

## Research Submissions

# Effect of Galcanezumab Following Treatment Cessation in Patients With Migraine: Results From 2 Randomized Phase 3 Trials

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**Objective.**—We examined the efficacy and safety of galcanezumab after treatment cessation in randomized double-blind, placebo-controlled, migraine prevention studies (EVOLVE-1; EVOLVE-2).

**Background.**—Galcanezumab is indicated for migraine prevention in adults.

**Methods.**—Adults with episodic migraine were enrolled into EVOLVE-1 and EVOLVE-2, which randomized 858 and 915 patients, respectively, to galcanezumab 120 mg (an initial 240-mg loading dose), galcanezumab 240 mg, or placebo, administered subcutaneously once monthly for 6 months. After treatment completion or discontinuation, patients entered a 4-month posttreatment period. Efficacy and safety from the posttreatment periods are reported.

**Results.**—Overall, 740 patients (EVOLVE-1) and 830 (EVOLVE-2) patients entered the posttreatment periods, about 95% and 96% of patients, respectively, completed. In EVOLVE-1, change from pre-randomization baseline in monthly migraine headache days decreased over the posttreatment period from (mean [SE]) 5.2 (0.4) days (Month 6) to 4.1 (0.4) days (Month 10) for 120 mg and from 5.3 (0.4) days (Month 6) to 3.8 (0.4) days (Month 10) for 240 mg, and was stable for placebo (3.4 [0.3] days [Month 6] to 3.3 [0.3] days [Month 10]); differences between each galcanezumab dose group and placebo were statistically significant at each month, except for galcanezumab 240 mg at Month 10 (120 mg vs placebo:  $P < .001$  Months 1-6,  $P = .007$  Month 7,  $P = .044$  Month 8,  $P = .016$  Month 9, and  $P = .042$  Month 10; 240 mg vs placebo:  $P < .001$  Months 1-7,  $P = .015$  Month 8,  $P = .021$  Month 9, and  $P = .238$  Month 10). EVOLVE-2 showed similar results. In both trials, there were no statistically significant differences between treatment groups and placebo for time-to-first loss of 50% response. During the posttreatment periods, 1.6% (EVOLVE-1) and 2.3% (EVOLVE-2) of patients initiated migraine preventive treatments. At Month 10, quality of life among galcanezumab-treated patients was similar to those taking placebo. The most common posttreatment emergent adverse event was upper respiratory tract infections. There were no discontinuations due to adverse events during the posttreatment periods.

**Conclusions.**—Galcanezumab treatment effects were reduced during the posttreatment periods, but did not return to baseline. There were no unexpected adverse events after galcanezumab cessation.

**Key words:** migraine, galcanezumab, clinical trial, treatment cessation, posttreatment period

**Abbreviations:** AE adverse event, CGRP calcitonin gene-related peptide, GLIMMIX generalized linear mixed models, HRQOL health-related quality of life, ICDH International Classification of Headache Disorders, MedDRA Medical Dictionary for Regulatory Activities, MHD migraine headache day, MMRM mixed model repeated measures, SAE serious adverse event, TEAE treatment emergent adverse event, US United States

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## INTRODUCTION

Migraine is a chronic disease causing debilitating headaches accompanied by sensory alterations.<sup>1</sup> In the United States (US), the prevalence of self-reported migraine and severe headache was 15.3% over a 3-month period.<sup>2</sup> Migraine disproportionately affects women of childbearing age and is among the top 5 reasons for emergency department visits. Globally, migraine is ranked second as a cause of disability expressed as years lived with disability.<sup>3</sup> According to researchers, preventive medication is indicated for a large proportion of patients (38.8%); however, many do not receive it.<sup>4</sup> Despite the personal and economic burden of migraine, only 12% of patients with migraine reported use of daily preventive migraine medication.<sup>4</sup> Oral preventive medications for migraine are available, but usage is frequently limited by adverse events (AE).<sup>5</sup> Thus, there is a medical need for new treatment options with improved tolerability.

The neuropeptide, calcitonin gene-related peptide (CGRP), is implicated in the pathophysiology of migraine and is hypothesized to be involved in the release of inflammatory mediators and transmission of nociceptive information from intracranial blood vessels to the nervous system.<sup>6,7</sup> CGRP or its receptor are targets for migraine preventive agents.<sup>5,6</sup> Small molecule receptor antagonists and monoclonal antibodies (ie, galcanezumab, erenumab, fremanezumab), directed against either CGRP or its receptor, are under development or approved by the US Food and Drug Administration (FDA) for migraine prevention.<sup>8-10</sup> Immunoglobulins of class G (IgG) have a half-life of approximately 3 weeks;<sup>11</sup> this can be exploited by drugs used as migraine preventive agents, which ideally should be administered infrequently and be long acting.

Galcanezumab is a humanized monoclonal antibody (IgG4) that binds to the CGRP ligand and blocks its binding to the receptor.<sup>9,12</sup> Galcanezumab was recently evaluated in 2 randomized double-blind, placebo-controlled phase 3 trials (EVOLVE-1;

EVOLVE-2) examining the effect of monthly galcanezumab (120 mg or 240 mg) on the prevention of episodic migraine.<sup>13,14</sup> In both trials, both galcanezumab dose groups showed statistically and clinically relevant greater reductions from baseline in the number of monthly migraine headache days during the 6-month double-blind treatment periods relative to placebo. Subsequently, the 120-mg dose (following a 240-mg starting dose) was approved by the FDA for preventive treatment of migraine in adults.<sup>9</sup> Because galcanezumab has an elimination half-life of 27 days,<sup>9</sup> its effect can persist after the last injection. Persistence of therapeutic effects is of interest to both patients and clinicians since migraine is a life-long disease and preventive therapy may need to be stopped and started for various reasons (eg, surgery, comorbid conditions, and economics). While persistence of response is desirable, persistence of adverse events is not. The objective was to examine the efficacy and safety of galcanezumab after treatment cessation (posttreatment period) of 2 randomized phase 3 studies (EVOLVE-1, EVOLVE-2) in patients with migraine. We hypothesized that a washout of galcanezumab treatment of approximately 5 elimination half-lives would diminish the treatment effects.

## METHODS

**Study Design and Patients.**—A migraine was defined as a headache, with or without aura, lasting at least 30 minutes and satisfying criteria from both features A (at least 2 of the following: unilateral location; pulsatile quality; moderate or severe pain intensity; aggravation caused by physical activity or avoidance of physical activity) and B (during headache, at least 1 of the following: nausea and/or vomiting; photophobia and phonophobia) of the International Headache Society International Classification of Headache Disorders-3 beta (ICHD-3 $\beta$ ).<sup>14,15</sup> A probable migraine was also a headache, with or without aura, lasting at least 30 minutes, but missing 1 feature from the criteria for feature A and/or B of the ICHD-3 $\beta$

*Conflict of Interest:* V. Stauffer, S. Wang, V. Skljarevski, A. Kovacic, and S. Aurora are full-time employees and minor stockholders of Eli Lilly and Company. M. Voulgaropoulos reports receiving honoraria for serving as an advisor and speaker for Eli Lilly and Company.

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*Trial registration:* *ClinicalTrials.gov* Identifiers: NCT02614183; NCT02614196.

definition. A migraine headache day (MHD) was defined as a calendar day on which a migraine or probable migraine occurred.

EVOLVE-1 (ClinicalTrials.gov Identifier: NCT02-614183) and EVOLVE-2 (ClinicalTrials.gov Identifier: NCT02614196) are randomized, multicenter, double-blind, placebo-controlled phase 3 trials of galcanezumab in patients with episodic migraine with identical study designs.<sup>13,14</sup> The primary and secondary outcomes and study details for the double-blind treatment period of both trials have been reported.<sup>13,14</sup> Of note, the ClinicalTrials.gov records report only the disposition and adverse events for the posttreatment period for each study. Briefly, these studies were comprised of 4 study periods (Supporting Information Fig. S1): (1) screening and washout of migraine preventive treatments (3–45 days); (2) prospective lead-in period (30–40 days) to determine frequency of MHD and determine patient eligibility; (3) double-blind treatment period (Months 1 to 6); and (4) a 4-month posttreatment period (Months 7 to 10).<sup>13,14</sup> All randomized patients, including those discontinuing treatment early, entered the 4-month posttreatment period, thus providing 5 months of observation, from the last galcanezumab injection at Month 5 to study conclusion at Month 10; this comprises approximately 5 galcanezumab elimination half-lives. This manuscript reports on the posttreatment period of these studies.

Detailed enrollment inclusion and exclusion criteria were previously described.<sup>13,14</sup> Key enrollment criteria included male or female patients aged 18–65 years diagnosed as having migraine with or without aura per ICHD-3 $\beta$  guidelines for at least the prior 1 year and migraine onset before age 50 years old. Patients had to experience a frequency of 4–14 MHDs and at least 2 migraine attacks per month during the baseline period; patients were blinded to these criteria.

Studies were conducted according to Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the institutional/ethical review board at each study site. Patients provided written informed consent before undergoing study procedures.

These studies were designed by the sponsor, Eli Lilly and Company, with input from migraine and headache

disorder experts. Data were analyzed and interpreted by Eli Lilly and Company in collaboration with the non-Lilly authors. All authors had access to the data and approved the final version for the manuscript prior to submission. All authors participated in the drafting of the manuscript and/or critical revisions of subsequent drafts. Writing and editorial assistance was provided by Syneos Health on behalf of the sponsor.

**Study Procedures.**—Detailed procedures including sample size determination, randomization, and blinding were previously reported.<sup>13,14</sup> During the trials, patients used a handheld diary device to record daily headache information. Patients were randomized (2:1:1) to receive either placebo, galcanezumab 120 mg, or galcanezumab 240 mg. Randomization was stratified by region and baseline migraine frequency (<8 vs  $\geq$ 8 MHD). Patients receiving the 120-mg dose received an initial loading dose of 240 mg. Galcanezumab or placebo was administered by monthly subcutaneous injection during office visits by site personnel. During the double-blind treatment period, patients could take acute migraine medications as needed, except medications containing opioids or barbiturates more than 3 days per month. Patients who completed or discontinued the double-blind treatment period entered the posttreatment period. Patients could initiate migraine prevention medications at the discretion of the investigator beginning at Month 7. The trial ended on the date of the last patient visit at Month 10.

**Clinical Efficacy Assessments.**—Efficacy assessments included change from baseline of monthly MHDs, proportion of patients (50% responders) with  $\geq$ 50% reduction of baseline of monthly MHD, time-to-first loss of 50% response, change from baseline of monthly MHDs with acute medication use, and Migraine-Specific Quality of Life Questionnaire (version 2.1) Role Function-Restrictive Domain score. Assessment details were previously reported.<sup>13,14</sup>

**Clinical Safety Assessments.**—The safety analysis of the posttreatment period included evaluation of treatment emergent adverse events (TEAE), serious adverse events (SAE), and AEs leading to discontinuation, vital signs, body weight, electrocardiograms, and laboratory measurements collected/performed at scheduled (per protocol) and unscheduled (as needed) visits. For the posttreatment period,

TEAE were defined as reported AEs that first occurred or worsened during the post-baseline period compared with baseline period. This report presents integrated safety data from the posttreatment period of EVOLVE-1 and EVOLVE-2, as well as results from the individual studies.

**Statistical Analyses.**—For efficacy analyses including data from the double-blind treatment period, all patients randomized and treated were included with results organized by randomized treatment group. For safety analyses including the double-blind treatment period, all patients randomized and treated were included with results organized by modal treatment group during double-blind treatment period. For analyses using data from the posttreatment period only, all patients who entered the posttreatment period were included, unless otherwise specified.

For repeated continuous efficacy and safety (vital signs and body weight) measures, the change from baseline (prior to randomization) to each post-baseline visit during the study was analyzed using a mixed model repeated measures (MMRM) analysis. The MMRM included the fixed, categorical effects of treatment, region, month, and treatment-by-month interaction, as well as the continuous, fixed covariates of baseline value, and baseline-by-month interaction. Baseline monthly MHD category (<8 vs ≥8) was also included in the models for efficacy measures except for the number of monthly MHD.

For the analyses of response rate (at least 50% improvement), the binary indicator of responders was analyzed in generalized linear mixed models (GLIMMIX) as pseudo-likelihood-based mixed effects repeated measures analysis. The GLIMMIX model included the same model terms as the MMRM, except for region and the baseline value-by-month interaction to increase the likelihood of convergence.

For time-to-event analyses, a stratified log-rank test was used with the baseline monthly MHD category (<8 vs ≥8) and region as covariates for time-to-event analyses. Categorical safety measures were analyzed using the Fisher's exact test.

For all analyses, statistical significance was defined as  $P$  values ≤.05, and tests of treatment effects were conducted at a 2-sided alpha level of 0.05. No adjustment was made for multiple comparisons. All

statistical analyses were performed with the use of SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC, USA).

## RESULTS

**Baseline Demographics and Disposition.**—Detailed demographics and patients' disposition for the double-blind treatment periods were published.<sup>13,14</sup> Across trials, approximately 84% of patients in the ITT population were female (Table S1). The mean age was approximately 41 years of age. Among the total number of patients from both trials who entered the treatment periods, approximately 88% entered the posttreatment periods and, of these patients, approximately 95% completed their respective trials (Table 1). The last patients completed on July 19, 2017 (EVOLVE-1) and August 4, 2017 (EVOLVE-2).

**Efficacy.**—*Change from Baseline in Monthly Migraine Headache Days.*—As shown previously, during each month of the 6-month double-blind treatment period, galcanezumab-treated patients reported significantly greater least squares (LS) mean reductions in the number of monthly MHDs compared with the placebo group.<sup>13,14</sup> Following treatment cessation, in EVOLVE-1, the reduction of monthly MHDs declined from (mean [SE]) 5.2 (0.4) days at Month 6 to 4.1 (0.4) days at Month 10 for the 120-mg dose, from 5.3 (0.4) days at Month 6 to 3.8 (0.4) days at Month 10 for the 240-mg dose, and remained stable for placebo (3.4 [0.3] days at Month 6 and 3.3 [0.3] days at Month 10). The differences relative to baseline remained statistically significant throughout the posttreatment period ( $P < .001$  for all treatments at all time points). The differences between the galcanezumab arms and placebo were statistically significant throughout the posttreatment period, except Month 10 for galcanezumab 240 mg (120 mg vs placebo:  $P < .001$  Months 1–6,  $P = .007$  Month 7,  $P = .044$  Month 8,  $P = .016$  Month 9, and  $P = .042$  Month 10; 240 mg vs placebo:  $P < .001$  Months 1–7,  $P = .015$  Month 8,  $P = .021$  Month 9, and  $P = .238$  Month 10).

In EVOLVE-2, the reduction of monthly MHDs declined from (mean [SE]) 4.5 (0.3) days at Month 6 to 3.5 (0.3) days at Month 10 for the 120-mg dose, and 4.5 (0.3) days at Month 6 to 3.7 (0.3) days for the 240-mg dose at Month 10, whereas the reduction remained stable for placebo (2.8 [0.2] days at Month

Table 1.—Patient Disposition of the Treatment and Posttreatment Periods in EVOLVE-1 and EVOLVE-2

	EVOLVE-1 <sup>a</sup>			EVOLVE-2 <sup>b</sup>		
	Placebo	GMB	GMB	Placebo	GMB	GMB
		120 mg	240 mg		120 mg	240 mg
Entered tx period <sup>c</sup>	433	213	212	461	231	223
Completed	351 (81%)	177 (83%)	175 (83%)	387 (84%)	203 (88%)	195 (87%)
Discontinued	82 (19%)	36 (17%)	37 (17%)	74 (16%)	28 (12%)	27 (12%)
Due to AEs	10 (2%)	9 (4%)	7 (3%)	8 (2%)	5 (2%)	9 (4%)
Entered post-tx period <sup>d</sup>	372	185	183	410	213	207
Completed	354 (95%)	179 (97%)	171 (93%)	390 (95%)	208 (98%)	199 (96%)
Discontinued	18 (5%) <sup>e</sup>	6 (3%) <sup>f</sup>	11 (6%) <sup>g</sup>	20 (5%) <sup>h</sup>	5 (2%) <sup>i</sup>	8 (4%) <sup>j</sup>
Due to AE	0	0	0	0	0	0

<sup>a</sup>Details for double-blind treatment period are reported in Stauffer et al.<sup>14</sup>

<sup>b</sup>Details for double-blind treatment period are reported in Skljarevski et al.<sup>13</sup>

<sup>c</sup>Randomized and received at least 1 dose of investigational product.

<sup>d</sup>Patients who discontinued the treatment period early were encouraged to continue in the posttreatment period, so the numbers of patients entering the posttreatment period are higher than the numbers of patients completing the treatment period.

<sup>e</sup>Reasons: 5 lost to follow-up; 5 physician decision; 1 protocol deviation; 7 patient withdrew.

<sup>f</sup>Reasons: 3 lost to follow-up; 1 physician decision; 2 patient withdrew.

<sup>g</sup>Reasons: 4 lost to follow-up; 2 physician decision; 5 patient withdrew; 1 reason unknown (not included in table).

<sup>h</sup>Reasons: 8 lost to follow-up; 2 pregnancy; 10 patient withdrew.

<sup>i</sup>Reasons: 3 lost to follow-up; 1 protocol deviation; 1 patient withdrew.

<sup>j</sup>Reasons: 3 lost to follow-up; 5 patient withdrew.

AE = adverse event; GMB = galcanezumab; tx = treatment.

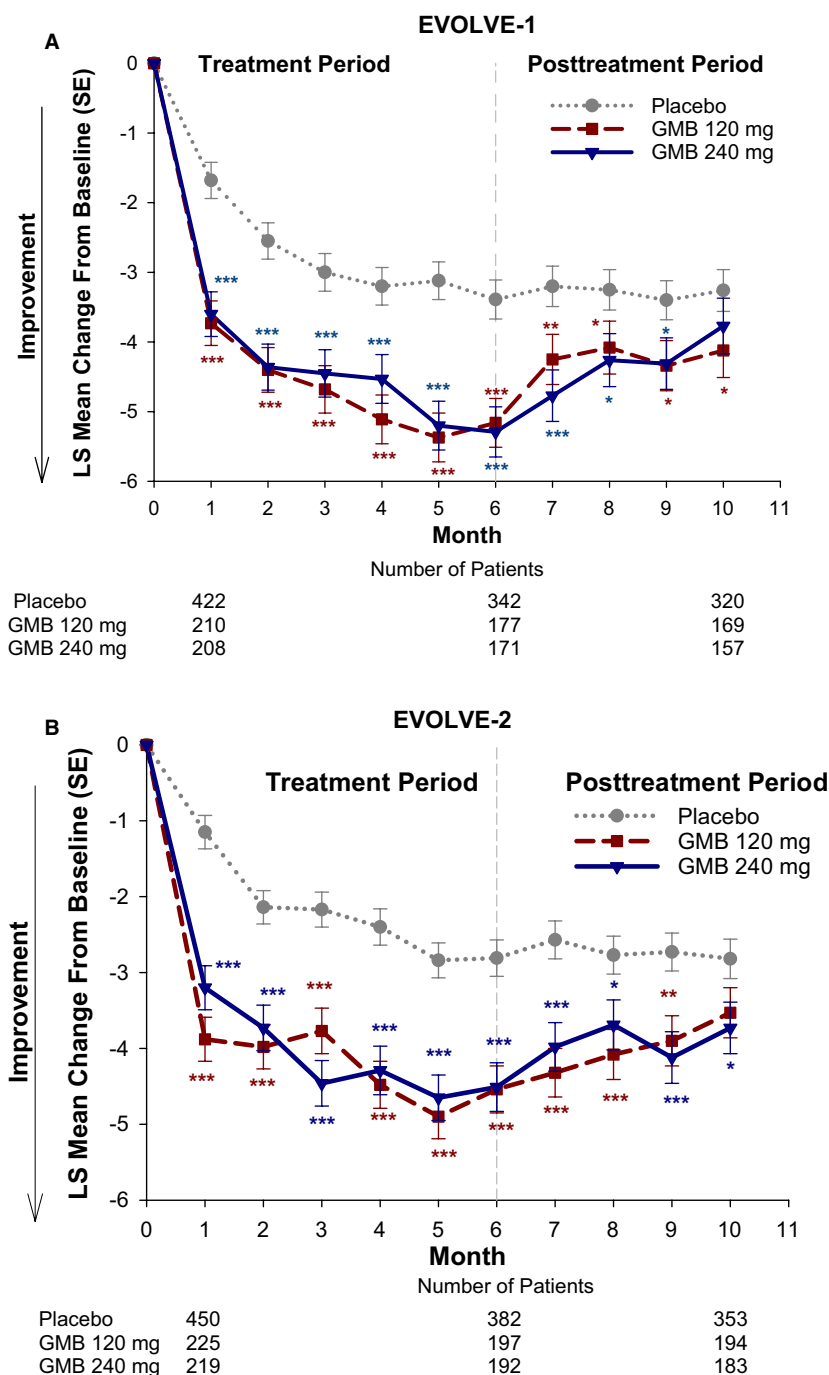
6 and 2.8 [0.3] days at Month 10) (Fig. 1A,B). Differences relative to baseline remained statistically significant throughout the posttreatment period ( $P < .001$  for all treatments at all time points). Likewise, the differences between the galcanezumab arms and placebo remained statistically significant throughout the posttreatment period; the exception was at Month 10 for galcanezumab 120 mg (120 mg vs placebo:  $P < .001$  Month 1–8,  $P = .002$  Month 9, and  $P = .066$  Month 10; 240 mg vs placebo:  $P < .001$  Months 1–7,  $P = .016$  Month 8,  $P < .001$  Month 9, and  $P = .019$  Month 10).

*Proportion of Patients with  $\geq 50\%$  Reduction from Baseline Migraine Headache Days.*—Figure 2 shows the proportion of patients (50% responders) meeting the predefined threshold of  $\geq 50\%$ , reduction from baseline in monthly MHDs at the end of the double-blind treatment period (Month 6) and of the posttreatment period (Month 10). The proportion of patients achieving  $\geq 50\%$  threshold of reduction from baseline monthly MHD was significantly greater among galcanezumab-treated patients compared with

placebo at Month 6 in both EVOLVE-1 and EVOLVE-2. Following treatment cessation, there was a reduction in the proportion of patients achieving the predefined thresholds from Month 6 to Month 10 with the difference between galcanezumab and placebo only being significant for the 120-mg dose in EVOLVE-1.

*Time to First Loss of 50% Response.*—Among patients with 50% response at Month 6, following treatment cessation, the percentages of patients that lost 50% response increased over time during the posttreatment period (Fig. 3A,B). At Month 10, which was 5 months after treatment cessation,  $>50\%$  of Month 6 responders across all treatment groups had lost their response. There were no significant differences between galcanezumab dose groups and placebo for time to first loss of response.

*Change from Baseline in Monthly Migraine Headache Days with Use of Acute Migraine Medication.*—During the treatment period, there was significantly more reduction in the number of monthly MHD with acute medication use among galcanezumab-



**Fig. 1.**—Mean change from baseline in monthly migraine headache day (MHDs) in the treatment and posttreatment periods of EVOLVE-1 (A) and EVOLVE-2 (B). LS mean change  $\pm$  SE is shown. *P* values are for the treatment vs placebo comparison. \**P* < .05; \*\**P* < .01; \*\*\**P* < .001. GMB, galcanezumab; LS, least squares; SE, standard error.

treated patients than in the placebo group at all time points (Fig. 4A,B). Following treatment cessation in EVOLVE-1 the reduction in the number of monthly MHD per month with acute medication use declined from 4.4 days at Month 6 to 3.2 days at Month 10 for the

120-mg dose, and 4.3 days at Month 6 to 3.0 days at Month 10 for the 240-mg group, and was stable for placebo (2.6 days at Month 6 and 2.4 days at Month 10). In EVOLVE-2, the reduction of monthly MHD with acute medication use declined from 3.6 days at Month

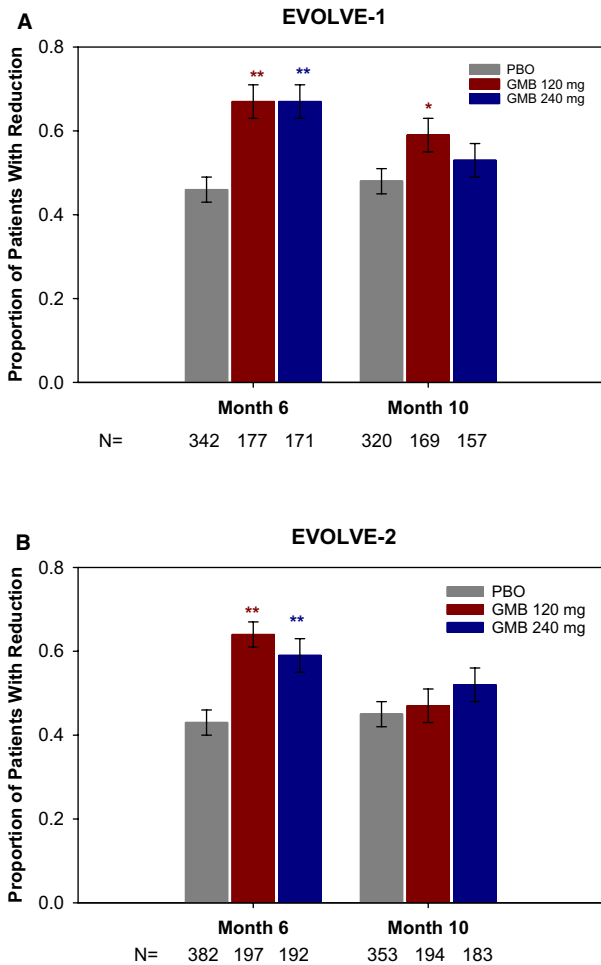


Fig. 2.—Proportion of patients (50% responders) with at least 50% reduction from baseline in monthly migraine headache days (MHDs) at Months 6 and 10 of EVOLVE-1 (A) and EVOLVE-2 (B). The proportion of patients ± SE with a ≥50% reduction from baseline in MHDs (model estimated rate) is shown. \**P* < .05 vs PBO; \*\**P* ≤ .001 vs PBO. GMB, galcanezumab, MHD, migraine headache day; N, population size; PBO, placebo; SE, standard error.

6 to 2.8 days at Month 10 for the 120-mg dose, and from 3.7 days at Month 6 to 3.0 days at Month 10 for the 240-mg dose, and was stable for placebo (2.3 days at Month 6 and 2.2 days at Month 10). The differences between each galcanezumab group and placebo maintained statistical significance at each month, with the exception of the 240-mg group in EVOLVE-1 at Month 10 and the 120-mg group in EVOLVE-2 at Month 10.

*Time-to-Initiation of Migraine Prevention Treatment.*—Patients were allowed to initiate treatment with alternative migraine preventives beginning at Month 7. The percentage of patients initiating mig-

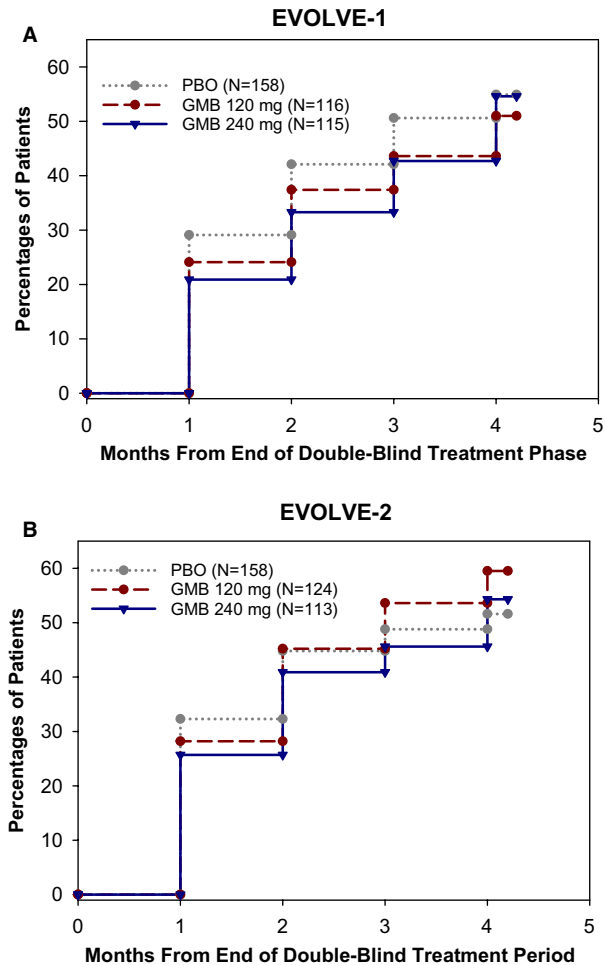


Fig. 3.—Percentage of patients demonstrating first loss of 50% response from after double-blind treatment of EVOLVE-1 (A) and EVOLVE-2 (B). The analysis includes patients who were 50% responders at the last month of the double-blind treatment period and who also entered the posttreatment period. Patients who were sustained 50% responders during the entire posttreatment period were censored. GMB, galcanezumab; N, population size; PBO, placebo.

raine preventives was low in both trials: 1.6% (12/739) in EVOLVE-1 (1.6% each in placebo [6/372], 120 mg [3/185], and 240 mg [3/182] groups) and 2.3% [19/830] in EVOLVE-2 (3.2% placebo [13/410]; 1.4% each in 120 mg [3/213] and 240 mg [3/207] groups). There were no statistically significant differences between placebo and galcanezumab-treated patients with regard to time-to-initiation (data not shown).

*Migraine-Specific Quality of Life Questionnaire (Version 2.1) Role Function-Restrictive Domain Score.*—Quality of life (QOL) was measured by the Migraine-Specific Quality of Life Questionnaire

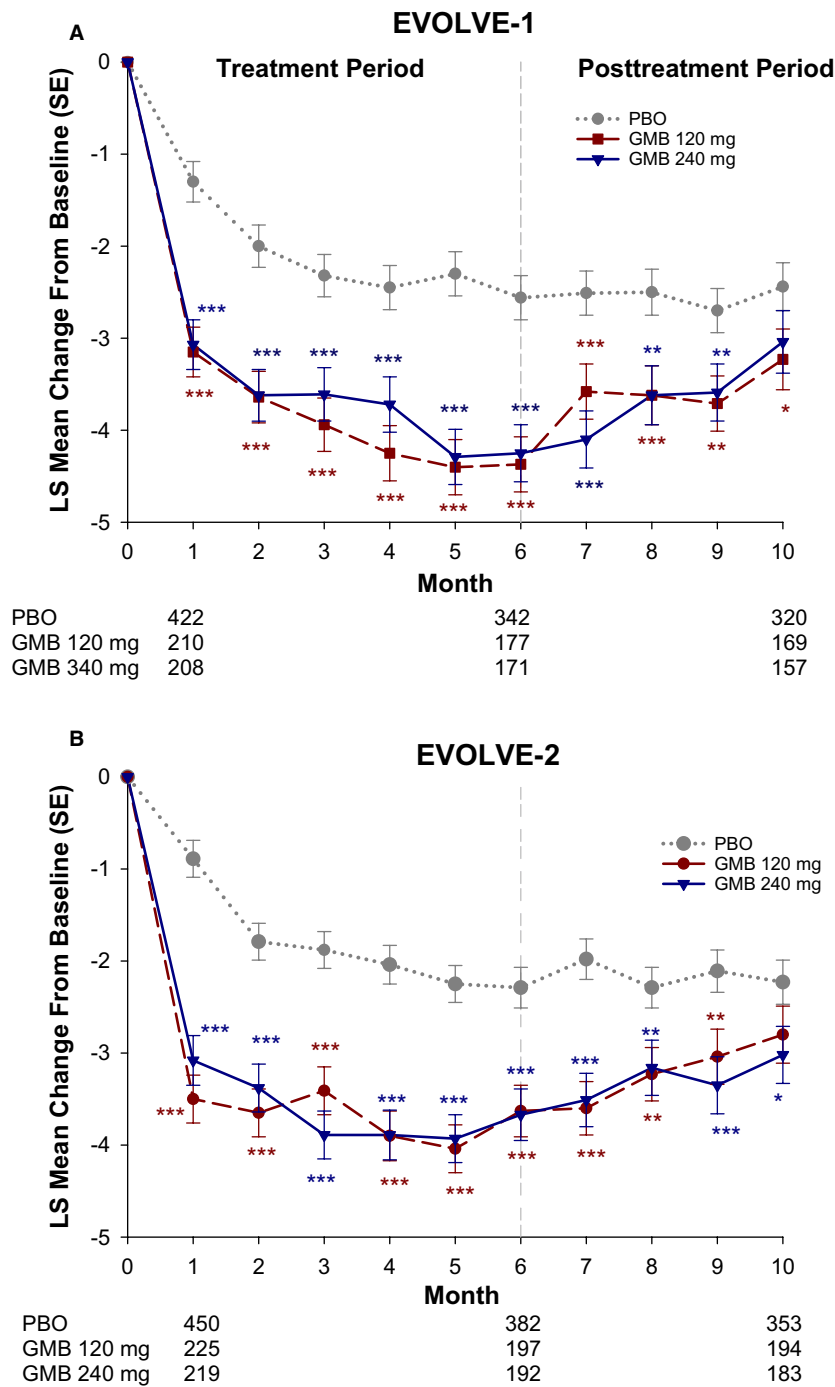


Fig. 4.—Mean change from baseline in monthly migraine headache days (MHD) with acute medication use during the treatment and posttreatment periods of EVOLVE-1 (A) and EVOLVE-2 (B). LS mean change  $\pm$  SE is shown. \* $P < .05$  vs PBO; \*\* $P < .01$  vs PBO; \*\*\* $P < .001$  vs PBO. GMB, galcanezumab; LS, least squares; N, population size; PBO, placebo; SE, standard error.

(version 2.1) Role Function-Restrictive Domain score. At Month 6 (end of treatment), there was statistically significant improvement in QOL as evidenced by greater LS-mean improvement from

baseline in scores, in both galcanezumab treatment groups compared with placebo in EVOLVE-1 and EVOLVE-2 (Fig. 5A,B). After treatment cessation at Month 10, the magnitude of the galcanezumab vs



Table 2.—Integrated EVOLVE-1 and EVOLVE-2 Safety Data During Posttreatment Period

	EVOLVE-1 + EVOLVE-2			
	Placebo	GMB 120 mg	GMB 240 mg	Pooled GMB
	N = 782	N = 395	N = 393	N = 788
Pts with $\geq 1$ post-TEAE, n (%)	195 (24.9)	99 (25.1)	87 (22.1)	186 (23.6)
Post-TEAEs, n (%)†	—	—	—	—
Viral upper respiratory tract infection	20 (2.6)	8 (2.0)	11 (2.8)	19 (2.4)
Upper respiratory tract infection	15 (1.9)	10 (2.5)	7 (1.8)	17 (2.2)
Discontinuations from study due to AEs, n (%)	0	0	0	0
Pts with $\geq 1$ SAE, n (%)	5 (0.6)‡	4 (1.0)§	7 (1.8)¶	11 (1.4)
Deaths, n	0	0	0	0

†Occurring in  $\geq 2.0\%$  of patients in pooled GMB group in EVOLVE-1 + EVOLVE-2.

‡One each of goiter, asthenia, appendicitis, pyelonephritis, urosepsis, and ureterolithiasis.

§Vomiting (n = 1), uterine leiomyoma (n = 2), and tonsil cancer (n = 1).

¶One each of congestive heart failure, cardiomyopathy, inner ear disorder, patellofemoral pain syndrome, abortion missed, adjustment disorder with mixed anxiety and depressed mood, panic attack, and posttraumatic stress disorder.

AE = adverse event; GMB = galcanezumab; N = population size; Pts = patients; SAE = serious adverse event; TEAE = treatment emergent adverse events; tx = treatment.

placebo treatment differences decreased and there were no longer statistically significant differences between galcanezumab and placebo.

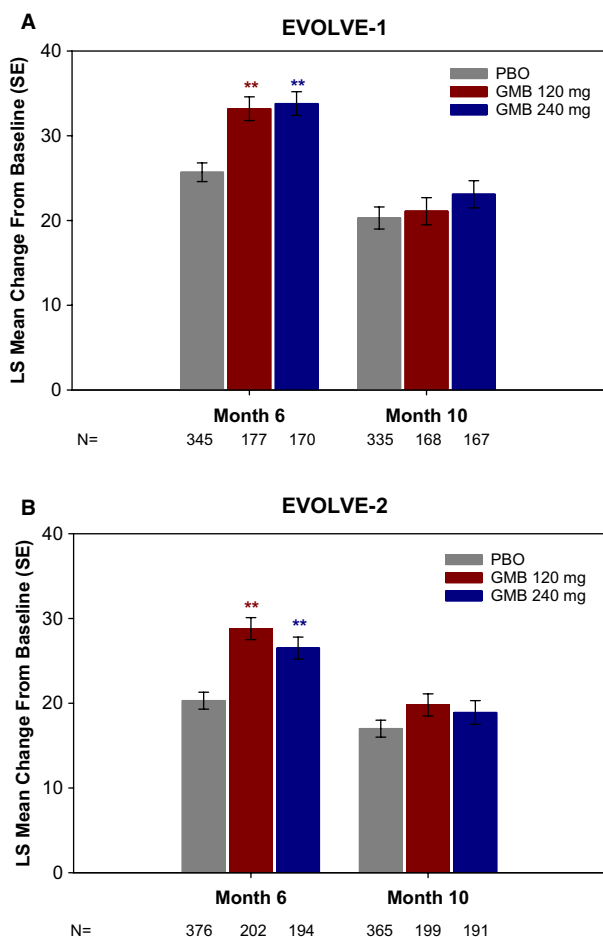
**Safety.**—Detailed safety data from the double-blind treatment periods of EVOLVE-1 and EVOLVE-2 were previously reported.<sup>13,14</sup> Data from the posttreatment periods of EVOLVE-1 and EVOLVE-2 were integrated (Table 2). The rate of patients experiencing post-TEAEs was similar in the placebo (25%) and galcanezumab groups (25% 120-mg; 22% 240-mg). The most common ( $>2\%$ ) post-TEAEs were upper respiratory tract infections (viral and otherwise) but there was no difference between the originally assigned galcanezumab treatment arms and placebo. Overall, there were no deaths or discontinuations from the study due to AEs. There was a higher frequency of patients with SAEs in the pooled galcanezumab group (1.4%) than in the placebo group (0.6%), but none were considered to be galcanezumab-related by investigators.

During the EVOLVE-1 posttreatment period, there was a greater increase in body weight in the galcanezumab groups compared with placebo in regard to continuous changes (mean change from baseline to Month 10: 0.8-kg placebo, 1.1-kg

120 mg, and 1.5-kg 240 mg) and categorical changes (increase  $\geq 7\%$  during the posttreatment period: 1.7% placebo, 3.9% 120 mg, and 3.4% 240 mg). However, there was not a statistical difference in either galcanezumab dose compared with placebo for the continuous analysis, and a statistical analysis for categorical changes was not performed. There were no clinically meaningful changes in laboratory parameters, vital signs, or electrocardiograms during the posttreatment period.

During the EVOLVE-2 posttreatment period, there was a similar increase in body weight in the galcanezumab groups compared with placebo in regard to continuous changes (mean change from baseline to Month 10: 1.0-kg placebo, 1.2-kg 120 mg, and 0.9-kg 240 mg) and categorical changes (increase  $\geq 7\%$  during the posttreatment period): 2.5% placebo, 2.9% 120 mg, and 2.5% 240 mg. There was not a statistical difference in either galcanezumab dose compared with placebo for the continuous analysis, and a statistical analysis for categorical changes was not performed.

There were no clinically meaningful changes in vital signs (blood pressure, pulse, or temperature)



**Fig. 5.**—Mean change from baseline in Migraine-Specific Quality of Life Questionnaire (version 2.1) Role Function-Restrictive Domain score at Months 6 and 10 of EVOLVE-1 (A) and EVOLVE-2 (B). LS mean change  $\pm$  SE is shown.  $**P \leq .001$  vs PBO. GMB, galcanezumab; LS, least squares; N, population size; PBO, placebo; SE, standard error.

during the posttreatment period. There was a greater incidence of high systolic and high diastolic blood pressures in the treatment groups originally randomized to galcanezumab (systolic: 1.3% placebo, 1.9% 120 mg, and 2.4% 240 mg; diastolic: 2.8% placebo, 4.8% 120 mg, and 4.9% 240 mg). However, this was not considered clinically significant because no patient exceeded pre-specified criteria for systolic ( $\geq 180$  and increase  $\geq 20$  among all patients, and those in  $<180$  or  $\geq 180$  categories at baseline) and diastolic ( $\geq 105$  and increase  $\geq 15$  among all patients and those in  $<105$  or  $\geq 105$  categories at baseline) blood pressure measurements, and the incidence of post-TEAEs of hypertension was lower in the galcanezumab groups (0.5% each) compared with placebo

(1.0%). In addition, there were no clinically meaningful changes in laboratory parameters, or electrocardiograms during the posttreatment period.

## DISCUSSION

Galcanezumab is a monoclonal antibody that significantly reduced the number of overall monthly MHDs in patients with episodic migraine by 4.7 days (120 mg) and 4.6 days (240 mg) compared with 2.8 days (placebo) during the 6-month treatment period of EVOLVE-1<sup>14</sup> and by 4.3 days (120 mg) and 4.2 days (240 mg) compared with 2.3 days (placebo) during the 6-month treatment period of EVOLVE 2.<sup>13</sup> It should be noted that the above numbers represent the *overall* mean change from baseline which is the treatment effect averaged across the multiple post-baseline assessment times during the 6-month treatment period. This is why the above numbers differ from those reported at Month 6 in the new analyses reported here. Galcanezumab is well tolerated as over 80% of patients in EVOLVE-1 and EVOLVE-2 completed the treatment period and less than 5% of patients discontinued the treatment period due to AEs.<sup>13,14</sup> This is considerably less than the withdrawal rate due to AEs in registration trials for topiramate (50 mg/day: 17%–18%; 100 mg/day: 19%–27%; 200 mg/day: 21%–34%;<sup>16,17</sup> and mean dose of 86.0 mg/day: 10.9%<sup>18</sup>), which is a commonly prescribed migraine prevention treatment<sup>19</sup> but similar to other available CGRP monoclonal antibodies.<sup>20-22</sup>

Because galcanezumab has migraine preventive activity and is safe during sustained treatment, it was important to determine if its activity persists after treatment ends. With a half-life of 27 days,<sup>9</sup> it is expected that galcanezumab activity would persist for a time after treatment ends. Persistence of clinical activity is of great importance to patients with migraine who may need to stop prevention medication temporarily or switch medications. Likewise, it was important to determine if the AE profile changed following treatment cessation.

Following cessation of galcanezumab therapy, the migraine-relevant outcome measures observed during the treatment periods were reduced over time, but did not return to baseline. Although the reduction in the numbers of monthly MHDs and MHDs with use of acute medications both declined during the

posttreatment period of EVOLVE-1 and EVOLVE-2, the reductions were still statistically significant, with the exception of the 240-mg dose at Month 10 in EVOLVE-1 and the 120-mg dose at Month 10 in EVOLVE-2 for monthly MHDs. The galcanezumab 120-mg and 240-mg dose groups had similar changes from baseline in the number of monthly MHDs and MHDs with use of acute medications during the treatment period in both studies. In the posttreatment follow-up period, the results between these 2 groups were also fairly consistent, except for Month 10 in EVOLVE-1 and EVOLVE-2. We did not observe consistent dose response in both studies for the treatment period and posttreatment period. The findings at Month 10 could be random and sporadic or potentially due to the persistent effect of the placebo arm in both studies in light of the galcanezumab effect diminishing.

It has been proposed that in episodic migraine clinical trials, more than half of the study population should experience at least 50% reduction in the number of monthly MHD (compared to MHD measured at baseline) for the change to be clinically relevant.<sup>23</sup> Although >50% of responders treated with galcanezumab 120 mg and 240 mg in EVOLVE-1 and 240 mg in EVOLVE-2 still met the 50% reduction threshold at the end of the posttreatment period (Month 10), the difference relative to placebo was only significant for the 120-mg dose in EVOLVE-1.

At Month 10 in EVOLVE-1 and EVOLVE-2, patients were no longer reporting improvements relative to placebo in HRQOL. In EVOLVE-1 and EVOLVE-2, patients received their last galcanezumab dose at Month 5 (approximately 5 galcanezumab half-lives). The decline of clinical activity following treatment cessation parallels pharmacokinetic findings in which galcanezumab concentrations at Month 8 and Month 10 reflected an elimination half-life of approximately 3–4 weeks (data not shown).

Regarding safety, a key issue was if stopping galcanezumab treatment would lead to the emergence of unexpected AEs. In EVOLVE-1 and EVOLVE-2, higher rates of patients with TEAEs were reported during the treatment period (EVOLVE-1: 60.4% placebo; 65.5% 120 mg; 67.7% 240 mg and EVOLVE-2: 62.3% placebo; 65.0% 120 mg; 71.5% 240 mg) than during the posttreatment period (24.9% placebo;

25.1% 120 mg; 22.1% 240 mg).<sup>13,14</sup> This is, in part, driven by the absence of injection site reactions during the posttreatment period.<sup>13,14</sup> Upper respiratory tract infections (upper respiratory tract infection and viral upper respiratory tract infection) were the most common post-TEAEs in EVOLVE-1 and EVOLVE-2, were reported in a similar incidence in the galcanezumab dose groups and placebo groups, and were also commonly reported during the treatment period.<sup>13,14</sup> All of the other post-TEAEs were reported in 1% or less of patients previously randomized to either the galcanezumab 120-mg or 240-mg dose groups. Of interest, there were 3 patients who reported the post-TEAE of migraine in the galcanezumab 120-mg dose group compared with 1 patient in the placebo group, and 1 patient in the galcanezumab 240-mg dose group compared with 2 patients in the placebo group who reported the post-TEAE of headache, suggesting a low concern of rebound headache. The SAE incidence was low during the treatment and posttreatment periods.<sup>13,14</sup> During the posttreatment period, no SAE occurred in more than 1 patient per study and there were no discontinuations due to adverse events. With regard to weight change, there was a greater mean change in weight for the galcanezumab 120-mg and 240-mg dose groups compared with placebo in the EVOLVE-1 study from baseline to Month 10, but this finding was not statistically significant; this was consistent with EVOLVE-2. In EVOLVE-2 and the treatment period results for both studies, weight increase in the galcanezumab dose groups was similar to placebo, so the findings in EVOLVE-1 likely reflect natural variation in body weight over time. There were no clinically relevant differences in laboratory measures, vital signs including blood pressure, and electrocardiogram during the treatment and posttreatment periods.

Limitations of this work include restrictions in enrollment criteria that could limit the generalizability of the results, the predominantly Caucasian patient population, and that most patients had not failed 1 prior preventive. EVOLVE-1 and EVOLVE-2 excluded patients with serious medical or psychiatric conditions, high body mass index ( $\geq 40$  kg/m<sup>2</sup>), use of opioid- or barbiturate-containing analgesics (more than twice monthly for the treatment of pain in more

than 2 of the past 6 months), or a high risk of serious cardiovascular events.

To our knowledge, EVOLVE-1 and EVOLVE-2 are the only phase 3 trials of anti-CGRP antibodies with a posttreatment period immediately following the double-blind treatment period. This provided the advantage of having a placebo comparator group during the 5 months in which patients were not receiving the active treatment. Galcanezumab was withdrawn 1 month before the end of the treatment period, and therefore galcanezumab underwent approximately 5 elimination half-lives by study end. This timeframe provides ample time to examine any treatment-related effects following treatment cessation and informs clinicians that the effects of galcanezumab do continue after cessation of treatment, which may be useful when treatment is stopped for a variety of reasons.

Placebo responses in clinical trials involving migraine prevention have been reported.<sup>20-22,24,25</sup> Of interest is persistence of the placebo response following treatment withdrawal in EVOLVE-1 and EVOLVE-2. In a meta-analysis of migraine prevention trials, the placebo response was higher in trials with a parallel (vs crossover) design and among European studies (vs North American).<sup>24</sup> Although transience of a placebo response is widely assumed, this notion is not data-driven and was reviewed by Diener and colleagues, who note that even treatment studies of longer than 6 months' duration, such as the botulinum toxin studies, showed persistent placebo response over the course of 11 months.<sup>26</sup> While it is noted that spontaneous remission may be a contributing factor to placebo response in migraine clinical trials, the factors certainly are multifactorial, such as expectation bias and parenteral treatments, which have been shown to induce a higher placebo response compared with oral treatments.<sup>27</sup>

Persistence of placebo response was reported in studies involving antidepressants.<sup>28</sup> In an analysis of trials involving an acute double-blind placebo-controlled phase lasting at least 6 weeks followed by a 12-week continuation phase whereby responders remained on the same treatment, 93% of initial responders treated with antidepressant and 79% of initial responders assigned to placebo did not relapse during the continuation phase.<sup>28</sup> Likewise, in an analysis of clinical trials of patients with

depression who responded to initial antidepressive therapy and were then randomized to continue active treatment or to placebo, the average rates of relapse were 41% for patients on placebo and 18% for patients on active therapy.<sup>29</sup> These data suggest that at least in some settings, once a patient feels better there is a reasonable chance that the patient will maintain the response regardless of whether the original (and subsequent) treatment is "active." In the case of EVOLVE-1 and EVOLVE-2, staying on study during the washout period may itself have had a placebo effect contributing the patients' continued feelings of well-being.

## CONCLUSIONS

As expected, the galcanezumab treatment effects observed for migraine-relevant outcome measures during the treatment periods were reduced during the posttreatment periods. However, migraine-relevant outcomes did not return to baseline levels. There were no unexpected adverse events following galcanezumab cessation.

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