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Evaluation of Galcanezumab for the Prevention of Episodic Migraine
The EVOLVE-1 Randomized Clinical Trial

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IMPORTANCE Migraine is a disabling neurological disease characterized by severe headache attacks. Treatment options reduce migraine frequency for many patients, but adverse effects lead to discontinuation in many patients.

OBJECTIVE To demonstrate that galcanezumab is superior to placebo in the prevention of episodic migraine with or without aura.

DESIGN, SETTING, AND PARTICIPANTS The EVOLVE-1 (Evaluation of LY2951742 in the Prevention of Episodic Migraine 1) trial was a double-blind, randomized, placebo-controlled (January 11, 2016, to March 22, 2017) trial comparing galcanezumab (120 mg and 240 mg) vs placebo. Patients received treatments once monthly for 6 months (subcutaneous injection via prefilled syringe) and were followed up for 5 months after their last injection. It was a multicenter, clinic-based study involving 90 sites in North America. Participants in the study were adults (aged 18 to 65 years) with at least a 1-year history of migraine, 4 to 14 migraine headache days per month and a mean of at least 2 migraine attacks per month within the past 3 months, and were diagnosed prior to age 50 years. During the study, no other preventive medications were allowed. A total of 1671 patients were assessed; 809 did not meet study entry or baseline criteria, and 858 were included in the intent-to-treat population.

INTERVENTIONS Patients were randomized (2:1:1) to monthly placebo, galcanezumab, 120 mg, and galcanezumab, 240 mg.

MAIN OUTCOMES AND MEASURES The primary outcome was overall mean change from baseline in the number of monthly migraine headache days during the treatment period. Secondary measures included at least 50%, at least 75%, and 100% reduction in monthly migraine headache days, migraine headache days with acute medication use, and scores from the Migraine-Specific Quality of Life questionnaire, Patient Global Impression of Severity, and Migraine Disability Assessment. Treatment-emergent adverse events and serious adverse events were reported.

RESULTS Of the 1671 patients assessed, 858 (mean age, 40.7 years; 718 women [83.7%]) met study entry criteria and received at least 1 dose of investigational product. The primary objective was met for both galcanezumab doses; treatment with galcanezumab significantly reduced monthly migraine headache days (both $P < .001$) by 4.7 days (120 mg) and 4.6 days (240 mg) compared with placebo (2.8 days). All key secondary objectives were also significant after multiplicity adjustment. There were no meaningful differences between 120-mg and 240-mg doses of galcanezumab on measures of efficacy. Completion rate during treatment was high (81.9%; n = 718), and the incidence of discontinuation owing to adverse events was less than 5% across all treatment groups.

CONCLUSIONS AND RELEVANCE Galcanezumab 120-mg and 240-mg monthly injections provided clinical benefits and improved functioning. The incidence rate of adverse events was low, demonstrating the favorable tolerability profile of galcanezumab.

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Supplemental content

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Migraine is a chronic, neurological disease found to be 1 of the top 10 global causes of disease-related disability.[1,2] While an estimated 38% of individuals with migraine should be offered preventive treatment,[3] only 3% to 13% receive preventive therapy.[4] Among patients receiving preventive treatment, discontinuation rates are high, largely owing to a lack of efficacy and/or poor tolerability.[5] As a result, more than half of patients who received a prescription for migraine-preventive medication discontinued its use.[6-8]

Calcitonin gene-related peptide (CGRP) is widely expressed throughout the central and peripheral nervous system and acts as a sensory neurotransmitter, vasodilator, and mediator of neurogenic inflammation.[9-14] Calcitonin gene-related peptide is implicated in the pathophysiology of migraine.[15] In studies of people with migraine, CGRP was detected in the external jugular vein and was significantly elevated during migraine attacks[11,12]; infusion of CGRP to individuals with a history of migraine can trigger migraine attacks.[14,16,17]

Galcanezumab is a humanized monoclonal antibody that binds CGRP and prevents its biological activity without blocking the CGRP receptor; it is being developed for the preventive treatment of migraine. Results from phase 2 studies[17,18] provided sufficient evidence to advance galcanezumab to larger phase 3 clinical studies. Evaluation of LY2951742 in the Prevention of Episodic Migraine 1 (EVOLVE-1) was a randomized, multicenter, double-blind, placebo-controlled phase 3 study of 2 dosing regimens of galcanezumab among patients with episodic migraine.

Key Points

Question Is galcanezumab effective for prevention of migraine in patients who experience 4 to 14 migraine headache days per month?

Findings In this randomized clinical trial, both galcanezumab doses (120 mg and 240 mg) achieved statistically significant overall mean reductions in the number of monthly migraine headache days during treatment compared with placebo. Galcanezumab was associated with low discontinuation rates owing to adverse events, and adverse events were transient and predominantly mild or moderate in severity.

Meaning Galcanezumab demonstrated clinically and statistically significant benefits across several migraine-relevant outcomes in this study, with a favorable tolerability profile.

Methods

Study Design and Patients

This was a phase 3 study of galcanezumab and placebo in people with episodic migraine conducted at 90 sites in North America. The study design consisted of 4 study periods: initial screening and washout of all migraine preventive treatments (3-45 days); a prospective lead-in (baseline) period (30-40 days) for determining the frequency of migraine headache days (MHD); a double-blind treatment period (month 1, 2, 3, 4, 5, and 6); and a 4-month posttreatment period (month 7, 8, 9, and 10). All randomized patients were to enter the 4-month posttreatment period (washout), including patients who discontinued treatment early and continued to be assessed for tolerability during the washout of galcanezumab. This provided a total of 5 months of observation, from the last injection of galcanezumab to study conclusion, which is approximately 5 elimination half-lives of galcanezumab. A migraine headache was defined as a headache, with or without aura, lasting at least 30 minutes with both features A (at least 2 of the following: unilateral location; pulsatile quality; moderate or severe pain intensity; and aggravation caused by physical activity or avoidance of physical activity) and B (during headache, at least 1 of the following: nausea and/or vomiting and/or photophobia and phonophobia) of the International Headache Society International Classification of Headache Disorders-3 β (ICHD-3β).[19] A probable migraine headache was defined the same as migraine headache, but failing to meet the criteria for either feature A or B of the ICHD-3β definition. An MHD was defined as a calendar day on which a migraine or probable migraine headache occurred.

Treatment with botulinum toxin-A or toxin-B in the head or neck was to have been discontinued at least 4 months prior to screening. Beginning in the baseline period, patients used a handheld diary device daily (80% compliance mandatory for randomization) to record their headache information. If eligible, patients were randomized to 1 of 3 treatment groups (2:1:1 ratio) to receive either placebo or 1 galcanezumab dose regimen (120 mg or 240 mg). Patients randomized to the 120-mg dose regimen of galcanezumab received a loading dose of 240 mg (2 subcutaneous [SC] injections of 120 mg each). Investigational product (IP; either galcanezumab dose or placebo) was administered by SC injection monthly during office visits. Patients continued daily-diary entries and could continue to take acute migraine medications (eg, triptans, ergots, nonsteroidal anti-inflammatory drugs, aspirin, and acetaminophen without limitations; opioid- and barbiturate-containing medications limited to 3 days monthly; and only 1 corticosteroid injection was allowed during any period). During the posttreatment period, patients received no IP.

The patient population consisted of male and female patients aged 18 to 65 years diagnosed as having migraine per ICHD-3β guidelines for at least 1 year prior, and migraine onset before age 50 years. For enrollment, patients had to experience a frequency of 4 to 14 MHDs and at least 2 migraine attacks per month during the baseline period. Patients with a history of failure to respond to 3 or more classes of migraine preventive treatments as defined by the American Academy of Neurology/American Headache Society treatment guidelines level A and B evidence[20] were excluded. Other patient factors leading to exclusion included enrollment in another clinical trial in the past 30 days; prior exposure to any CGRP antibody; having taken a therapeutic antibody in the past 12 months; currently receiving preventive migraine medication within 30 days of the baseline period; or presence of a medical condition that would preclude study participation including but not limited to pregnancy, suicidal ideation within the past month, history

of substance abuse or dependence in the past year, recent history of acute cardiovascular events, and/or serious cardiovascular risk based on history or electrocardiogram findings. All patients provided written informed consent prior to initiating study procedures. The study was approved by Quorum Review Inc institutional review board services and Montreal Neurological Institute and Hospital, Montreal, Canada. The trial protocol is available in the Supplement.

Randomization and Blinding

Patients who met criteria for enrollment were randomized to treatment by a computer-generated randomization sequence using an interactive web-response system. Patients received 2 SC injections of IP at each dosing visit. Site personnel and patients remained blinded to treatment assignments. To achieve between-group balance in region (defined as eastern United States, western United States, Puerto Rico, and Canada) and baseline migraine frequency, the randomization was stratified by region and migraine frequency at baseline (<8 vs >8 MHDs per month).

Outcomes

The primary objective was to assess whether at least 1 dose of galcanezumab was superior to placebo in overall mean change from baseline of monthly MHDs during double-blind treatment. Secondary outcomes included proportion of patients with reduction in monthly MHDs (at least 50%, at least 75%, and 100% response rates); MHDs with acute medication use; Migraine-Specific Quality of Life Questionnaire (MSQ), version 2.1, scores (represents patient functioning where all domains are scored from 0 to 100, with higher scores indicating improved functioning)[21]; Patient Global Impression of Severity (PGI-S) scores (7-point scale ranking severity of illness from normal [1] to severely ill [7])[22] scores; and Migraine Disability Assessment (MIDAS) scores (numerical scores represent number of days patients missed or lost productivity at work or school, as well as missed days from family/social/leisure activities, and range from little or no disability [0-5] to severe disability [>20]).[23]

Safety measures included the occurrence of spontaneously reported treatment-emergent adverse events (TEAE), serious adverse events (SAE), deaths, discontinuation rates, vital signs (blood pressure, pulse, and temperature), and weight. Immunogenicity measures included antidrug antibody (ADA), neutralizing ADA, and treatment-emergent ADA (TE ADA). Additional safety measures will be addressed in a separate manuscript.

Statistical Analyses

Efficacy

Analyses were conducted by treatment group on all intent-to-treat patients (those randomized and received at least 1 dose of IP). Continuous longitudinal efficacy end points (including change from baseline in MHDs [month 1 to 6], MHDs with acute medication use [month 1 to 6], MSQ role function-restrictive [month 4 to 6], MIDAS [month 6, where the questions were asked for the previous 3 months], and PGI-S [month 4 to 6]) were analyzed using a mixed-model repeated measures analysis. Categorical longitudinal efficacy measures, including at least 50%, at least 75%, and 100% reduction from baseline in the number of monthly MHD (month 1 to 6), were analyzed using a categorical, pseudolikelihood-based repeated measures analysis. For nonrepeated binary-response measures, such as 50% response maintained from month 1 to 6, a logistic regression analysis was conducted. The primary and key secondary end points for each galcanezumab dose-regimen vs placebo were tested using an overall superchain, multiple-testing approach[24] which provided strong control of the family-wise type 1 error rate with a 2-sided, .05 α level.

Safety and Tolerability

The safety population included data from all randomized patients who received at least 1 dose of IP with analyses conducted based on modal treatment the patient received during the double-blind treatment phase. Adverse events were coded by Medical Dictionary for Regulatory Activities, version 19.1. Categorical safety measures were analyzed using the Fisher exact test. Continuous longitudinal safety measures were analyzed using mixed-model repeated measures analysis; changes from baseline to last observation carried forward end points were analyzed using an analysis of covariance model.

Immunogenicity

The incidence of TE ADA for each treatment group during the double-blind treatment was summarized; TE ADA positive was defined as a negative baseline and a positive postbaseline ADA result with a titer at least 1:20, or a positive baseline and a positive postbaseline result with an at least 4-fold increase in titer (ie, baseline titer of 1:10 increasing to ≥1:40 following baseline).

Sample Size

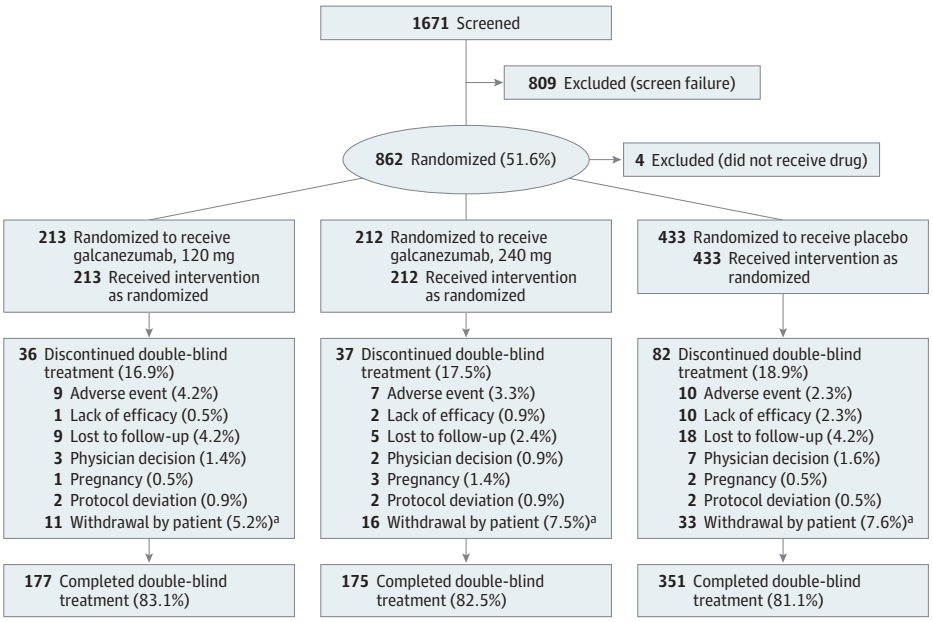
A planned sample size of approximately 413 patients in placebo and 206 patients in each of the galcanezumab dose groups was expected to provide approximately 95% power that at least 1 dose of galcanezumab would separate from placebo at a 1-sided .03 significance level based on simulations using Dunnett test. SAS software, version 9.4 (SAS Institute) was used for all statistical analyses.

Results

Patient Disposition and Baseline Characteristics

A total of 1671 patients entered the study; 862 were randomized (**Figure 1**). The most common reason for screen failure was failure to meet criteria for enrollment based on migraine headache information collected in the diary during the baseline period. In total, 858 randomized patients received at least 1 dose of IP and were included in the intent-to-treat population. Overall, 703 patients (81.9%) completed the double-blind treatment period and thus, 155 patients (18.1%) discontinued from treatment (Figure 1); of those discontinuations, 27.1% completed the posttreatment period. The most frequent reason given for discontinuing from treatment was "withdrawal by patient," which occurred at similar rates across treatment groups. Discontinuations owing to AEs (Figure 1) were few and

Figure 1. Flow Diagram of Patient Disposition During the Double-blind Treatment Period (Month 1 Through Month 6)



[a] Reasons for patient decision to discontinue treatment: concerns about study procedures, perceived risks, scheduling conflicts, and patient is relocating or has relocated.

not statistically different for either galcanezumab treatment group compared with placebo. A total of 740 patients entered the posttreatment period, and 704 patients completed the posttreatment period (galcanezumab, 120 mg, 96.8%; galcanezumab, 240 mg, 93.4%; and placebo, 95.2%). None of the discontinuations in the posttreatment period were owing to an AE, and the primary reason for discontinuation was "withdrawal by patient."

Patients were predominately women (83.7%; n = 718) and white (80.4%; n = 690), with a mean age of 40.7 years. Baseline demographics (**Table 1**) of sex, age, race/ethnicity, and body mass index were similar across treatment groups.

On average, patients were diagnosed as having migraine 20.1 years prior to study enrollment, with 4.7 comorbid conditions other than migraine (Table 1). Mean monthly MHDs were 9.1, mean monthly migraine attacks were 5.7, and mean monthly headache hours were 60.6 at baseline. The most common preexisting conditions (≥10% total) were seasonal allergy, drug hypersensitivity, anxiety, depression, back pain, gastroesophageal reflux disease, insomnia, and myopia. Most patients (60.0%; n = 515) reported using prior migraine preventive treatment; 18.5% (n = 159) and 4.9% (n = 42) of those failed 1 or more and 2 or more such treatments owing to lack of efficacy in the previous 5 years, respectively. Mean baseline MIDAS total score was 33.2, which represented the total number of days migraine limited activity during the previous 3-month period, and reflects severe disability.[25]

Primary and Key Secondary Efficacy Analyses

Of the 858 intent-to-treat patients, 843 with nonmissing change in MHDs were analyzed for the primary efficacy measure. The primary objective of the study was achieved. After multiplicity adjustment, monthly galcanezumab doses of 120 mg and 240 mg resulted in statistically significantly greater least-square (LS) mean change from baseline of monthly MHDs compared with placebo (**Figure 2**). The LS mean (SE) change difference from placebo was −1.9 (0.3) days for galcanezumab, 120 mg, and −1.8 (0.3) days for galcanezumab, 240 mg (both $P < .001$). Onset of effect (the earliest month in which a statistically significant improvement in change from baseline of MHDs was observed and maintained during treatment) was observed in month 1 for both galcanezumab treatment groups (Figure 2). Based on the prespecified multiplicity adjustment method, and because the primary objective was met, the key secondary objectives were tested according to the predefined multiple testing procedure (**Table 2**). After multiplicity adjustment, galcanezumab 120 mg and 240 mg statistically significantly reduced the number of monthly MHDs with acute medication use compared with placebo by −1.8 (0.2) and −1.6 (0.2) days ($P < .001$), respectively.

Response Analysis

After multiplicity adjustment, the mean percentage of patients with at least 50%, at least 75%, and 100% reduction from baseline in monthly MHD during treatment was statistically significantly greater in both galcanezumab dose groups compared with placebo (Table 2). In addition to the rapid onset of effect, both doses of galcanezumab were superior to placebo in the proportion of patients who maintained at least 50% response at the individual patient level for 6 consecutive months of treatment (120 mg, 20.5%, $P < .001$; 240 mg, 19.2%, $P < .001$; placebo, 8.9%).

Patient-Reported Health Outcomes

After multiplicity adjustment, galcanezumab treatment statistically significantly improved MSQ RFR scores compared

Table 1. Baseline Patient Demographics and Disease Characteristics

Characteristic	Mean (SD)		
		Galcanezumab	
	Placebo (n = 433)	120 mg (n = 213)	240 mg (n = 212)
Demographics			
Age, y	41.3 (11.4)	40.9 (11.9)	39.1 (11.5)[a]
Female, No. (%)	362 (83.6)	181 (85.0)	175 (82.6)
White race/ethnicity, No. (%)	356 (82.2)	169 (79.3)	165 (77.8)
BMI	28.6 (5.5)	27.8 (5.3)	28.6 (5.7)
Disease characteristics			
Duration of migraine, y	19.9 (12.3)	21.1 (13.0)	19.3 (11.9)
No. of comorbidities	4.8 (3.6)	4.7 (3.8)	4.4 (3.6)
MHD/mo	9.1 (3.0)	9.2 (3.1)	9.1 (2.9)
Migraine attacks/mo	5.8 (1.7)	5.6 (1.7)	5.7 (1.8)
Headache hours/mo	58.8 (39.4)	59.9 (40.0)	65.0 (60.2)
MHD category ≥8, %	285 (65.8)	140 (65.7)	139 (65.6)
MHD with acute medication use/mo	7.4 (3.5)	7.4 (3.7)	7.3 (3.3)
Patients with acute medication overuse, No. (%)[b]	87 (20.2)	39 (18.3)	42 (19.8)
Prior preventive treatment, No. (%)	257 (59.4)	133 (62.4)	125 (59.0)
Fail ≥1 prior preventive due to efficacy, No. (%)	79 (18.2)	40 (18.8)	40 (18.9)
MSQ RF-R	52.9 (15.4)	51.4 (16.2)	48.8 (16.8)[c]
PGI-S severity of illness	4.2 (1.1)	4.4 (1.1)	4.5 (1.1)[c]
MIDAS total score	31.8 (27.3)	32.9 (28.2)	36.1 (27.8)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; MHD, migraine headache days; MIDAS, Migraine Disability Assessment; MSQ RF-R, Migraine-Specific Quality of Life Questionnaire Role Function-Restrictive domain; PGI-Severity, Patient Global Impression of Severity.

[a] Comparison with placebo, $P < .05$.

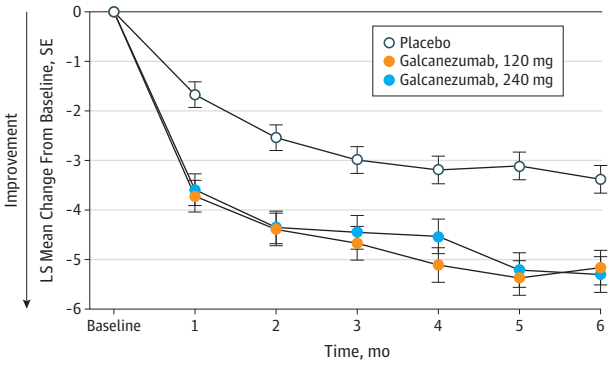
[b] Overuse of acute medication is defined by the use of ergotamine, triptans, or drug combinations for 10 days or more per month or by the use of simple analgesics (nonsteroidal anti-inflammatory agents, aspirin, and paracetamol/acetaminophen) for 15 days or more per month, for the 1-month prospective baseline period. This does not indicate a diagnosis of medication overuse headache, but refers to those patients who have overused acute medications during the baseline period.

[c] Comparison with placebo, $P < .01$.

with placebo during treatment (month 4 to 6 LS mean [SE] change difference 120 mg, 7.7 [1.3]; 240 mg, 7.4 [1.3]; each $P < .001$). Both galcanezumab doses also demonstrated superiority in other domains of the MSQ scale (LS mean [SE] change difference compared with placebo; mean of month 4 to 6, all $P < .001$): role function-preventive (120 mg, 5.6 [1.1] and 240 mg, 4.7 [1.2]); emotional function (120 mg, 8.3 [1.5] and 240 mg, 7.2 [1.5]); and total (120 mg, 7.3 [1.2] and 240 mg, 6.7 [1.3]).

After multiplicity adjustment, there was a statistically significantly greater mean (SE) improvement from baseline in PGI-S rating in both the galcanezumab 120-mg (−0.3 [0.1]; $P = .002$) and 240-mg (−0.3 [0.1]; $P = .008$) dose groups compared with placebo for month 4 to 6. For the MIDAS total score, the LS mean (SE) change at month 6 was statistically significantly improved in both the galcanezumab 120-mg (−21.2 [1.7]; $P < .001$) and 240-mg (−20.1 [1.7]; $P < .002$) treatment groups compared with placebo (−14.9 [1.4]). Although not part of the multiplicity adjustment, there were no statistically significant differences between galcanezumab dose groups for any of the efficacy measures.

Figure 2. Least Square (LS) Mean Change From Baseline in Number of Migraine Headache Days and Onset of Effects of Galcanezumab (120 mg or 240 mg) Compared With Placebo During the Double-blind Treatment Period (Month 1 Through Month 6)



$P < .001$.

Other Secondary Efficacy Outcomes

Least squares mean (SE) change from baseline (mean of month 1 to 6) for monthly headache hours was statistically significantly different (no multiplicity adjustment) for both galcanezumab 120-mg (−29.7 [2.7]; $P < .001$) and 240-mg (−29.3 [2.7]; $P < .001$) treatment groups compared with placebo (−15.7 [2.2]).

Safety and Tolerability

Eleven patients (5 in the placebo group and 6 in the galcanezumab 120-mg group) reported a total of 12 SAEs. One patient (120-mg group) reported 2 SAEs (incarcerated incisional hernia and seroma). No patients in the 240-mg dose group reported a SAE. Two placebo-treated patients reported an SAE of cholelithiasis. No other SAEs were reported by more than 1 patient, and no SAEs were considered by the investigator to be associated with IP. Tubular breast carcinoma (120-mg group), deep vein thrombosis (placebo), cholelithiasis (1 placebo-treated patient), and vertebral osteophyte (120-mg group) led to discontinuation of treatment. One patient (120-mg group) experienced an SAE of acute pancreatitis that was moderate in severity; the event began and resolved during treatment (patient completed both treatment and posttreatment periods) and was not considered by the investigator to be related to IP.

The percentage of patients who reported at least 1 TEAE (**Table 3**) was greater in the galcanezumab dose groups; none was statistically significant. Injection-site pain was the most frequently reported TEAE among all treatment groups, but there were no statistically significant differences. Treatment-emergent AEs related to injection site other than injection-site pain that were reported at a greater rate in 1 or both galcanezumab dose groups (>2%) compared with placebo were injection-site erythema, injection-site pruritus, and injection-site reaction.

Table 2. Primary and Key Secondary Outcome Results (Least Square Means or Estimated Rate and Odds Ratio) During Double-blind Treatment and After Adjustment for Multiplicity

End Point/Treatment	Time Span in Treatment Period, mo	No.	LS Mean Change/ Estimated Rate	Comparison With Placebo			
				LS Mean Change Difference	*P* Value	Adjusted Significance Level[a]	Significant After Multiplicity Adjustment?
Monthly MHDs							
Placebo	1-6	425	−2.8	NA	NA	NA	NA
GMB 120		210	−4.7	−1.9 (−2.5 to −1.4)	<.001	0.026	Yes
GMB 240		208	−4.6	−1.8 (−2.3 to −1.2)	<.001	0.026	Yes
Monthly MHDs with acute medication use							
Placebo	1-6	425	−2.2	NA	NA	NA	NA
GMB 120		210	−4.0	−1.8 (−2.3 to −1.3)	<.001	0.0125	Yes
GMB 240		208	−3.8	−1.6 (−2.1 to −1.1)	<.001	0.0125	Yes
MSQ R-FR							
Placebo	4-6	377	24.7	NA	NA	NA	NA
GMB 120		189	32.4	7.7 (5.2-10.3)	<.001	0.025	Yes
GMB 240		184	32.1	7.4 (4.8-10.0)	<.001	0.025	Yes
PGI-S							
Placebo	4-6	377	−1.3	NA	NA	NA	NA
GMB 120		189	−1.6	−0.3 (−0.5 to −0.1)	.002	0.025	Yes
GMB 240		184	−1.6	−0.3 (−0.5 to −0.1)	.008	0.025	Yes
≥50% Response, OR (95% CI)							
Placebo	1-6	425	38.6	NA	NA	NA	NA
GMB 120		210	62.3	2.6 (2.0-3.4)	<.001	0.025	Yes
GMB 240		208	60.9	2.5 (1.9-3.2)	<.001	0.025	Yes
≥75% Response, OR (95% CI)							
Placebo	1-6	425	19.3	NA	NA	NA	NA
GMB 120		210	38.8	2.7 (2.0-3.5)	<.001	0.025	Yes
GMB 240		208	38.5	2.6 (2.0-3.4)	<.001	0.025	Yes
100% Response, OR (95% CI)							
Placebo	1-6	425	6.2	NA	NA	NA	NA
GMB 120		210	15.6	2.8 (2.0-4.0)	<.001	0.025	Yes
GMB 240		208	14.6	2.6 (1.8-3.7)	<.001	0.025	Yes

Abbreviations: GMB 120, 120-mg dose of galcanezumab; GMB 240, 240-mg dose of galcanezumab; LS, least square; MHD, migraine headache day; MSQ RFR, Migraine Specific Quality of Life questionnaire, version 2.1, Role-Function Restrictive; NA, not applicable; OR, odds ratio; PGI-S, Patient Global Impression-Severity.

[a] If *P* value is less than or equal to the adjusted significance level, then the results are statistically significant after adjustment for multiplicity.

Most patients reported these TEAEs as mild or moderate in severity; however, 2 galcanezumab patients discontinued treatment owing to a TEAE related to the injection site. The TEAE of pruritus was reported more frequently (>2%) among galcanezumab-treated patients (240 mg) compared with placebo.

The most common posttreatment emergent AE was upper respiratory tract infection, which occurred at a similar rate across treatment groups (galcanezumab, 120 mg, 3.3% [n = 6 of 183]; galcanezumab, 240 mg, 2.7% [n = 5 of 185]; and placebo, 3.2% [n = 12 of 372]). Other posttreatment emergent AEs that occurred in 1% or more of patients in the combined galcanezumab group were viral upper respiratory tract infection, sinusitis, and influenza, and these events occurred at a rate similar to placebo.

Vital Signs and Weight

There were no statistically significant differences between galcanezumab dose groups and placebo on mean change from baseline of systolic blood pressure and pulse at any visit. A statistically significant but not clinically meaningful mean decrease in diastolic blood pressure (DBP) was observed in the galcanezumab 240-mg dose group compared with placebo at month 6. At month 6, the LS mean change from baseline in the placebo, galcanezumab 120-mg, and galcanezumab 240-mg dose groups were 0.2 mm Hg, 0.12 mm Hg, and −1.20 mm Hg, respectively. There were no statistically significant differences between the 120-mg galcanezumab group and the placebo group at any visit or at end point. No galcanezumab-treated patient had treatment-emergent sustained elevation in systolic blood pressure. Eleven patients had treatment-emergent sustained elevation in diastolic blood pressure, with a similar incidence in the placebo, galcanezumab 120-mg, and galcanezumab 240-mg dose groups (1.3%, 2.1%, and 1.1%, respectively). No patient met criteria for treatment-emergent sustained elevation in pulse; no galcanezumab-treated patient had treatment-emergent low or high heart rate. For temperature, statistically significant mean increases (<17.6°C) were observed, were transient, and not sustained. Body weight was measured at month 6 only; mean change from baseline to last observation carried forward end point were small (<1 kg) and not statistically significant between any treatment groups.

Table 3. TEAEs Reported by at Least 2% of Galcanezumab-Treated Patients and More Frequently Than Placebo-Treated Patients During the Double-blind Treatment Period in Order of Decreasing Frequency

	No. (%)		
		Galcanezumab	
TEAE	Placebo (n = 432)	120 mg (n = 206)	240 mg (n = 220)
Patients with ≥1 TEAE	261 (60.4)	135 (65.5)	149 (67.7)
Injection site pain	75 (17.4)	33 (16.0)	45 (20.5)
Nasopharyngitis	27 (6.3)	16 (7.8)	6 (2.7)
Urinary tract infection	15 (3.5)	8 (3.9)	13 (5.9)
Injection site erythema	11 (2.6)	10 (4.9)	9 (4.1)
Injection site pruritus	1 (0.2)	9 (4.4)[a]	10 (4.6)[a]
Injection site reaction	4 (0.9)	7 (3.4)[a]	12 (5.5)[a]
Sinusitis	13 (3.0)	10 (4.9)	8 (3.6)
Nausea	15 (3.5)	5 (2.4)	8 (3.6)
Back pain	6 (1.4)	5 (2.4)	7 (3.2)
Dizziness	11 (2.6)	6 (2.9)	5 (2.3)
Bronchitis	6 (1.4)	3 (1.5)	7 (3.2)
Cough	7 (1.6)	4 (1.9)	6 (2.7)
Influenza	5 (1.2)	5 (2.4)	4 (1.8)
Pruritus	1 (0.2)	2 (1.0)	6 (2.7)[a]
Migraine	4 (0.9)	2 (1.0)	5 (2.3)
Neck pain	4 (0.9)	3 (1.5)	4 (1.8)
Oropharyngeal pain	3 (0.7)	4 (1.9)	3 (1.4)
Injection site bruising	6 (1.4)	2 (1.0)	4 (1.8)
Nasal congestion	4 (0.9)	1 (0.5)	5 (2.3)
Vertigo	2 (0.5)	2 (1.0)	4 (1.8)
Weight increased	6 (1.4)	4 (1.9)	2 (0.9)
Dysmenorrhea[b]	2 (0.6)	1 (0.6)	4 (2.2)
Contusion	5 (1.2)	5 (2.4)	0 (0.0)[c]

Abbreviation: TEAE, treatment-emergent adverse event.

[a] Comparison with placebo, $P < .05$.

[b] Denominator adjusted to include female patients only.

[c] Comparison with galcanezumab 120 mg, $P < .05$.

Immunogenicity

At baseline, 5.9% of patients in the placebo group (n = 25 of 422) and 8.9% (n = 18 of 202; 120-mg group) and 10.8% (n = 23 of 213; 240-mg group) in the galcanezumab dose groups had ADA present. The percentage of patients who were TE ADA positive during the double-blind treatment phase was 1.7% in the placebo group (n = 7 of 422) and 3.5% (n = 7 of 202; 120-mg group), and 5.2% (n = 11 of 213; 240-mg group) in the galcanezumab dose-groups. Of these patients, all but 1 placebo-treated patient had neutralizing ADA present. Neutralizing ADA recognizes the target-binding sites on galcanezumab and competes with binding to CGRP in vitro; an observable clinical effect requires sufficiently high titers of neutralizing ADA to effectively reduce the activity of galcanezumab in vivo.

Discussion

Galcanezumab 120 mg and 240 mg both achieved a statistically significant overall mean reduction in the number of monthly MHDs during treatment (4.7 and 4.6 days, respectively) compared with placebo (2.8 days). This benefit included patients who either had or had not received a preventive migraine treatment in the previous 5 years, as well as those with frequent acute medication use (other than opioids and barbiturates). The reduction among galcanezumab-treated patients during 6 months of treatment translates to the equivalent of approximately 8 weeks of additional migraine-free days over the course of a year. Galcanezumab demonstrated a rapid onset of effect with a significant effect beginning at month 1 that continued through month 6.

In this study, most people receiving galcanezumab treatments (120 mg, 62.3% [n = 131 of 210] and 240 mg, 60.9% [n = 126 of 208]) on average had an at least 50% reduction in monthly MHD during the entire 6-month treatment period; clinically significant improvements are considered to have occurred when more than half of the episodic migraine study population experienced at least 50% reduction in monthly MHD.[26]

Considering a complex set of tests and judgements helps to determine clinical meaningfulness of a given treatment regimen[27]; therefore, we have reported a variety of results in addition to primary efficacy that showed both positive and meaningful effects on the lives of people with migraine who participated in this study. Monthly MHDs with acute medication use were reduced by galcanezumab 120 mg (−1.8 days) and 240 mg (−1.6 days) more than placebo; thus, patients had fewer MHDs that required acute treatment. Daily functioning scores (all domains of MSQ) were increased by galcanezumab in a range of 4.7 to 8.3 points compared with placebo; a positive change in scores reflects functional improvement.[28] Galcanezumab treatment changed PGI-S scores from moderately ill (4.0)[22] at baseline to mildly ill (3.0)[22] at month 6, which was significantly better than placebo. For the MIDAS total score, galcanezumab treatment reduced the baseline mean score (34.5) by approximately 20 points, resulting in a score of approximately 15.0, which can be graded as "moderately limiting disability."[23]

Efficacy results from this study confirmed those reported in phase 2 studies,[17,18] and the treatment duration was twice as long in this study (6 months vs 3 months). These results were replicated in a similarly designed study (EVOLVE-2)[29] in which 915 patients were randomized and received at least 1 dose of IP.

Injection-site erythema, injection-site pruritus, and injection-site reaction were the most frequently reported TEAEs related to the injection site for galcanezumab compared with placebo, but most events were mild to moderate in severity. Discontinuations owing to AEs of galcanezumab-treated patients were low (3.8%). Overall, across both previous phase 2 studies[17,18] and this phase 3 study, monthly galcanezumab has shown a consistently safe and tolerable profile. Monthly administration and resulting sustained efficacy, along with favorable tolerability, should improve adherence and ultimately the outcomes for people with migraine.

The large sample size and high completion rate during the 6-month treatment period (81.9%; n = 703 of 858) provided more definitive conclusions with regard to efficacy and safety/tolerability than phase 2 studies. The 6-month duration of treatment allowed for an appropriate assessment of response durability. This longer treatment duration may have contributed to a higher rate of discontinuations during treatment than those observed in other studies of CGRP monoclonal antibodies with only 3-month treatment periods.

Limitations

A limitation of this study was that patients were not tested to determine whether galcanezumab could be effective as an adjunctive treatment (ie, concurrent with other preventive medications). This study was conducted in North America (primarily United States), which may limit the generalizability of these results to patients in other geographies. Although patients with comorbid cardiovascular conditions and cardiovascular risk were included in the galcanezumab clinical studies, caution should be used when treating patients with acute cardiovascular events and/or serious cardiovascular risk because these patients have not been studied in galcanezumab clinical trials. Pregnant women were excluded from the galcanezumab studies; therefore, there is insufficient human data to establish the safety of galcanezumab during pregnancy.

Conclusions

Both dosing regimens of galcanezumab were superior to placebo in the reduction of monthly MHDs, with a rapid onset of effect starting at month 1. These data provided consistent, clinically meaningful evidence that treatment with galcanezumab reduced migraine frequency and migraine-related disability and improved patient functioning. Galcanezumab demonstrated statistically significant results with respect to the mean percentage of people with a reduction of at least 50%, at least 75%, and 100% in monthly MHDs. Data from this study demonstrated the favorable safety profile of galcanezumab in people with migraine; discontinuations owing to AEs were low, providing further support for the tolerability of galcanezumab.

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