acute medications use, and a greater proportion of patients achieving a response anchored by patient-reported improvement were observed for galcanezumab vs placebo.

Key words: episodic cluster headache, patient-reported outcomes, acute medication use frequency, time-to-first occurrence, responder threshold, responder rate

Abbreviations: CH cluster headache, CI confidence interval, NSAID nonsteroidal anti-inflammatory drugs, SD standard deviation

BACKGROUND

Cluster headache (CH) is a primary headache disorder with a lifetime prevalence of approximately 0.1% and is characterized by severe attacks of pain that are strictly unilateral in nature.[1,2] The CH attacks last anywhere between 15 and 180 minutes when left untreated, with frequencies ranging from once every other day up to 8 times a day.[1] In episodic CH, these attacks occur in a series lasting for weeks or months (cluster periods), typically 2-12 weeks (cluster periods), separated by periods of remission lasting at least 3 months.[1] Episodic CH is associated with a substantial negative impact on health-related quality of life, functioning, and ability to work.[3-5] The pain that patients suffer during an attack is described as their worst pain,[6] and suicidal ideation is often reported during the attacks.[7]

Acute treatments recommended by treatment guidelines to abort CH attacks and reduce the pain[8,9] include subcutaneous sumatriptan, sumatriptan nasal spray, zolmitriptan nasal spray, and high-flow oxygen. Preventive treatment options reduce the frequency of attacks during the cluster period. These include verapamil, steroids, suboccipital steroid injections, lithium, and topiramate.[8,9] However, these preventive treatments are recognized in guidelines to varying degrees due to a lack of substantial clinical evidence and many are associated with adverse effects.[9-11] This has resulted in a large unmet need for preventive medications that are safe, well-tolerated, and efficacious for the treatment of CH. In a recent cross-sectional survey of physicians[12] and their patients in the United States of America, United Kingdom, and Germany, the treatment of episodic CH was marked by high acute medication use and low use of preventive medications.

Currently, galcanezumab (300 mg/month subcutaneous injections administered at the onset of and until the end of the cluster period) is the only medication approved in the United States of America for the treatment of episodic CH and has been shown to reduce the frequency of CH attacks during a cluster period.[13] Galcanezumab is a humanized monoclonal antibody that selectively binds and blocks the activity of calcitonin gene-related peptide. In a Phase 3 study in patients with episodic CH, treatment with galcanezumab vs placebo showed a significantly greater mean reduction in the weekly frequency of CH attacks from baseline (8.7 vs 5.2 attacks, *P* value = .04) across Weeks 1-3 and greater number of patients achieving 50% CH attack reduction with galcanezumab (71%) vs placebo (53%) at week 3.[14] With the exception of injection site pain, which occurred in 8% of galcanezumab-treated patients (n = 4) vs 0% for placebo, no notable differences were observed between galcanezumab and placebo in the incidence of adverse events.

To date, characterization of outcomes in the preventive treatment of episodic CH, including precise definitions of clinically meaningful reduction in attack frequency and impact on acute treatment management, is lacking. In this post hoc analysis, we aim to characterize the clinical importance of galcanezumab treatment in patients with episodic CH in terms of median time-to-first occurrence of ≥50, ≥75, and 100% reduction from baseline in CH attack frequency and the observed changes in acute medication use. We hypothesize that greater improvement in these outcomes will be observed in the galcanezumab group compared with placebo. Additionally, a response definition that incorporates a patient's rating of improvement in their health condition was used to define a clinically meaningful threshold of CH attack reduction and evaluated in subsequent responder analyses.

METHODS

The study design, patient demographics, and key results have been described in detail previously.[14] Briefly, this was a Phase 3, multi-center, randomized, double-blind, placebo-controlled study in patients with episodic CH (Clinicaltrials.gov identifier: NCT02397473). Outpatients (men or women aged 18-65 years) with a diagnosis of episodic CH as defined by the International Classification of Headache Disorders-3 beta criteria were included.[15]

The use of acute medications including high-flow oxygen, sumatriptan subcutaneous injection, sumatriptan nasal spray, zolmitriptan nasal spray, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs) was allowed throughout the study for the acute management of CH attacks. Each class of acute medication use was analyzed in the current post hoc analyses. However, for simplicity, these were categorized into 4 classes: (1) oxygen; (2) subcutaneous sumatriptan; (3) oral/intranasal sumatriptan/zolmitriptan; and (4) acetaminophen/NSAIDs. Change from baseline in weekly frequencies of these 4 classes of acute medications as well as weekly frequencies of all 4 medication classes pooled (combined) was analyzed. Subcutaneous sumatriptan was considered separately from oral/nasal triptans because the subcutaneous formulation is generally considered first-line therapy for the acute treatment of CH attacks (as is high-flow oxygen).[16] While intranasal zolmitriptan nasal spray has level A evidence[8] according to AHS guidelines, the intranasal triptans are often less preferred by patients since their autonomic symptoms often include nasal congestion or rhinorrhea. In addition, oral triptans have level B evidence for the acute treatment of CH. As such, subcutaneous sumatriptan was assigned its own group, and the intranasal and oral formulations were combined into a separate grouping.

Additionally, oral triptans were not originally permitted as an acute medication but, following a protocol amendment, were later allowed for the management of CH.

The study consisted of a screening phase (0 to 12 months), prospective baseline phase (10 to 15 days), double-blind, placebo-controlled treatment Phase (8 weeks), and a post-treatment follow-up Phase (16 weeks). The primary objective of reducing mean weekly CH attack frequency was assessed across Weeks 1-3 of the 8-week double-blind, placebo-controlled treatment phase.[14] Eligibility and baseline weekly CH characteristics were assessed over 7 consecutive days during the prospective baseline period. Eligible patients were randomized (1:1) to receive either placebo or galcanezumab 300 mg/month (Fig. S1). Patients could enter the study either in an active cluster period or in remission. For patients who entered remission, they remained in the screening phase until the onset of their next cluster period and the maximum duration of the screening phase was 12 months. For all patients, the prospective baseline phase began on the day the patient first recorded a CH attack in the electronic patient-reported outcome (ePRO) diary. Eligible patients were then randomized (1:1) to receive either placebo or galcanezumab 300 mg/month (Fig. S1).

The study protocol was reviewed and approved by the respective ethics review boards of the participating study sites. The studies were conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki guidelines. All patients provided written informed consent prior to study participation.

Exploratory Outcomes.—The analysis assessed the median time-to-first occurrence of ≥50, ≥75, and 100% reduction from baseline in CH attack frequency for galcanezumab vs placebo. Additionally, the frequency of individual classes and pooled acute medication use (high-flow oxygen, subcutaneous sumatriptan, oral/intranasal triptans, NSAIDs/acetaminophen) was compared for galcanezumab vs placebo. The patients recorded their CH attacks in a daily eDiary, and if the patient experienced an attack, they recorded the number of times each acute medication was used. Finally, a responder definition was derived from the threshold of weekly reduction in CH attack frequency that corresponded to patients who reported feeling "much better" on the Patient Global Impression of Improvement (PGI-I) at Week 4. The PGI-I is a global measure that captures a patient's assessment of how their condition has changed relative to the baseline state.[17] The patients were asked to respond to the prompt that best describes their CH condition since starting their medi-

cation using a range of ordinal responses from 1 "very much better" to 4 "no change" to 7 "very much worse."

Statistical Analysis.—Analyses were performed on patients with baseline value and at least 1 post-baseline measurement for the corresponding outcome. Categorical variables (nominal baseline demographics and clinical characteristics) were summarized using frequency and percentage, while numeric or interval variables and ordinal variables were summarized using appropriate statistics such as mean, standard deviation (SD), median, and quantiles.

The median time-to-first occurrence of ≥50, ≥75, and 100% reduction from baseline in CH attack frequency, along with 95% CI, was estimated using the Kaplan-Meier method. To reduce the variability of daily data which are inherent given the nature of the disease, for each patient, the percentage reduction from baseline was calculated on a 7-day moving window (ie, current day, preceding 3 days, and following 3 days), moving 1 day at a time. Time-to-first occurrence of a response threshold was recorded as the middle day of the earliest 7-day window during which the threshold was reached. Patients who never reached a particular responder threshold were considered to be censored.

The frequency of CH attacks and acute medication use was recorded by patients in their daily electronic diary. The mean change from baseline in the weekly frequency of total acute medication use, and each individual acute medication use from Weeks 1-3, was analyzed using a restricted maximum likelihood-based mixed model repeated measures analysis for continuous repeated measures data. These analyses included all patients from the intent-to-treat population with a non-missing baseline value and ≥1 post-baseline value during Weeks 1-3. These models included the following variables: baseline value, treatment group, week, treatment-by-week interaction, sex, baseline CH frequency category (up to 4 CH attacks per day, >4 CH attacks per day), and pooled investigative site. The responder definition was derived using an anchor-based technique. The median percentage weekly CH attack frequency reduction across Weeks 1-3 was stratified by the PGI-I response category at Week 4. The responder criteria were, therefore, defined by the threshold of attack reduction that corresponded to patients who reported

feeling "much better" on the PGI-I at Week 4. The proportion of patients who achieved a PGI-I based percentage reduction from baseline during Weeks 1-3 (yes vs no) was analyzed using a pseudo-likelihood based generalized linear mixed effect model using a log link with the following variables: baseline CH attack frequency, treatment, sex, week, and treatment-by-week interaction.

Handling of Missing Data.—Mean compliance with the ePRO diary averaged across Weeks 1-3 (corresponding to the interval for the primary endpoint) was similar in both treatment groups (98.1% galcanezumab, 97.4% placebo). In the calculation of the moving average data, CH attacks in a 7-day window were calculated if data were available for at least 4 days within the 7-day period. Furthermore, in this study, only 7 patients (4 in placebo and 3 in galcanezumab) had missing data at Week 3, for the analyses concerning the percentage of patients who reach a 42.9% threshold reduction in weekly attacks from baseline (Fig. 1), suggesting a very minimal impact of missing data due to attrition.

Other General Considerations.—Treatment effects from the mixed models were assessed using least squared mean differences between treatment groups and 95% CIs, while effects from the generalized linear mixed models (GLIMMIX) for binary data were estimated using odds ratios and associated 95% CIs. In each of these models, an unstructured variance-covariance structure was assumed to model the correlation among repeated observations measured on the same subject. All analyses were performed using the software SAS® Enterprise Guide. All statistical tests were performed assuming a 2-sided significance level of 5% and no adjustments were made for multiplicity.

RESULTS

All 106 patients (placebo, n = 57; galcanezumab, n = 49) from the study, were included in this post hoc analyses. The baseline disease characteristics and demographics between placebo and galcanezumab groups were balanced. The baseline oxygen, acetaminophen/NSAIDs, oral/intranasal triptans, and subcutaneous sumatriptan use were similar between the placebo and galcanezumab treatment groups (Table 1). The average weekly pooled acute medication use during the
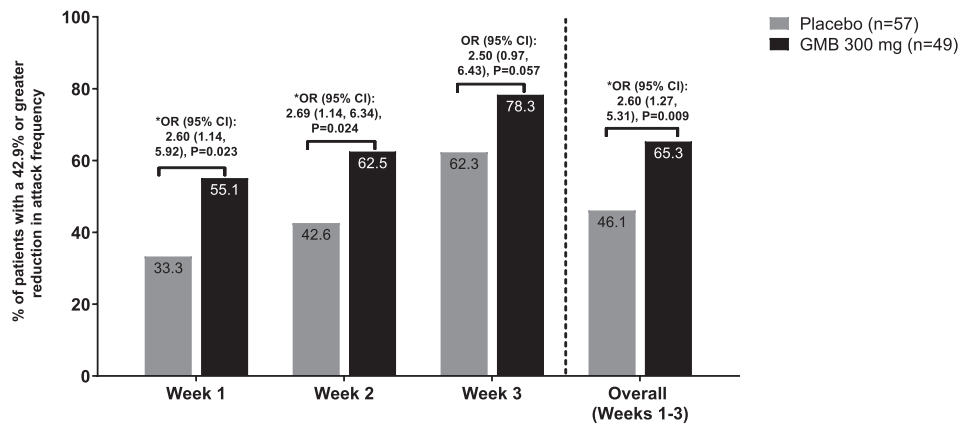
Fig. 1.—Odds of achieving an attack reduction threshold corresponding to patients reporting feeling "much better" on the PGI-I. *P value < .05 vs placebo, generalized linear repeated measures analysis for binary outcomes. ᵃResponders defined as patients achieving a 42.9% cluster headache (CH) attack reduction from baseline each week. This responder threshold was the median reduction in weekly attack frequency across Weeks 1-3 in patients who reported feeling "much better" on the patient global impression of improvement (PGI-I) at Week 4. Confidence interval (CI), galcanezumab (GMB), odds ratio (OR).

Table 1.—Baseline Demographic and Disease Characteristics

	Placebo (n = 57)	Galcanezumab 300 mg (n = 49)
Age, years, mean (SD)	45 (11.3)	48 (10.7)
Male, n (%)	47 (82.5)	41 (83.7)
Attacks per week, mean (SD)	17.3 (10.1)	17.8 (10.1)
Duration of cluster headache illness, years, mean (SD)	17.6 (11.5)†	15.8 (11.1)‡
Severity of pain, mean (SD)§	2.6 (0.7)	2.5 (0.7)
≤4 Cluster headache attacks per day, n (%)	50 (87.7)	41 (83.7)
Baseline acute medication use per week, mean (SD), number of patients		
Oxygen¶	9.2 (9.5), 35	9.5 (9.6), 30
Acetaminophen/NSAIDs	8.9 (12.8), 24	7.0 (14.2), 21
Oral/intranasal triptans	4.9 (5.5), 21	4.7 (5.2), 12
Subcutaneous sumatriptan	9.1 (7.2), 36	9.1 (10.8), 37
Weekly number of times of using pooled acute medication	16.9 (14.9)	17.1 (15.1)

†n = 56.
‡n = 47.
§Pain severity was rated using a 5-point pain scale: 0 "no pain", 1 "mild pain", 2 "moderate pain", 3 "severe pain", and 4 "very severe pain".
¶Mean number of times of oxygen use; two patients were excluded due to data entry issues.
max = maximum; min = minimum; n = number of patients; NSAID = nonsteroidal anti-inflammatory drug; SD = standard deviation.

baseline period was approximately 17 administrations in the placebo and galcanezumab groups.

Median Time-to-First Occurrence.—Figure 1 shows Kaplan-Meier estimates of the percentage of patients who reached 50, 75, and 100% reduction from baseline as a function of time and CH attack frequency. The median time-to-first occurrence of ≥50, ≥75, or 100%

reduction from baseline in CH attacks was consistently shorter (9-10 days sooner) with galcanezumab vs placebo (medians: ≥50%, 5 vs 14 days; ≥75%, 11 vs 21 days; 100%, 22 vs 32 days; Fig. 2).

Acute Medication Use.—Mean reduction from baseline in the overall frequency of weekly pooled acute medication use across Weeks 1-3 was significant-
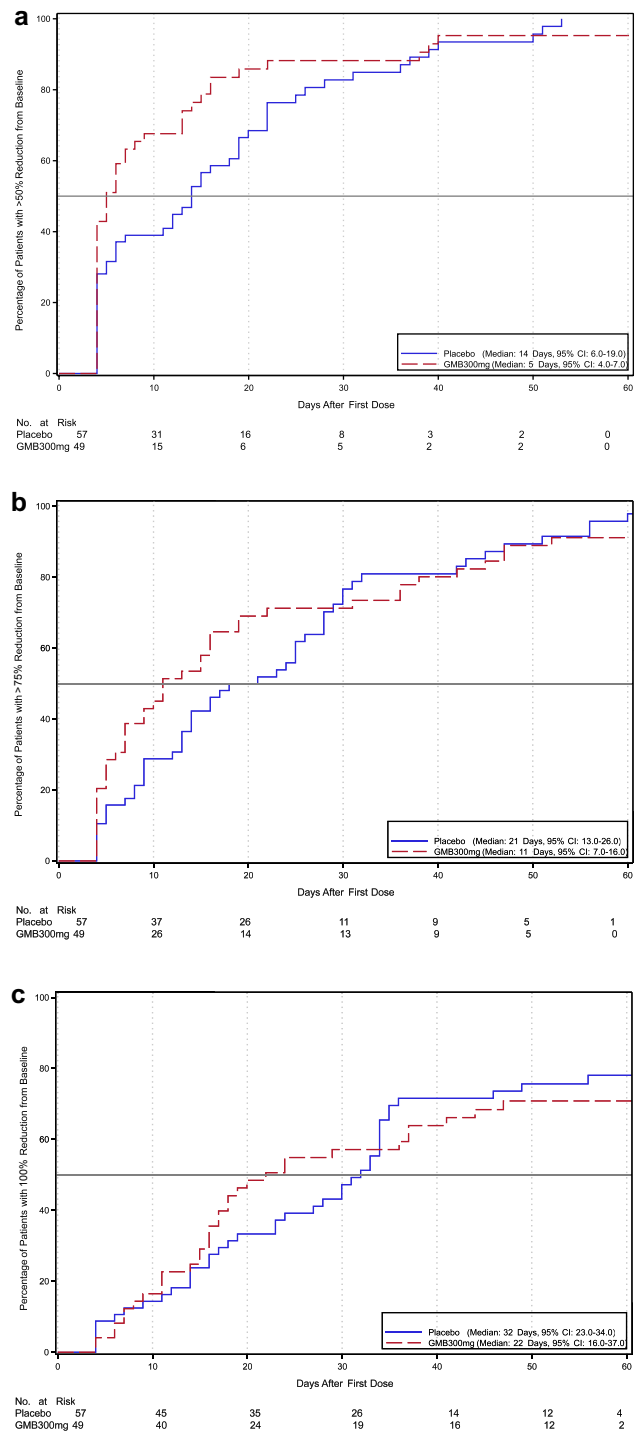
Fig. 2.—Kaplan-Meier plots for the median time-to-first occurrence of ≥50, ≥75, and 100% reduction from baseline in episodic cluster headache attack frequency for galcanezumab vs placebo. (A) Time to 50% reduction in cluster headache attack, (B) time to 75% reduction in cluster headache attack, and (C) time to 100% reduction in cluster headache attack. CI = Confidence interval; GMB = galcanezumab.

ly larger in the galcanezumab group vs placebo group (11.0 for galcanezumab vs 5.5 for placebo) (Fig. 3).

In 3 of the 4 classes of acute medications, greater numerical reductions in frequency were observed with

galcanezumab vs placebo, but none reached statistical significance (Fig. 4). Mean reduction from baseline in the overall weekly frequency of oxygen use across Weeks 1-3 was greater for galcanezumab vs placebo
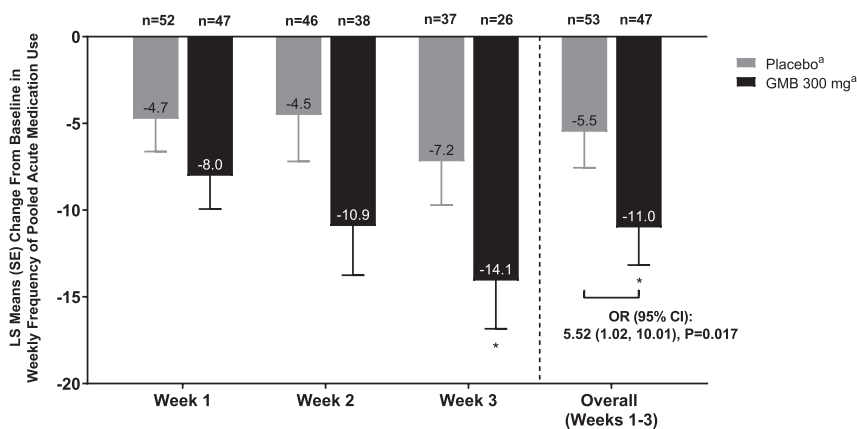
Fig. 3.—Mean change from baseline in the weekly frequency of pooled acute medication use across Weeks 1-3. *P value < .05, repeated measures analysis, least squares (LS) mean change from baseline vs placebo. [a]Number of patients (n) in the intention-to-treat population with a non-missing baseline value and ≥1 post-baseline value during Weeks 1-3. Confidence interval (CI), galcanezumab (GMB), odds ratio (OR), standard error (SE).

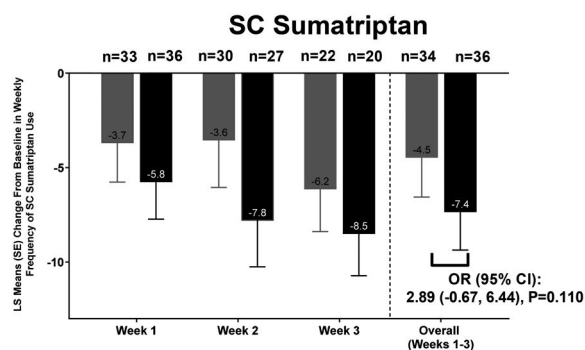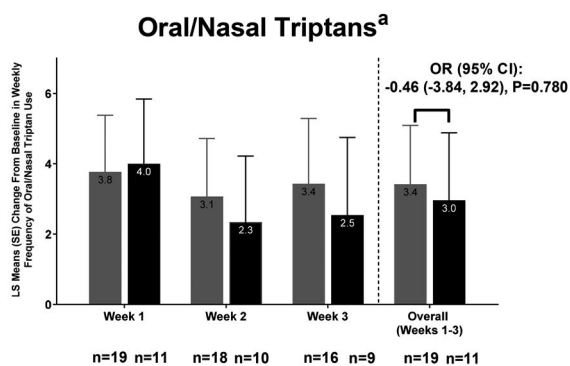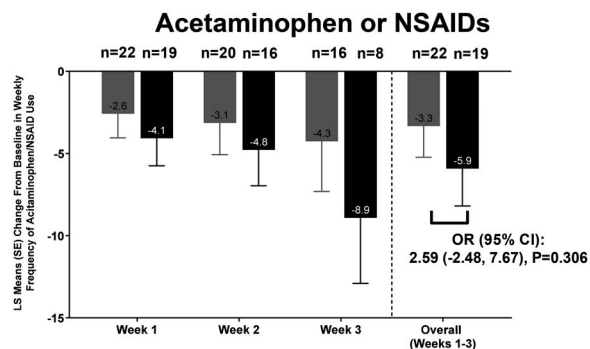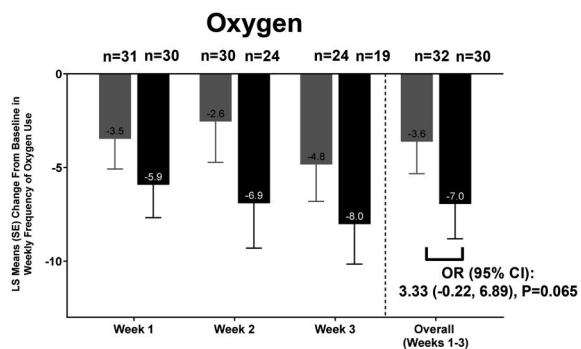Fig. 4.—Mean change from baseline in the weekly frequency of acute medication use across Weeks 1-3. [a]The use of oral triptans was permitted by a protocol amendment that was performed after the start of the study. Confidence interval (CI), galcanezumab (GMB), least squares (LS), number of patients (n), nonsteroidal anti-inflammatory drug (NSAID), odds ratio (OR), subcutaneous (SC), standard error (SE).

Table 2.—Median Percentage Reduction From Baseline in Weekly Cluster Headache Attacks Across Weeks 1-3 Associated With Week 4 PGI-I Response

PGI-I Category	n	Median Change From Baseline in the Weekly Number of Attacks	Median % Reduction in Weekly Attacks
1 (Very much better)	34	−10.3	78.3
2 (Much better)§	**21**	**−6.0**	**42.9**
3 (A little better)	14	−3.7	30.3
4 (No change)	12	−3.0	26.7
5 (A little worse)	2	5.3	−35.2
6 (Much worse)	7	1.7	−10.2
7 (Very much worse)	3	1.0	−4.6

§The median CH attack reduction across Weeks 1-3 of patients who reported a response of "much better" on the PGI-I scale at Week 4 was used as the threshold for responders.
CH = cluster headache; n = number of patients; PGI-I = patient global impression of improvement.
Bold text represents selected threshold.

(−7.0 for galcanezumab vs −3.6 for placebo). Similarly, numerically greater mean reductions from baseline in the overall weekly frequency of subcutaneous sumatriptan and acetaminophen/NSAIDs were observed for galcanezumab vs placebo (subcutaneous sumatriptan, −7.4 for galcanezumab vs −4.5 for placebo; acetaminophen/NSAIDs, −5.9 for galcanezumab vs 3.3 for placebo). Whereas, the use of oral triptans increased from baseline for both the placebo and galcanezumab groups. The estimated mean increase from baseline was 3.0 for the galcanezumab group and 3.4 for the placebo group, mean difference −0.46, 95% CI −3.84 to 2.92, *P* value = .78.

Responder Definition Based on PGI-I.—Patients who reported feeling "much better" at Week 4 on the PGI-I experienced a median weekly CH attack reduction of 42.9% from baseline across Weeks 1-3. Therefore, a response threshold defined as a 42.9% reduction (ie, a change correlated with "much better" on PGI-I) served as the responder definition for subsequent analyses. Of note, the reduction from baseline in both the absolute median change and percentage median change in weekly attacks was larger for PGI-I responses that represented categories of greater improvement. For example, patients who reported feeling "very much better" from baseline at Week 4 experienced a median weekly decrease of 10.3 attacks from baseline, which corresponded to a 78.3% median reduction from baseline in weekly attacks across Weeks 1-3 (Table 2).

By comparison, patients who reported feeling "a little better" experienced a median weekly decrease of 3.7 attacks and a 30.3% reduction from baseline. This is further contrasted by the median changes observed for PGI-I responses that represent categories of worsening. Patients who reported feeling "a little worse," "much worse," or "very much worse" from baseline experienced a percentage median increase in attacks from baseline of 35.2%, 10.2%, and 4.6%, respectively.

Responder Rate Based on PGI-I.—Figure 4 shows the odds of achieving an approximately 43% or greater reduction in attack frequency. A significantly higher percentage of patients at Week 1 and Week 2, and a relatively higher percentage of patients at Week 3, achieved higher odds of attack reduction threshold per the PGI-I responder analysis definition (ie, 42.9%); Week 1, odds ratio (95% CI): 2.60 (1.14, 5.92), *P* value = .023; Week 2, 2.69 (1.14, 6.34), *P* value = .024, and Week 3; 2.50 (0.97, 6.43), *P* value = .057. The overall odds of achieving a weekly attack reduction threshold of ≥43% corresponding to patients feeling "much better" on the PGI-I across Weeks 1-3 was also significantly higher with galcanezumab vs placebo; odds ratio (95% CI): Weeks 1-3, 2.60 (1.27, 5.31) *P* value = .009.

DISCUSSION

The findings from these post hoc analyses address clinically important outcomes related to the treatment of episodic CH. Faster median time-to-first occurrence

of ≥50, ≥75, and 100% reduction in CH attack frequency was observed for galcanezumab vs placebo. Significant reduction from baseline in the overall weekly frequency of pooled acute medication use across Weeks 1-3 was observed. Likewise, a significantly higher proportion of patients on galcanezumab vs placebo achieved a responder threshold of 43% across Weeks 1-3 that corresponded to patients feeling "much better" on the PGI-I scale at Month 1.

A noted challenge in guidelines for episodic CH is the variability related to preventive treatment onset latency.[8] In this study, we observed a median time-to-first occurrence of ≥50% reduction in weekly CH attack frequency of 5 days following the first dose for patients treated with galcanezumab. This suggests that approximately 50% of patients treated with galcanezumab may reach a 50% reduction in weekly CH attack frequency beginning as early as 5 days following the initiation of treatment with galcanezumab. Overall, the median time-to-first occurrence of ≥50, ≥75, and 100% reduction in weekly CH attack frequency was approximately 9-10 days earlier with galcanezumab vs placebo across all response rates, suggesting that treatment with galcanezumab vs placebo may result in faster achievement of important thresholds of attack reduction. Future efforts aimed at characterizing the time to full remission and maintenance of important thresholds of attack reduction are warranted.

Real-world evidence is needed to answer the question if starting treatment with galcanezumab immediately when the cluster period begins has an impact on the treatment response. The study design mandated a prospective baseline period of 10-15 days to establish weekly CH attack frequencies – effectively delaying the initiation of treatment. The overall impact of the prospective baseline period (10-15 days) that was required in this study remains unknown.

The weekly baseline acute medication use showed medications commonly utilized in clinical practice and endorsed by guidelines were administered at a high rate, demonstrating a substantial acute medication treatment burden in this trial. The reduction in pooled acute medication use observed in this post hoc analysis could be due to the reduction in CH attacks and/or severity with galcanezumab.[14] It should be noted that the use of oral/intranasal triptans increased from baseline for both groups. The use of oral triptans was not

permitted at the study start and only later allowed by protocol amendment. Thus, it is possible that patients who enrolled prior to the amendment would not have a baseline frequency recorded for oral triptans, but following the amendment, did use oral triptans post-baseline and could have contributed to the increased use that was observed. Additionally, the use of oral triptans with long half-lives, eg, frovatriptan, was extremely low in this study (1 patient who received placebo), and dosing of frovatriptan as a preventive or transitional treatment was not allowed. This outcome on overall acute treatment management reinforces the clinical impact of attack frequency reduction observed with galcanezumab treatment. This may have important implications beyond the impact on the management of episodic CH and may include minimizing the cost burden of acute medication resources on the healthcare system, recognized as the primary direct medical cost driver associated with episodic CH.[18] The reduction in acute medication use observed in the present analysis is consistent with previous findings shown with verapamil that demonstrated a reduction in acute medication use with prophylactic treatment.[19] Of additional interest, a large number of patients were using NSAIDs at baseline. The use of treatments with little supporting evidence for episodic CH may be reflective of the unmet need related to available treatment options as well as gaps in the uptake and application of current treatment guidelines.

Patient-reported outcome instruments that gather patients' perspectives often provide valuable insights on the impact of the disease on health-related quality of life and provide a more realistic quantification of treatment effects.[20] However, currently, available responder definitions do not incorporate patients' rating of change to define a threshold for meaningful CH attack reduction. In this post hoc analysis, response definitions were anchored on the median percentage reduction in weekly CH attack frequency in patients who reported feeling "much better" on PGI-I at Week 4. The derived responder threshold (42.9%) was then used to determine the "PGI-I based responder rates" for galcanezumab vs placebo. Based on the above response criterion, treatment with galcanezumab vs placebo resulted in 2.5 times higher odds of achieving a 43% attack reduction threshold corresponding to patients feeling "much better" on the PGI-I scale. Of note,

the attack frequency reductions that corresponded to patients feeling "a little better" or "much better" on the PGI-I, 30.3 and 42.9%, respectively, were within the range of the prespecified study responder definitions of 30 and 50%. This analysis further validates that these responder thresholds are clinically meaningful to the patient, and in the case of the 50% responder rate, may even represent a threshold of change that exceeds that which is considered "much better" to a patient (ie, 43%). Furthermore, a 30% reduction has been represented as a substantial clinical benefit in another primary headache disorder[21] and considered clinically meaningful in chronic migraine. The anchor-based approach to deriving a threshold in the percentage of weekly attack reduction from baseline was derived by anchoring the average weekly percentage reductions seen in Weeks 1-3 (which coincides with the primary end-point), with the PGI-I score at Week 4 and not at Week 3. Therefore, the 43% threshold reduction could be an approximate estimate of the true threshold reduction corresponding to patients feeling "much better" on the PGI-I scale at Week 3.

The findings from this analysis should be interpreted with caution due to the post hoc nature and lack of adjustments for multiplicity. Additionally, this study did not collect if a patient was subject to quantity limits imposed by insurance plans or other restrictions related to the use of acute medications. It is, therefore, unknown how this may impact the results. However, these analyses provide important information to clinicians regarding the onset of response and impact on acute medication use with galcanezumab in episodic CH.

CONCLUSION

Galcanezumab administered at a dose of 300 mg once monthly achieved faster median time-to-first occurrence of response rates, reduced the frequency of pooled acute medication use, and resulted in higher proportion of patients achieving a responder threshold anchored by patient-reported improvement. This post hoc analysis supports the primary efficacy result of a reduction in CH attack frequency across Weeks 1-3 and provides further evidence of the clinical meaningfulness of galcanezumab treatment for patients with episodic CH.

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Data Availability Statement*: 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 to request 6 months after the indication studied has been approved in the United States and European Union 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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