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Efficacy of Galcanezumab for Migraine Prevention in Patients With a Medical History of Anxiety and/or Depression: A Post Hoc Analysis of the Phase 3, Randomized, Double-Blind, Placebo-Controlled REGAIN, and Pooled EVOLVE-1 and EVOLVE-2 Studies

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Research Submission

Efficacy of Galcanezumab for Migraine Prevention in Patients With a Medical History of Anxiety and/or Depression: A Post Hoc Analysis of the Phase 3, Randomized, Double-Blind, Placebo-Controlled REGAIN, and Pooled EVOLVE-1 and EVOLVE-2 Studies

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Objective.—This post hoc analysis evaluated the efficacy of galcanezumab for the prevention of migraine in patients with and without comorbid anxiety and/or depression.

Background.—Patients with migraine have a higher risk of anxiety and/or depression. Given the high prevalence of psychiatric symptoms and their potential negative prognostic impact, determining the efficacy of migraine treatments in patients with these comorbidities is important.

Methods.—The results of 2 phase 3 episodic migraine studies of patients with 4-14 migraine headache days (MHD) per month were pooled. A third chronic migraine study, which was evaluated separately, enrolled patients with ≥15 headache days per month, of which ≥8 had migraine-like features. Patients in all 3 studies were randomized 2:1:1 to placebo, galcanezumab 120 mg, or galcanezumab 240 mg. The efficacy of galcanezumab on migraine was measured in subgroups of patients with anxiety and/or depression (current or past) and patients without. A repeated measures model was used to compare treatment groups within each subgroup and to test for consistency of treatment effect across the anxiety/depression subgroups (subgroup-by-treatment interaction) during the double-blind treatment phases.

Results.—Among 1773 intent-to-treat patients with episodic migraine, both doses of galcanezumab demonstrated statistically significant improvements relative to placebo in overall number of MHD for the subgroups of patients with anxiety and/or depression (mean change difference from placebo [95% CI]: −2.07 [−2.81, −1.33] for galcanezumab 120 mg [$P < .001$], −1.91 [−2.78, −1.04] for 240 mg [$P < .001$]) and without anxiety and/or depression (mean change difference from placebo [95% CI]: −1.92 [−2.36, −1.47] for 120 mg [$P < .001$], −1.77 [−2.20, −1.33] for 240 mg [$P < .001$]), as was observed for the secondary outcomes of MHD with acute medication use and functional impairment. Among 1113 intent-to-treat patients with chronic migraine, those with anxiety and/or depression had significant reductions in overall MHD frequency with the 240-mg dose (mean change difference from placebo [95% CI]: −1.92 [−3.52, −0.33]; $P = .018$), whereas significant reductions were observed at both the 120-mg (mean change

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difference from placebo [95% CI]: −2.29 [−3.26, −1.31]; $P < .001$) and 240-mg (−1.85 [−2.83, −0.87]; $P < .001$) doses in patients without anxiety and/or depressions. Significant reductions ($P < .01$) in MHD with acute medication use were observed at both doses within both anxiety/depression subgroups and for overall functional impairment for patients without anxiety and/or depression, though neither dose significantly reduced overall functional impairment beyond placebo in the subgroup with anxiety and/or depression. In the episodic and chronic migraine studies, the subgroup-by-treatment interaction was not statistically significant for MHD, MHD with acute medication use, or functional impairment (chronic study only), suggesting a lack of evidence of differential effect between subgroups. Furthermore, differences between subgroups in the mean change differences from placebo, as well as overlapping 95% confidence intervals for the subgroups, indicated lack of a clinical or statistical difference between subgroups for these outcome variables. There was a significantly higher percentage of patients with episodic migraine attaining ≥50%, ≥75%, and 100% reductions, and a higher percentage of patients with chronic migraine attaining ≥50% and ≥75% reductions from baseline with galcanezumab compared with placebo, regardless of medical history of anxiety and/or depression.

Conclusions.—A medical history of anxiety and/or depression does not seem to interfere with response to galcanezumab among patients with episodic migraine, and both doses of galcanezumab appear efficacious for these individuals regardless of this psychiatric history. Among patients with chronic migraine and comorbid anxiety and/or depression, the 240-mg dose, but not the 120-mg dose, significantly decreased overall MHD, but neither dose resulted in significantly greater functional improvement. Patients with migraine and comorbid anxiety and/or depression often require additional interventions, and this may be more important in chronic migraine.

Key words: galcanezumab, migraine, comorbid, anxiety, depression, prevention

Abbreviations: ANOVA analysis of variance, CGRP calcitonin gene-related peptide, IHS International Headache Society, ICHD-3 International Classification of Headache Disorders-3rd edition, MIDAS Migraine Disability Assessment, MHD migraine headache days, MMRM mixed model repeated measures, MSQ Migraine-Specific Quality of life Questionnaire

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INTRODUCTION

Migraine is a chronic, debilitating neurological disease that affects approximately 12% of the world's population[1] and is the second highest cause of years lost due to disability globally.[2] Although more than 25% of patients with migraine could benefit from preventive therapy,[3] only a fraction of patients receive preventive treatment.

Numerous studies have shown that migraine carries increased risk for comorbid psychiatric disorders, particularly anxiety[4,5] and depression,[6] such that risk for these conditions is more than double compared with patients without migraine.[7-9] The prevalence of comorbid psychiatric conditions is highest among those with chronic (vs episodic) migraine.[10] Comorbid anxiety and depression account for a substantial portion of role disability in migraine,[11] increase the risk for migraine progression over time,[12] and have been associated with poor response to both acute and preventive migraine pharmacotherapies.[13,14,15] Given the high prevalence of comorbid psychiatric symptoms in patients with migraine, it is important to understand the efficacy of novel treatments for those with comorbid anxiety and/or depression.

Calcitonin gene-related peptide (CGRP) has been strongly implicated in the pathophysiology of migraine,[16] and a number of small-molecule CGRP receptor antagonists and monoclonal antibodies to CGRP have shown efficacy as CGRP-targeted therapies for migraine.[16-18] Galcanezumab is a humanized monoclonal antibody that binds to CGRP and prevents its biological activity without blocking the CGRP receptor.[19] Galcanezumab is FDA approved for preventive treatment of migraine in adults. In phase 3 studies, galcanezumab at both 120-mg and 240-mg doses was shown to significantly reduce the number of migraine headache days (MHD) compared with placebo in patients with episodic migraine[20,21] and chronic migraine.[22] Given the results from recent trials of galcanezumab and high rates of psychiatric comorbidities in migraine, the

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present post hoc analysis sought to evaluate the efficacy of galcanezumab for preventive treatment of migraine in patients with comorbid anxiety and/or depression.

METHODS

In this post hoc analysis of 3 randomized, double-blind, placebo-controlled, phase 3 studies, data from 2 episodic migraine studies were pooled; the chronic migraine study was analyzed separately. The efficacy of galcanezumab was evaluated both within and between the subgroups of patients who had anxiety and/or depression and those who did not. Anxiety and/or depression were determined by a medical history taken by each investigator (patient reported experiencing anxiety and/or depression in the past and/or currently) and by review of available medical records. The 2 studies that were pooled, EVOLVE-1 (NCT02614183)[20] and EVOLVE-2 (NCT02614196),[21] were designed to examine whether galcanezumab at doses of 120 or 240 mg per month was superior to placebo in the preventive treatment of episodic migraine. The third study, REGAIN (NCT02614261),[22] was designed to determine whether galcanezumab at doses of 120 or 240 mg per month was superior to placebo in the preventive treatment of chronic migraine. The trial study designs are shown in Figure 1, and more information is available in the primary manuscripts.[20-22] The study protocols were approved by the institutional review board for each study site, and patients provided written informed consent before undergoing study procedures.

Patients were included in the anxiety/depression subgroup if their medical history or medical record included coded terms specific to 1 or more anxiety and depression diagnosis, and were either ongoing ("current") or in the past, that is, resolved prior to randomization ("past only"). Anxiety-related terms included anxiety, agoraphobia, phobia of flying, social anxiety disorder, panic disorder, generalized anxiety disorder, anxiety disorder, panic attack, panic reaction, and adjustment disorder with anxiety. Depression-related terms included depression, adjustment disorder with depressed mood, premenstrual dysphoric disorder, major depression, perinatal depression, depressive symptom, depressed mood, persistent depressive disorder, and menopausal depression. Concomitant medication indications were not collected, so it was not possible to determine which patients were being treated for anxiety and/or depression.

Participants.—All 3 studies included patients who were 18-65 years of age with onset of migraine prior to age 50 and excluded patients who had failed to respond to 3 or more classes of adequately dosed migraine preventive treatments with Level A or Level B evidence for efficacy.[23] In addition, EVOLVE-1 and EVOLVE-2 included patients who met criteria for a diagnosis of migraine with or without aura. Patients had a diagnosis of migraine as defined by International Headache Society (IHS) International Classification of Headache Disorders-3rd edition (ICHD-3),

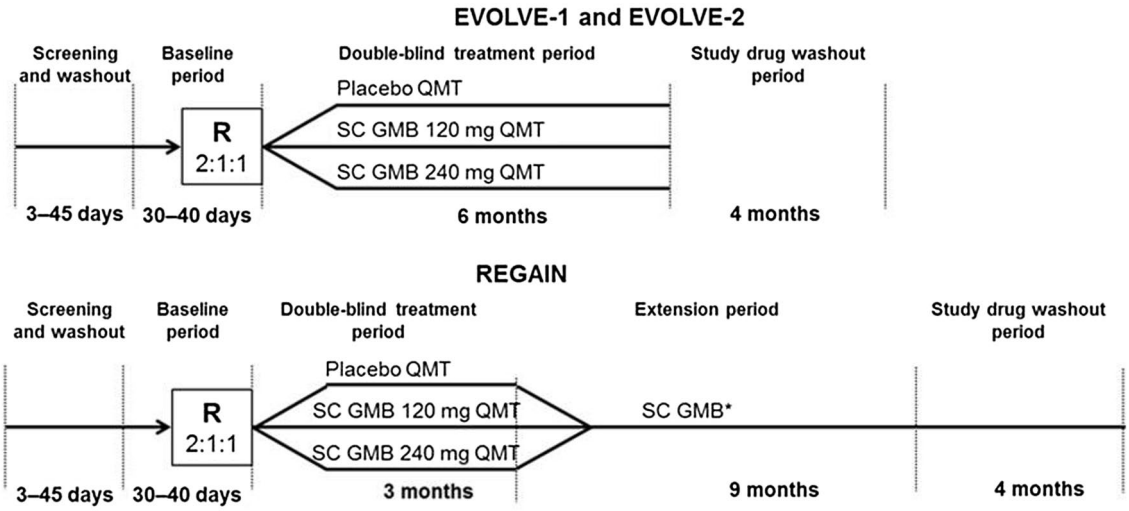

Fig. 1.—Study design. Galcanezumab (GMB); once monthly (QMT); randomization (R); subcutaneous (SC). *All patients had the option of receiving GMB with flexible dosing (120 or 240 mg) decided at the discretion of the investigator.

beta.[24] They had a history of migraine headaches for at least 1 year prior to visit 1 and a history of 4-14 MHD per month occurring during at least 2 migraine attacks per month on average over the past 3 months. Randomization was stratified by region/country and baseline migraine frequency (<8 MHD vs ≥8 MHD). These studies were conducted at 199 study sites in 12 countries.

The REGAIN study included patients diagnosed with chronic migraine as defined by the IHS ICHD-3 beta guidelines (1.3):[24] headache occurring on 15 or more days per month for more than 3 months, which has the features of migraine headache on at least 8 days per month. Prior to Visit 1, patients had to have a history of at least 1 headache-free day per month for the past 3 months. Randomization was stratified by country, acute headache medication overuse (yes/no) as determined during the prospective baseline period, and use of concurrent migraine prophylactic medication (yes/no). This study was conducted at 117 sites in 12 countries.

Outcome Measures.—In all 3 studies, the primary outcome was overall mean change from baseline in the number of monthly MHD. The term "overall" denotes the average treatment effect during the double-blind treatment period, which was estimated from the mixed model repeated measures (MMRM) analysis model. The number of MHD, number of MHD with acute medication use, and scores on the Role Function-Restrictive domain of the Migraine-Specific Quality of Life Questionnaire (MSQ)[25,26] were also examined on a monthly basis. Scores on this subscale of the MSQ quantify role impairment resulting from migraine on a 0-100 scale, with higher scores indicating better functioning. Since no analyses were conducted to determine the appropriate responder thresholds for other domains of the MSQ, analyses to support the tertiary objective for categorical change in other MSQ domains (Role Function-Preventive and Emotional Function) were not conducted. Response rates (50%, 75%, and 100% reduction from baseline in monthly MHD) were also examined by month and overall.

Statistical Analyses.—All analyses were conducted on the intent-to-treat population which included randomized patients who received at least 1 dose of study drug. As the efficacy outcomes analyzed changes from baseline, patients must have had a nonmissing baseline and post-baseline value to be included in the analysis at a particular month. For the analysis of MHD, MHD with acute medication use, and MSQ Role Function-Restrictive domain score, differences from placebo in least squares mean changes from baseline are presented for galcanezumab 120 and 240 mg along with associated 95% confidence intervals. Figures display least square mean changes from baseline and associated 95% confidence intervals for the placebo, galcanezumab 120, and 240 mg groups.

Analyses within subgroups of MHD, MHD with acute medication use, and MSQ Role Function-Restrictive domain score were conducted using a MMRM approach with terms for treatment, baseline value, pooled country, month, treatment-by-month, and baseline-by-month. For the pooled episodic studies, a term for study was also included. The model used to compare subgroups had additional terms for subgroup, subgroup-by-treatment, subgroup-by-month, and subgroup-by-treatment-by-month. For the chronic migraine study, additional covariates of baseline medication overuse as determined during the prospective baseline period, and concurrent prophylaxis use were added to both models just as was done for the analyses within the primary publication. Response rates were analyzed using a categorical, pseudolikelihood-based repeated measures model for binary outcomes similar to the models described above except without the pooled country term, so as to avoid convergence problems. Continuous demographic and baseline characteristics, all of which were ratio variables, were compared between treatment groups using a 1-way analysis of variance (ANOVA) with treatment in the model, and between subgroups using a 1-way ANOVA with anxiety/depression subgroup in the model. An additional term for study was added to the model for the pooled episodic studies. The number of failed migraine preventative treatments, an ordinal variable, was compared between treatments and subgroups using the Cochran-Mantel-Haenszel test (adjusted for study, for the pooled episodic studies).

For demographic and baseline variables analyzed using parametric tests (eg, ANOVA), the normality assumption was assessed using Q-Q plots. Sensitivity

analyses were performed on the primary outcome (change from baseline in MHD) to assess the potential impact of missing data assumptions and the robustness of MMRM results to deviations from normality. The results of these sensitivity analyses were consistent with the primary analysis.

Treatment effects were evaluated based upon a 2-sided, .05 significance level. The subgroup-by-treatment interaction was tested at a 2-sided, .1 significance level. All statistical analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics.—Anxiety and/or depression was reported in 26.0% of patients with episodic migraine (461/1773 patients) and 28.4% of patients with chronic migraine (316/1113 patients). The majority of these patients (77% [357/461] of patients with episodic migraine and 81% [257/316] of patients with chronic migraine) reported ongoing anxiety and/or depression at randomization ("current"); the remaining patients had anxiety and/or depression that resolved prior to randomization ("past only"; median symptom resolution occurred 4 years prior to study enrollment). In the episodic migraine studies, patients with anxiety and/or depression (compared with patients without anxiety and/or depression) had a significantly greater number of conditions comorbid with migraine ($P < .001$), significantly lower MSQ Role Function-Restrictive domain scores ($P = .038$), and significantly higher Migraine Disability Assessment (MIDAS)[27,28] total scores ($P < .001$). In addition, patients with episodic migraine with anxiety and/or depression were slightly older ($P = .044$) and had more MHD ($P = .046$) and MHD with acute medication use ($P = .013$) compared with patients without anxiety and/or depression (Table 1).

In the chronic migraine study, the patients with anxiety and/or depression had a greater number of migraine comorbidities ($P < .001$), lower MSQ Role Function-Restrictive domain scores ($P = .003$), higher MIDAS total score ($P = .003$), and a greater number of MHD ($P = .036$), compared with patients without anxiety and/or depression (Table 2).

There were no significant differences in the number of failed migraine preventative treatments (none, 1-3, and ≥4) between the subgroups with anxiety and/or depression vs those without in the episodic migraine studies or in the chronic migraine study.

Migraine Headache Days.—In the episodic migraine studies, both doses of galcanezumab demonstrated statistically significant improvements compared with placebo in the overall (months 1-6) and monthly change from baseline in the number of MHD in patients with anxiety and/or depression and patients without (overall mean change difference from placebo [95% CI]: −2.07 [−2.81, −1.33] for galcanezumab 120 mg [$P < .001$], −1.91 [−2.78, −1.04] for 240 mg [$P < .001$] in patients with anxiety and/or depression; −1.92 [−2.36, −1.47] for galcanezumab 120 mg [$P < .001$], −1.77 [−2.20, −1.33] for 240 mg [$P < .001$] in patients without anxiety and/or depression) (Table 3) (Fig. 2A,B). Overlapping 95% confidence intervals indicated that treatment effects were not statistically different between the subgroups. Subgroup differences in these mean change differences of −0.15 for galcanezumab 120 mg and −0.14 for 240 mg were not clinically significant. Furthermore, the comparison of both doses of galcanezumab was not statistically significant within the subgroups, and the subgroup-by-treatment interaction was not statistically significant ($P = .827$).

In the chronic migraine study, statistically significant improvements in the number of MHD were seen in the subgroup with anxiety and/or depression for galcanezumab 240 mg compared with placebo overall (mean change difference from placebo [95% CI]: −1.92 [−3.52, −0.33] [$P = .018$]) but not for galcanezumab 120 mg (−1.50 [−3.15, 0.15] [$P = .074$]), and for both galcanezumab doses compared with placebo at month 1 (Fig. 3A). Both doses of galcanezumab also demonstrated statistically significant improvements compared with placebo in the overall (months 1-3) and monthly change from baseline in the number of MHD in the subgroup without anxiety and/or depression (overall mean change difference from placebo [95% CI]: −2.29 [−3.26, −1.31] for galcanezumab 120 mg [$P < .001$], −1.85 [−2.83, −0.87] for 240 mg [$P < .001$]) (Fig. 3B). Overlapping 95% CIs between the subgroups as well as small subgroup differences in the mean change differences of

Table 1.—Baseline Demographics, Disease Characteristics, and Baseline Symptoms by Anxiety/Depression Subgroup (Episodic Migraine Studies)

	Patients With Anxiety and/or Depression				Patients Without Anxiety and/or Depression				
Variable	PBO Mean (SD) N = 233	GAL 120 mg Mean (SD) N = 127	GAL 240 mg Mean (SD) N = 101	Total Mean (SD) N = 461	PBO Mean (SD) N = 661	GAL 120 mg Mean (SD) N = 317	GAL 240 mg Mean (SD) N = 334	Total Mean (SD) N = 1312	*P* Value Between Subgroups
Age	43.20 (11.14)	42.21 (11.40)	**39.52 (12.00)****	42.12 (11.47)	41.37 (11.39)	40.40 (11.50)	40.83 (10.97)	41.00 (11.31)	**.044**
Number of comorbid conditions other than migraine (excluding anxiety/depression)	4.48 (3.70)	4.62 (3.85)	4.50 (3.98)	4.53 (3.79)	2.87 (3.06)	2.76 (3.24)	2.60 (2.68)	2.78 (3.01)	**<.001**
Years since migraine diagnosis	21.62 (12.76)	20.75 (12.73)	19.72 (12.49)	20.96 (12.69)	20.16 (12.45)	20.41 (12.20)	19.65 (11.86)	20.09 (12.24)	.169
MSQ Role Function-Restrictive	49.92 (15.94)†	51.43 (15.53)	49.76 (15.73)	50.30 (15.76)‡	52.89 (15.40)§	52.16 (15.45)¶	**50.45 (16.88)***,††	52.09 (15.82)‡‡	**.038**
MIDAS total score	41.10 (32.11)†	37.29 (32.46)	37.60 (26.37)	39.28 (31.03)‡	30.25 (27.71)§	29.67 (25.76)¶	33.37 (28.88)††	30.90 (27.57)‡‡	**<.001**
Baseline symptoms									
Number of migraine headache days	9.31 (3.04)	9.12 (3.06)	9.78 (2.84)	9.36 (3.01)	9.07 (2.96)	9.14 (2.91)	8.89 (2.91)	9.04 (2.93)	**.046**
Number of migraine headache days with acute medication use	7.85 (3.42)	7.46 (3.53)	8.06 (3.36)	7.79 (3.44)	7.38 (3.44)	7.44 (3.49)	7.21 (3.22)	7.35 (3.40)	**.013**
Number of failed migraine preventative treatments, n (%)									
	N = 294	N = 167	N = 157	N = 618	N = 294	N = 167	N = 157	N = 618	
None	28 (9.52)	19 (11.38)	11 (7.01)	58 (9.39)	50 (17.01)	22 (13.17)	35 (22.29)	107 (17.31)	.122
1-3	58 (19.73)	34 (20.36)	24 (15.29)	116 (18.77)	143 (48.64)	79 (47.31)	77 (49.04)	299 (48.38)	.285
≥4	5 (1.70)	2 (1.20)	1 (0.64)	8 (1.29)	10 (3.40)	11 (6.59)	9 (5.73)	30 (4.85)	.430

Patients with anxiety and/or depression had a greater ($P < .001$) number of comorbid conditions other than migraine (mean [SD] = 5.48 [3.96]), compared with patients without anxiety and/or depression (mean [SD] = 2.78 [3.01]); results remained statistically significant ($P < .001$) when anxiety and/or depression comorbidities were excluded.
Bold values indicate values that are statistically significant.
GAL = galcanezumab; MIDAS = Migraine Disability Assessment; MSQ = Migraine-Specific Quality of Life Questionnaire; N = number of intent-to-treat patients with nonmissing demographic measures; PBO = placebo.
*$P \leq .05$ vs PBO,
**$P \leq .01$ vs PBO.
†N = 231.
‡N = 459.
§N = 656.
¶N = 316.
††N = 329.
‡‡N = 1301.

Table 2.—Baseline Demographics, Disease Characteristics, and Baseline Symptoms by Anxiety/Depression Subgroup (Chronic Migraine Study)

Variable	Patients With Anxiety and/or Depression				Patients Without Anxiety and/or Depression				*P* Value Between Subgroups
	PBO Mean (SD) N = 159	GAL 120 mg Mean (SD) N = 75	GAL 240 mg Mean (SD) N = 82	Total Mean (SD) N = 316	PBO Mean (SD) N = 399	GAL 120 mg Mean (SD) N = 203	GAL 240 mg Mean (SD) N = 195	Total Mean (SD) N = 797	
Age	40.95 (12.50)	39.77 (13.43)	42.49 (12.29)	41.07 (12.67)	41.89 (11.91)	**39.62 (11.29)***	40.44 (12.43)	40.96 (11.91)	.891
Number of comorbid conditions other than migraine (excluding anxiety/depression)	4.87 (4.00)	5.24 (3.84)	4.76 (3.54)	4.93 (3.84)	2.84 (3.11)	2.39 (2.39)	2.50 (2.57)	2.64 (2.82)	**<.001**
Years since migraine diagnosis	21.26 (12.49)	20.74 (12.79)	20.42 (12.11)	20.92 (12.43)	22.22 (12.99)	20.23 (12.75)	19.91 (12.99)	21.15 (12.96)	.790
MSQ Role Function-Restrictive	34.49 (16.62)†	37.61 (15.66)‡	38.41 (18.41)§	36.25 (16.93)¶	39.93 (17.18)††	39.91 (17.86)‡‡	39.15 (16.88)§§	39.73 (17.26)¶¶	**.003**
MIDAS total score	76.67 (59.28)†	69.59 (49.25)‡	77.72 (78.18)§	75.26 (62.57)¶	65.45 (56.33)††	59.79 (49.42)‡‡	65.54 (56.91)§§	64.04 (54.79)¶¶	**.003**
Baseline symptoms									
Number of migraine headache days	20.29 (4.42)	19.35 (4.05)	19.49 (4.67)	19.86 (4.41)	19.26 (4.63)	19.37 (4.36)	19.03 (4.57)	19.23 (4.55)	**.036**
Number of migraine headache days with acute medication use	16.06 (6.69)	14.73 (6.40)	15.15 (6.42)	15.51 (6.56)	15.30 (6.51)	15.27 (6.20)	14.22 (6.18)	15.03 (6.36)	.261
Number of failed migraine preventative treatments, n (%)									
	N = 333	N = 155	N = 176	N = 664	N = 333	N = 155	N = 176	N = 664	
None	14 (4.20)	4 (2.58)	11 (6.25)	29 (4.37)	45 (13.51)	21 (13.55)	20 (11.36)	86 (12.95)	.336
1-3	69 (20.72)	31 (20.00)	39 (22.16)	139 (20.93)	162 (48.65)	82 (52.90)	76 (43.18)	320 (48.19)	.245
≥4	16 (4.80)	3 (1.94)	5 (2.84)	24 (3.61)	27 (8.11)	14 (9.03)	25 (14.20)	66 (9.94)	.613

Patients with anxiety and/or depression had a greater ($P < .001$) number of comorbid conditions other than migraine (mean [SD] = 5.99 [4.08]), compared with patients without anxiety and/or depression (mean [SD] = 2.65 [2.82]); results remained statistically significant ($P < .001$) when anxiety and/or depression comorbidities were excluded.

Bold values indicate values that are statistically significant.

GAL = galcanezumab; MIDAS = Migraine Disability Assessment; MSQ = Migraine-Specific Quality of life Questionnaire; N = number of intent-to-treat patients with nonmissing demographic measures; PBO = placebo.

*$P \leq .05$ vs PBO.

†N = 156.

‡N = 74.

§N = 81.

¶N = 311.

††N = 390.

‡‡N = 198.

§§N = 191.

¶¶N = 779.

Table 3.—Overall Least Squares Mean Change Differences from Placebo by Anxiety/Depression Subgroup (Episodic Migraine Studies)

	Patients With Anxiety and/or Depression		Patients Without Anxiety and/or Depression	
Variable	GAL 120 mg Mean Chg Diff (95% CI) N = 127	GAL 240 mg Mean Chg Diff (95% CI) N = 99	GAL 120 mg Mean Chg Diff (95% CI) N = 309	GAL 240 mg Mean Chg Diff (95% CI) N = 329
Migraine headache days†	−2.07*** [−2.81, −1.33]	−1.91*** [−2.78, −1.04]	−1.92*** [−2.36, −1.47]	−1.77*** [−2.20, −1.33]
Migraine headache days with acute medication use†	−1.88*** [−2.53, −1.22]	−1.86*** [−2.57, −1.14]	−1.79*** [−2.18, −1.40]	−1.62*** [−2.00, −1.24]
MSQ Role Function-Restrictive‡	10.37*** [7.45, 13.29]	8.44*** [5.07, 11.82]§	7.49*** [5.64, 9.34]¶	7.06*** [5.26, 8.87]††

CI = confidence Interval; GAL = galcanezumab; Mean Chg Diff = Least Squares Mean Change Difference from placebo; MSQ = Migraine-Specific Quality of Life Questionnaire; PBO = placebo.
*$P < .05$ vs PBO,
**$P < .01$ vs PBO,
***$P < .001$ vs PBO.
†N = 227 PBO patients with anxiety and/or depression; N = 648 PBO patients without anxiety and/or depression.
‡N = 186 PBO patients with anxiety and/or depression; N = 638 PBO patients without anxiety and/or depression.
§N = 98.
¶N = 306.
††N = 323.

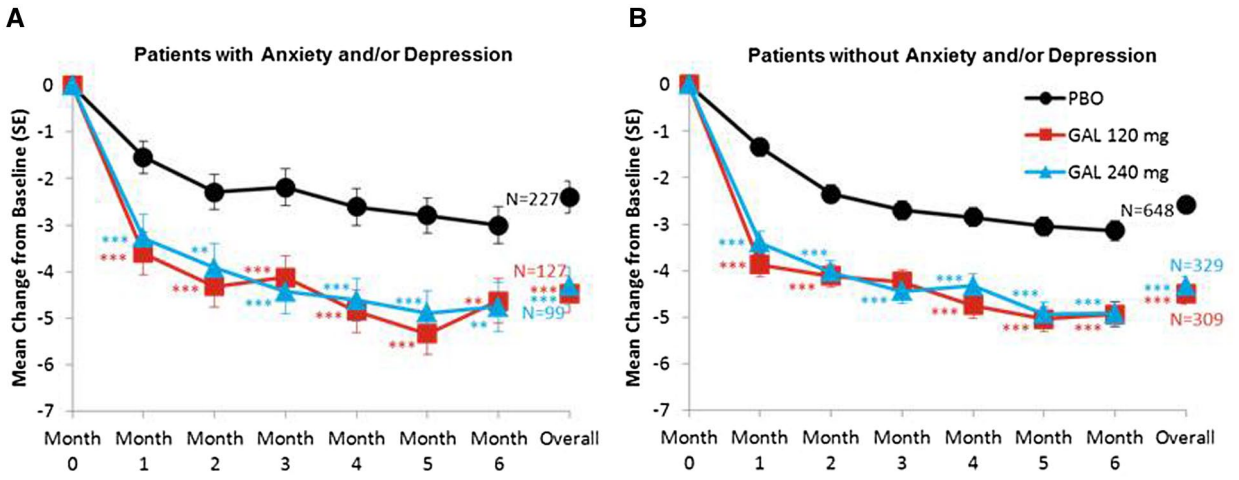

Fig. 2.—Overall and monthly change from baseline in number of migraine headache days (episodic migraine studies). Subgroup-by-treatment *P* value = .827; Subgroup-by-treatment interaction: .60 (GAL 120 mg vs PBO), .627 (GAL 240 mg vs PBO), .997 (GAL 240 mg vs GAL 120 mg), ****P* ≤ .001, ***P* ≤ .01 vs PBO. Galcanezumab (GAL); number of patients (N); placebo (PBO); standard error (SE).

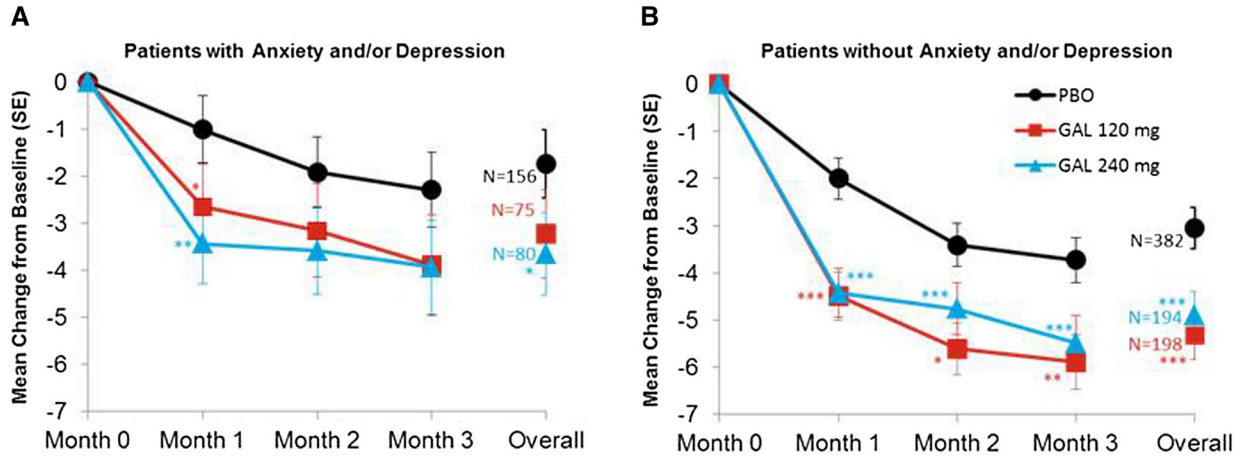

Fig. 3.—Overall and monthly change from baseline in number of migraine headache days (chronic migraine study). Subgroup-by-treatment *P* value = .697; Subgroup-by-treatment interaction: 0.447 (GAL 120 mg vs PBO), 0.918 (GAL 240 mg vs PBO), 0.451 (GAL 240 mg vs GAL 120 mg), ****P* ≤ .001, ***P* ≤ .01, **P* ≤ .05 vs PBO. Galcanezumab (GAL); number of patients (N); placebo (PBO); standard error (SE).

0.79 and −0.07 for galcanezumab 120 and 240 mg, respectively, indicated lack of a clinically meaningful or statistical difference. Treatment comparisons of both doses of galcanezumab were not statistically significant within the subgroups overall or monthly. The subgroup-by-treatment interaction was not statistically significant ($P = .697$).

MHD With Acute Medication Use.—In the episodic migraine studies, both doses of galcanezumab demonstrated statistically significant improvements compared with placebo in the number of MHD with acute medication use overall in the subgroup with anxiety and/or depression and the subgroup without (subgroup with anxiety and/or depression, mean change difference from placebo [95% CI]: −1.88 [−2.53, −1.22] for galcanezumab 120 mg [$P < .001$], −1.86 [−2.57, −1.14] for 240 mg [$P < .001$]; subgroup without anxiety and/or depression: −1.79 [−2.18, −1.40] for galcanezumab 120 mg [$P < .001$], −1.62 [−2.00, −1.24] for 240 mg [$P < .001$]) (Table 3). The monthly change from baseline in the number of MHD with acute medication use in both subgroups

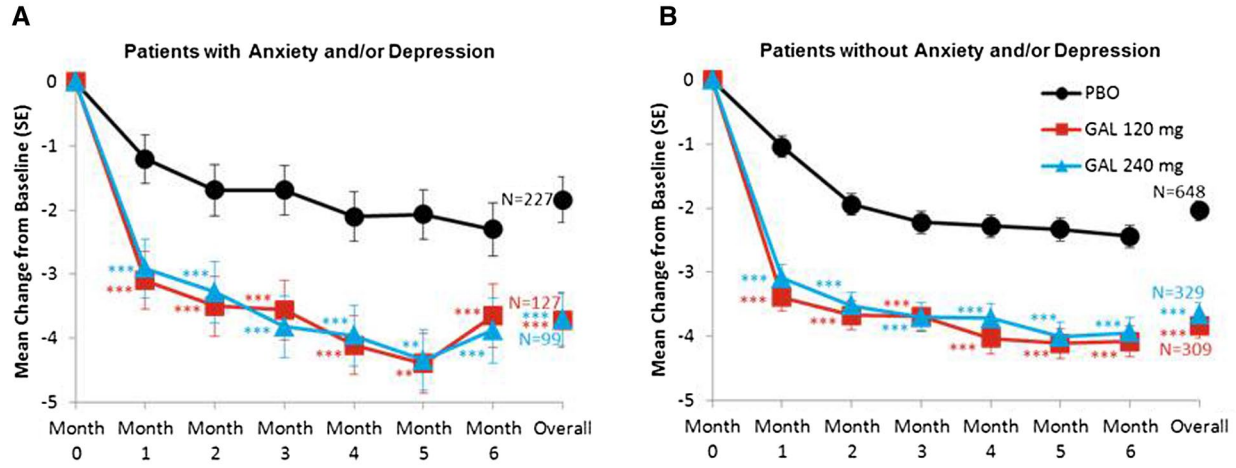

Fig. 4.—Overall and monthly change from baseline in number of migraine headache days with acute medication use (episodic migraine studies). Subgroup-by-treatment *P* value = .751; Subgroup-by-treatment interaction: 0.700 (GAL 120 mg vs PBO), 0.458 (GAL 240 mg vs PBO), 0.736 (GAL 240 mg vs GAL 120 mg), ***$P \leq .001$, **$P \leq .01$ vs PBO. Galcanezumab (GAL); number of patients (N); placebo (PBO); standard error (SE).

paralleled the overall results (Fig. 4A,B). Overlapping 95% confidence intervals and small subgroup differences in the mean change differences from placebo of −0.09 and −0.24 for galcanezumab 120 and 240 mg, respectively, suggested that there were no clinically meaningful or statistically significant differences between subgroups. Treatment comparisons of both doses of galcanezumab were not statistically significant within the subgroups, and the subgroup-by-treatment interaction was not statistically significant ($P = .751$).

Similarly, among patients with chronic migraine with anxiety and/or depression and without, both doses of galcanezumab outperformed placebo overall in the number of MHD with acute medication use (subgroup with anxiety and/or depression, mean change difference from placebo [95% CI]: −2.19 [−3.68, −0.69] for galcanezumab 120 mg [$P = .004$], −1.94 [−3.39, −0.50] for 240 mg [$P = .009$]; subgroup without anxiety and/or depression, mean change difference from placebo [95% CI]: −2.59 [−3.47, −1.70] for galcanezumab 120 mg [$P < .001$], −2.06 [−2.95, −1.16] for 240 mg [$P < .001$]) (Table 4) (Fig. 5A,B). Overlapping 95% confidence intervals indicated that overall treatment effects were not statistically different between the subgroups. Subgroup differences in these mean change differences of 0.4 for galcanezumab 120 mg and 0.12 for 240 mg were not clinically significant. For patients with anxiety and/or depression, galcanezumab 120 mg was superior to placebo at all months and 240 mg was superior at month 1 (Fig. 5A). For patients without anxiety and/or depression, MHD with acute medication use were significantly reduced with both doses of galcanezumab at all months (Fig. 5B). Within the subgroups, galcanezumab 120 mg did not differ significantly from 240 mg overall. In addition, the subgroup-by-treatment interaction was not significant ($P = .937$).

Functional Impairment (MSQ Role Function-Restrictive Domain).—For patients with episodic migraine with anxiety and/or depression and patients without, there was a significantly greater mean improvement in the overall (subgroup with anxiety and/or depression, mean change difference from placebo [95% CI]: 10.37 [7.45, 13.29] for galcanezumab 120 mg [$P < .001$], 8.44 [5.07, 11.82] for 240 mg [$P < .001$]; subgroup without anxiety and/or depression: 7.49 [5.64, 9.34] for galcanezumab 120 mg [$P < .001$], 7.06 [5.26, 8.87] for 240 mg [$P < .001$]) (Table 3), and monthly change from baseline in the MSQ Role Function-Restrictive domain score for both galcanezumab doses compared with placebo (Fig. 6A,B). Overlapping 95% confidence intervals and small subgroup differences in the mean change differences from placebo of 2.88 and 1.38 for galcanezumab 120 and 240 mg, respectively, indicated a lack of clinically or statistically significant differences between subgroups. Treatment

Table 4.—Overall LS Mean Change Differences from Placebo by Anxiety/Depression Subgroup (Chronic Migraine Study)

	Patients With Anxiety and/or Depression		Patients Without Anxiety and/or Depression	
Variable	GAL 120 mg Mean Chg Diff (95% CI) N = 75	GAL 240 mg Mean Chg Diff (95% CI) N = 80	GAL 120 mg Mean Chg Diff (95% CI) N = 198	GAL 240 mg Mean Chg Diff (95% CI) N = 194
Migraine headache days†	−1.50 [−3.15, 0.15]	−1.92* [−3.52, −0.33]	−2.29*** [−3.26, −1.31]	−1.85*** [−2.83, −0.87]
Migraine headache days with acute medication use†	−2.19** [−3.68, −0.69]	−1.94** [−3.39, −0.50]	−2.59*** [−3.47, −1.70]	−2.06*** [−2.95, −1.16]
MSQ Role Function-Restrictive‡	2.59 [−2.69, 7.87]§	5.04 [−0.07, 10.15]¶	5.94*** [2.85, 9.02]††	7.84*** [4.73, 10.95]‡‡

CI = confidence interval; GAL = galcanezumab; Mean Chg Diff = Least Squares Mean Change Difference from placebo; MSQ = Migraine-Specific Quality of Life Questionnaire; PBO = placebo.
*$P < .05$ vs PBO,
**$P < .01$ vs PBO,
***$P < .001$ vs PBO.
†N = 156 PBO patients with anxiety and/or depression; N = 382 PBO patients without anxiety and/or depression.
‡N = 152 PBO patients with anxiety and/or depression; N = 372 PBO patients without anxiety and/or depression.
§N = 74.
¶N = 79.
††N = 195.
‡‡N = 188.

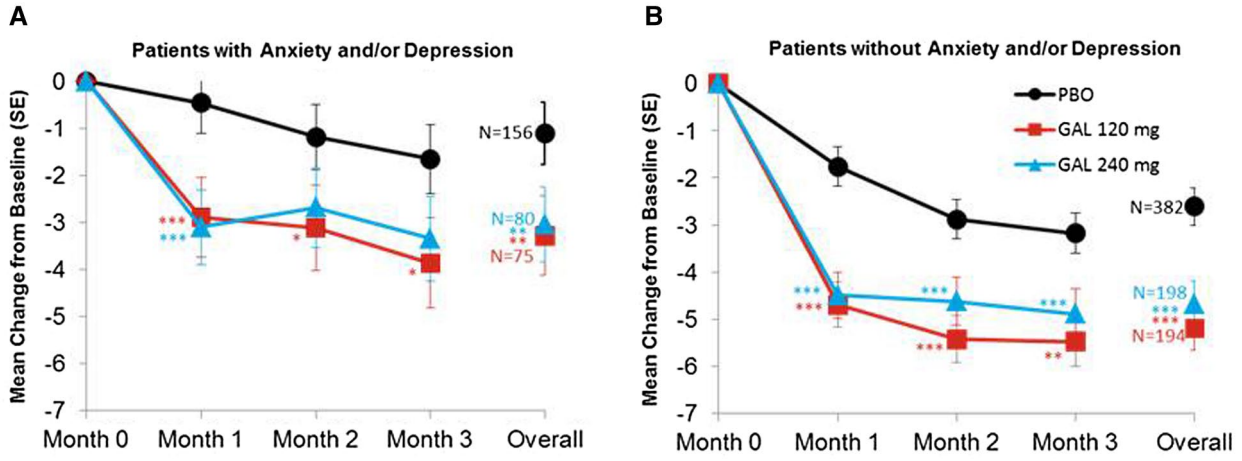

Fig. 5.—Overall and monthly change from baseline in number of migraine headache days with acute medication use (chronic migraine study). Subgroup-by-treatment *P* value = .937; Subgroup-by-treatment interaction: 0.719 (GAL 120 mg vs PBO), 0.890 (GAL 240 mg vs PBO), 0.845 (GAL 240 mg vs GAL 120 mg), ***$P \leq .001$, **$P \leq .01$, *$P \leq .05$ vs PBO. Galcanezumab (GAL); number of patients (N); placebo (PBO); standard error (SE).

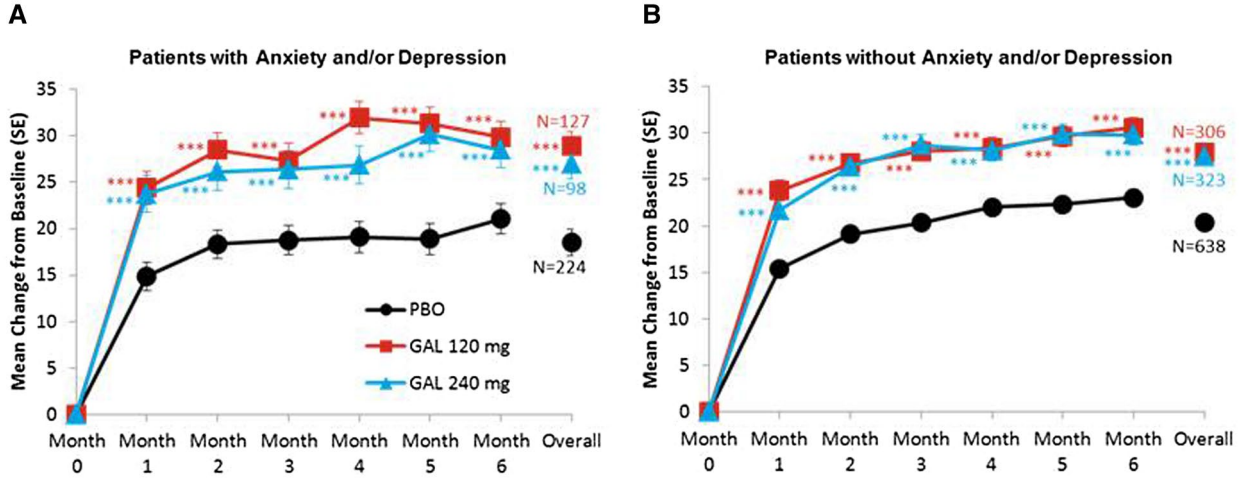

Fig. 6.—Overall and monthly change from baseline in MSQ role function-restrictive domain score (episodic migraine studies). Subgroup-by-treatment *P* value = .187; Subgroup-by-treatment interaction (Average of months 4 to 6): 0.018 (GAL 120 mg vs PBO), 0.308 (GAL 240 mg vs PBO), 0.280, (GAL 240 mg vs GAL 120 mg), ***$P \leq .001$ vs PBO. Galcanezumab (GAL); Migraine-Specific Quality of life Questionnaire (MSQ); number of patients (N); placebo (PBO); standard error (SE).

comparisons of both doses of galcanezumab were not statistically significant within the subgroups. There was a statistically significant subgroup-by-treatment interaction (P = .018) for the average of months 4-6 for galcanezumab 120 mg compared with placebo, but this interaction was deemed spurious and not clinically meaningful, as neither the subgroup-by-treatment interaction for galcanezumab 240 mg vs placebo, nor the overall (months 1-6) interaction was statistically significant (P = .187). Furthermore, the direction of the treatment effect (for the average of months 4-6) for the galcanezumab 120-mg-minus-placebo difference was consistent across the subgroups.

In the chronic migraine study, in patients with anxiety and/or depression, there was a significantly greater improvement in the mean change from baseline on the MSQ Role Function-Restrictive domain score in the galcanezumab 240-mg group compared

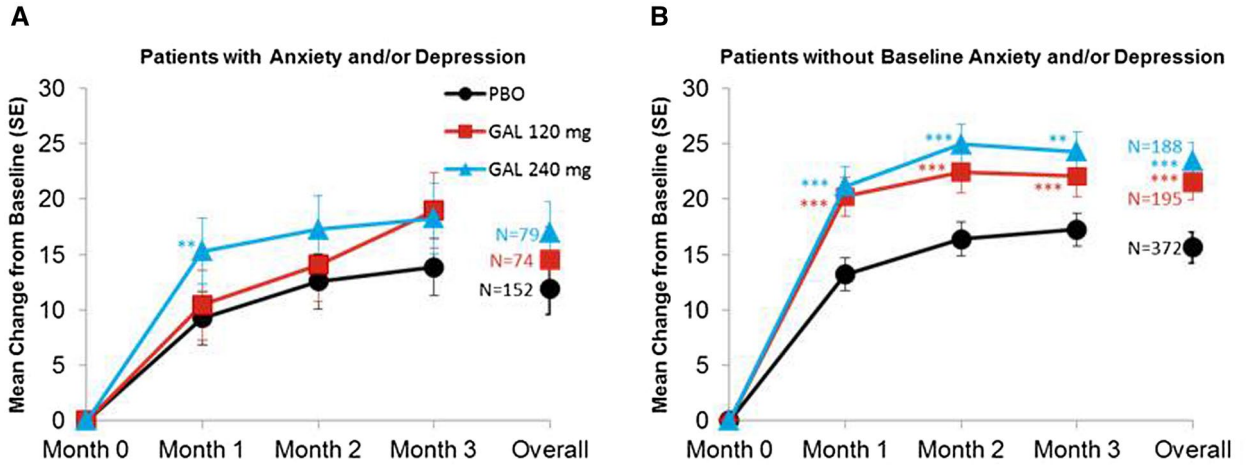

Fig. 7.—Overall and monthly change from baseline in MSQ role function-restrictive domain score (chronic migraine study). Subgroup-by-treatment *P* value = .515; Subgroup-by-treatment interaction (month 3): 0.849 (GAL 120 mg vs PBO), 0.478 (GAL 240 mg vs PBO), 0.437 (GAL 240 mg vs GAL 120 mg), ***$P \leq .001$, **$P \leq .01$ vs PBO. Galcanezumab (GAL); Migraine-Specific Quality of life Questionnaire (MSQ); number of patients (N); placebo (PBO); standard error (SE).

with placebo only at month 1; however, there was no significant improvement relative to placebo in the overall change from baseline at either dose (mean change difference from placebo [95% CI]: 2.59 [−2.69, 7.87] for galcanezumab 120 mg [$P = .335$]; 5.04 [−0.07, 10.15] for 240 mg [$P = .053$]) (Fig. 7A). For patients without anxiety and/or depression, there was a significantly greater improvement in the overall (mean change difference from placebo [95% CI]: 5.94 [2.85, 9.02] for galcanezumab 120 mg [$P < .001$]; 7.84 [4.73, 10.95] for 240 mg [$P < .001$]) (Table 4), and monthly changes from baseline on the MSQ Role Function-Restrictive domain score in both the galcanezumab 120-mg and 240-mg treatment groups compared with placebo (Fig. 7B). Overall treatment effects were not statistically different between the subgroups as indicated by overlapping 95% confidence intervals, and small subgroup differences in mean change differences of −3.35 and −2.8 for galcanezumab 120 and 240 mg, respectively, were not clinically significant. Within the subgroups, galcanezumab 120 mg did not differ significantly from 240 mg overall. The subgroup-by-treatment interaction was not significant ($P = .515$).

50%, 75%, and 100% Reduction in Monthly MHD.— Among patients with episodic migraine and anxiety and/or depression, 59% of patients in the galcanezumab 120-mg (N = 127) and 240-mg groups (N = 99), compared with 36% (N = 227) of patients in the placebo group, had ≥50% reduction from baseline ("50% response") in MHD overall ($P \leq .001$) (Fig. 8A). Similar results were seen in the group without anxiety and/or depression (61% and 58% for galcanezumab 120 mg [N = 309] and 240 mg [N = 329], respectively, vs 38% in placebo [N = 648] overall; $P \leq .001$) (Fig. 8B). The 50% response rates at each month were significantly greater with both galcanezumab doses compared with placebo in both anxiety/depression subgroups (Fig. 8A,B). Within the subgroups, galcanezumab 120 mg did not differ significantly from 240 mg overall. The subgroup-by-treatment interaction was not significant ($P = .822$).

Among patients with chronic migraine and anxiety and/or depression, 21% (N = 75) and 27% (N = 80) of patients receiving galcanezumab 120 mg ($P = .040$) and 240 mg ($P = .001$), respectively, vs 13% (N = 156) of patients receiving placebo, had ≥50% reduction from baseline in MHD overall (Fig. 9A). Similar results were seen in patients without anxiety and/or depression (30% [N = 198] and 28% [N = 194] of patients receiving galcanezumab 120 mg [$P < .001$] and 240 mg [$P < .001$], respectively, vs 17% [N = 382] in placebo overall) (Fig. 9B). Monthly 50% response rates were significantly greater with both galcanezumab doses in patients without anxiety and/or depression; in the subgroup with anxiety and/or depression, 50%

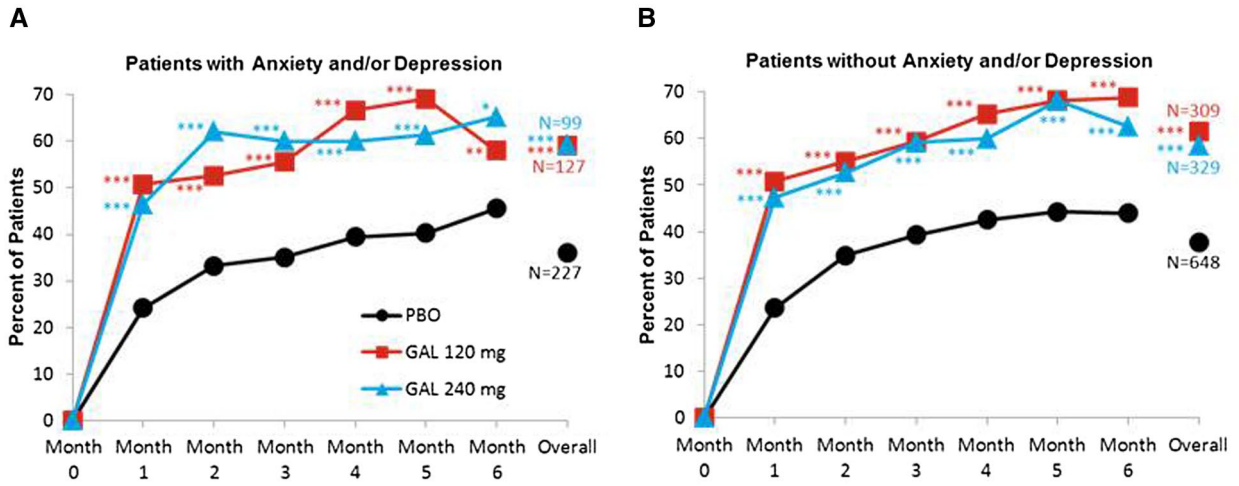

Fig. 8.—Overall and monthly percentage of patients with ≥50% reduction in monthly MHD (episodic migraine studies).† Subgroup-by-treatment *P* value = .822; Subgroup-by-treatment interaction: 0.566 (GAL 120 mg vs PBO), 0.585 (GAL 240 mg vs PBO), 0.920, (GAL 240 mg vs GAL 120 mg), ***$P \leq .001$, **$P \leq .01$, *$P \leq .05$ vs PBO. †Using Model Estimated Rate (SE). Galcanezumab (GAL); migraine headache days (MHD); number of patients (N); placebo (PBO); standard error (SE).

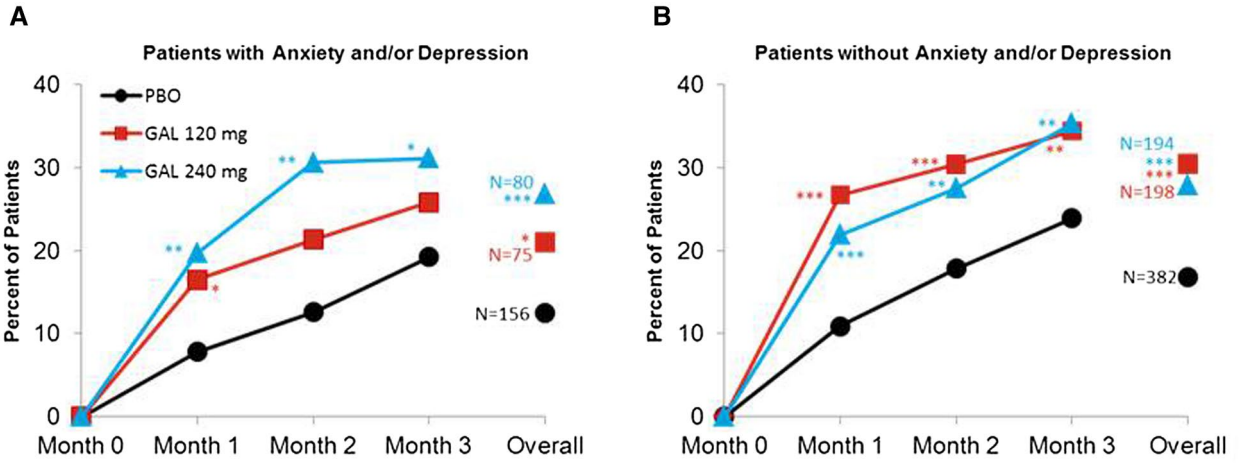

Fig. 9.—Overall and monthly percentage of patients with ≥50% reduction in monthly MHD (chronic migraine study).† Subgroup-by-treatment *P* value = .428; Subgroup-by-treatment interaction: 0.210 (GAL 120 mg vs PBO), 0.350 (GAL 240 mg vs PBO), 0.690 (GAL 240 mg vs GAL 120 mg), ***$P \leq .001$, **$P \leq .01$, *$P \leq .05$ vs placebo. †Using Model Estimated Rate (SE). Galcanezumab (GAL); migraine headache days (MHD); number of patients (N); placebo (PBO); standard error (SE).

response rates were significantly greater than placebo in the galcanezumab 240-mg group at all visits and at month 1 in the galcanezumab 120-mg group. The subgroup-by-treatment interaction was not significant ($P = .428$).

Monthly 75% response rates also favored those receiving either dose of galcanezumab compared with placebo, in both patients with episodic migraine and chronic migraine, regardless of comorbid anxiety and/or depression. Approximately 35% of patients with episodic migraine and anxiety and/or depression who received either dose of galcanezumab (N = 127 for galcanezumab 120 mg and N = 99 for galcanezumab 240 mg) had ≥75% reduction from baseline in MHD overall vs 17% for placebo (N = 227) ($P < .001$). Similar results were seen in the group without anxiety and/or depression (approximately 36% for galcanezumab 120 mg [N = 309] and 37% for galcanezumab

240 mg [N = 329], respectively, vs 19% in placebo [N = 648] overall; $P < .001$ for both doses vs placebo). Among those with chronic migraine and anxiety and/or depression, a significantly greater proportion of patients receiving 240-mg galcanezumab compared with placebo achieved ≥75% overall MHD reduction from baseline (approximately 8% [N = 80] vs 4% [N = 156], respectively, $P = .025$). A greater proportion of patients receiving either galcanezumab dose achieved ≥75% overall MHD reduction from baseline compared with placebo, among patients with chronic migraine without anxiety and/or depression (approximately 8% [N = 198] and 9% [N = 194] for galcanezumab 120 mg [$P = .028$] and 240 mg [$P = .009$], respectively, vs 5% [N = 382] in placebo overall).

In the episodic migraine studies, in the subgroup with anxiety and/or depression, 13% of patients in the galcanezumab 120-mg (N = 127) and 240-mg (N = 99) groups, vs 6% in the placebo group (N = 227), had 100% reduction from baseline ("100% response") in MHD overall ($P < .001$). Similar results were seen in the subgroup without anxiety and/or depression (14% and 15% for galcanezumab 120 mg [N = 309] and 240 mg [N = 329], respectively, vs 6% in placebo [N = 648] overall [$P < .001$]). In the chronic migraine study, in the subgroup with anxiety and/or depression, the analysis model did not converge for the analysis of 100% response. In the subgroup without anxiety and/or depression, there was no significant difference from placebo in the percentage of patients who had 100% reduction from baseline in MHD overall (0.8% and 1.6% for galcanezumab 120 mg [N = 198] and 240 mg [N = 194], respectively, vs 0.8% [N = 382] in placebo).

DISCUSSION

This post hoc analysis evaluated the efficacy of galcanezumab among patients with either episodic or chronic migraine as a function of anxiety and/or depression. In patients with episodic migraine, both galcanezumab doses yielded significant improvements compared with placebo across clinical (reductions in MHD, MHD with acute medication use, MHD response rates) and functional outcomes pertaining to quality of life, regardless of anxiety and/or depression suggesting that the treatment effect was not meaningfully impacted by the presence of anxiety and/or depression. The majority of patients with episodic migraine who received galcanezumab reported at least a 50% reduction in migraine frequency, compared with slightly more than one-third of those receiving placebo, irrespective of anxiety and/or depression.

The positive treatment effects and lack of significant or meaningful subgroup-by-treatment interactions suggest that galcanezumab is efficacious in reducing migraine headache and improving quality of life among patients with episodic migraine, regardless of whether comorbid anxiety and/or depression is present. Studies have shown that treatment satisfaction perceived by patients with either anxiety alone or anxiety with depression is lower than in patients without these comorbid conditions,[13] and higher anxiety is associated with a lower probability of treatment response.[14] Although a recent study suggested that depression is associated with inadequate response to preventive migraine pharmacotherapy, specifically Onabotulinumtoxin A for chronic migraine,[15] our data do not indicate that anxiety and/or depression confer risk for poor response to galcanezumab, at least among patients with episodic migraine. Instead, they add to a small but growing body of studies suggesting that patients with migraine and anxiety and/or depression respond well to preventive pharmacotherapy or behavioral interventions for migraine.[29-31]

The efficacy of galcanezumab for adults with chronic migraine and anxiety and/or depression was not as consistent as that observed among patients with episodic migraine. Both doses of galcanezumab outperformed placebo on all outcome measures among patients with chronic migraine without anxiety and/or depression. Among patients with chronic migraine and anxiety and/or depression, improvements in most clinical outcomes (ie, MHD, MHD with acute medication use, 50% MHD response rates) over placebo were evident, though only the 240-mg dose outperformed placebo on the primary outcome of MHD. However, among patients with chronic migraine with anxiety and/or depression, reductions in headache were not reflected in differential improvements in role functioning beyond placebo.

A high placebo response, apparent in these and other trials of preventive agents targeting CGRP,[32] does not appear responsible for this variability, as

superiority over placebo on most other outcome variables emerged despite high placebo response and as patients with chronic migraine without anxiety and/or depression demonstrated greater functional improvement vs placebo at both doses of galcanezumab. The decoupling of clinical improvement and functional outcomes as measured by the MSQ has been observed previously among individuals with chronic migraine receiving topiramate[33] and was thus not entirely unexpected. Perhaps differential functional improvement would be evident with a greater observed reduction in MHD, a longer duration of treatment, or use of an outcome measure that more broadly quantifies functional impairment (eg, incorporating assessment of emotional functioning or changes in psychiatric symptoms over time). As, to our knowledge, this is the first study of an agent targeting CGRP to compare headache outcomes as a function of psychiatric symptoms, further investigation is clearly warranted to better clarify the effects among individuals with chronic migraine and anxiety and/or depression. Such patients may also benefit from combining galcanezumab with evidence-based behavioral interventions (eg, stress management, relaxation, or biofeedback) that focus on teaching coping skills with applicability to psychiatric symptoms.[34,35]

Strengths of this study include the large sample sizes, utilization of ICHD-3 beta diagnostic criteria, and rigorous randomized-controlled trials multisite design. The most notable limitation of this study is that presence of anxiety and/or depression was determined via baseline medical interview and review of records rather than assessment of established diagnostic criteria, as the studies were not originally designed to address questions of psychiatric comorbidity. Furthermore, since the indication for concomitant medication use was not recorded, it was not possible to determine which patients received medications for anxiety and/or depression. Although a more rigorous psychiatric evaluation would have been achieved via administration of a structured diagnostic interview or validated psychiatric questionnaires, the observed rates of anxiety and/or depression (roughly one-quarter of the sample) approximate those obtained within the American Migraine Prevalence and Prevention study.[10]

Another limitation is that this was a post hoc analysis of 3 trials, so the studies were not originally designed to compare the comorbidity subgroups. Therefore, failing to find statistically significant subgroup-by-treatment interactions is not conclusive evidence of absence of a differential subgroup effect in light of reduced statistical power. Although the studies were not powered to compare treatment groups as a function of anxiety and/or depression, the results suggest that the sample size for episodic migraine was adequate to address these questions. However, the sample size of the chronic migraine subgroup with anxiety and/or depression was the smallest, which may have resulted in reduced power to detect treatment effects. The fact that the criteria of the clinical trials excluded persons failing more than 2 classes of Level A/B migraine preventive medications may limit the generalizability to persons who have been refractory to 3 or more preventive medications. Finally, these studies did not assess changes in psychiatric symptoms over time as a function of treatment, and thus, the effect of galcanezumab on psychiatric symptoms is unknown. Future studies should endeavor to assess psychiatric symptoms over time to determine whether galcanezumab favorably impacts comorbid psychiatric symptoms in addition to headache variables and whether addition of a behavioral intervention might yield more substantial improvements among patients with chronic migraine and anxiety and/or depression.

CONCLUSION

The prevention of migraine remains an important unmet clinical need, particularly among the many patients with comorbid psychiatric symptoms. The results of these 3 phase 3 clinical trials suggest that, regardless of medical history of comorbid anxiety and/or depression, galcanezumab is efficacious for reducing migraine frequency and improving quality of life among those with episodic migraine. Among those with chronic migraine and comorbid anxiety and/or depression, only the 240-mg dose significantly reduced migraine frequency, but neither dose differentially improved quality of life.

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