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Research Submission

100% Response Rate to Galcanezumab in Patients With Episodic Migraine: A Post Hoc Analysis of the Results From Phase 3, Randomized, Double-Blind, Placebo-Controlled EVOLVE-1 and EVOLVE-2 Studies

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Objective.—To characterize adult patients with episodic migraine who achieved 100% response to galcanezumab treatment.

Background.—Galcanezumab is a humanized monoclonal antibody that selectively binds to the calcitonin gene-related peptide (CGRP) and has demonstrated efficacy in reducing migraine headache days (MHD) in patients with episodic and chronic migraine.

Methods.—A post hoc analysis of the proportion of patients with 100% response (100% reduction from baseline in monthly MHD) was calculated for each month from pooled data of 2 double-blind, 6-month galcanezumab studies in patients with episodic migraine (4 to 14 MHD and ≥ 2 migraine attacks per month at baseline). The patients were randomized (1:1:2) to monthly subcutaneous galcanezumab, 120 mg (after 240 mg initial loading dose) or 240 mg, or placebo. A generalized linear mixed model with effects for baseline MHD, treatment, month, and treatment-by-month interaction was used to estimate the mean monthly response rate.

Results.—The analysis included 1739 patients treated with galcanezumab, 120 mg ($n = 436$) or 240 mg ($n = 428$), or placebo ($n = 875$). The mean monthly 100% response rate on an average month in the 6-month double-blind phase was greater for galcanezumab 120 mg (13.5%) and 240 mg (14.3%) groups vs placebo (5.9%) with odds ratios of 2.5 (95% confidence interval [CI] 1.9, 3.2) and 2.6 (95% CI 2.0, 3.4), respectively ($P < .001$). The rate of 100% monthly response increased at each month over the 6-month double-blind phase with higher rates for galcanezumab dose groups (9 to 21%) than placebo (2 to 10%) ($P < .02$). Evaluation of 100% response by the number of months showed a greater proportion of galcanezumab-treated patients in either dose group, compared to placebo, were able to achieve a 100% response ($P < .001$ up to 3 months); however, though greater than placebo, few galcanezumab patients had ≥ 4 months of 100% response ($P < .02$). The proportions of patients with 100% response were greatest in the last 3 months of the treatment. Considering the average number days between nonconsecutive MHD across the 6-month period (not just during the times of 100% response), the duration of migraine headache-free periods in the galcanezumab groups was 29 days for those with at least 1 month of 100% response and 55 days for those with at least 3 months of 100% response. This gap was approximately 6 to 11 times greater than the mean gap of 5 days observed at baseline.

Conclusions.—More than a third of the patients with episodic migraine treated with galcanezumab 120 mg or 240 mg achieved 100% response for at least 1 month. More patients had 100% monthly response in the last 3 months of the 6-month double-blind period. For those with 100% response for at least 1 month, the average time between nonconsecutive MHD for the entire treatment period was nearly 1 month and approached 2 months for patients with 3 or more months of 100% response.

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Key words: migraine, prevention, galcanezumab, CGRP, 100% response

Abbreviations: AMHFP average length (in days) of migraine headache-free periods; CGRP calcitonin gene-related peptide; MHD migraine headache days

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INTRODUCTION

Migraine is a chronic neurological disease found to be one of the top 10 causes of disease-related disability globally.^{1,2} Although the worldwide prevalence of migraine and its associated medical and societal costs are well recognized, inadequate treatment is not uncommon.³⁻⁷ Options for preventive therapy are limited by reasons that include lack of efficacy or intolerance to current therapies. New lines of care are necessary to address the unmet needs of patients with migraine who remain untreated.⁸⁻¹²

Patients seeking acute migraine treatment have reported that complete pain relief and no recurrence are important factors when considering treatment options. Efficacy was identified by patients with migraine as the most important aspect of preventive migraine therapy.¹³ Guidelines from the International Headache Society Clinical Trials Subcommittee recommend that the achievement of $\geq 50\%$ reduction from baseline in the number of monthly migraine headache days (MHD) or migraine attack frequency is an important clinical measure. While the reduction of 50% or greater may seem an arbitrary choice, it is a very clinically relevant and standard measure in the evaluation of the effectiveness of a preventive migraine therapy.¹⁴ Approximately 70% of the patients with migraine are non-adherent to oral preventive medications.¹⁵ One of the main reasons cited

for discontinuation is the lack of efficacy.¹³ Only 29% of the patients report being very satisfied with their current level of treatment.¹⁶ Preventive medications with higher response rates of $\geq 75\%$ reduction or 100% reduction in MHD may improve medication adherence. Further, the opportunity for 100% reduction of MHD may be more in line with the patient's desires than what has previously been available or possible. To date, the data regarding 100% response rate with migraine therapies are lacking. Galcanezumab is under development for the prevention of migraine and is a humanized monoclonal antibody that binds to the calcitonin gene-related peptide (CGRP) and prevents its biological activity without blocking the CGRP receptor. Two randomized, double-blind, placebo-controlled, Phase 3 studies examined the efficacy of galcanezumab 120 mg/month and 240 mg/month in patients with episodic migraine (studies EVOLVE-1 and EVOLVE-2).^{17,18} The patients treated with galcanezumab experienced on an average approximately 4 fewer MHD/month (vs 2 with placebo).^{17,18} In both the trials, the mean monthly proportions of galcanezumab-treated patients who achieved a $\geq 50\%$, $\geq 75\%$, or 100% reduction of MHD on an average month from baseline in the 6-month double-blind phase were similar between the dose groups and superior to placebo. Specifically, the proportions of patients with a $\geq 50\%$ reduction of MHD on an average month was

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Consultant: Curelator.

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approximately 60% of either galcanezumab 120 mg or 240 mg dose groups compared with 39% of the placebo group ($P < .001$). A $\geq 75\%$ reduction of MHD on an average month was achieved by approximately 34 to 39% of the patients in the galcanezumab groups and 19% in the placebo group ($P < .001$). Though lower, approximately 12 to 16% of the patients treated with galcanezumab who achieved 100% reduction of MHD on an average month were significantly greater than the 6% of the placebo group ($P < .001$).

The results from these 2 trials demonstrated that a good percentage of patients treated with galcanezumab were able to achieve a meaningful reduction in MHD beyond the clinically relevant cut-off of at least a 50% reduction of MHD. The fact that the proportions of the galcanezumab-treated patients who achieved 100% reduction of MHD, a key secondary endpoint in the studies, was statistically significantly greater than placebo-treated patients warranted further evaluation to better characterize the nature of the response. The availability of data from a large population of patients with episodic migraine treated for 6 months allows for better characterization of efficacy with galcanezumab, the robustness of the response, and the duration of the response over a 6-month period. More specifically, the pooled, larger database provides an opportunity to begin to understand what percentages of patients respond strongly or have a minimal or worsening response with treatment. Galcanezumab is a new class of migraine preventive medication and this further characterization should allow clinicians to set appropriate expectations regarding efficacy. Moreover, this characterization should provide clinicians with a better understanding of what this potentially means for patients given that efficacy and complete response have been indicated as important attributes of a preventive migraine therapy. The current analyses further characterized patients from the EVOLVE-1 and EVOLVE-2 trials who achieved 100% response with galcanezumab treatment.^{17,18}

METHODS

Study Design.—Detailed descriptions of the study design of the 2 episodic migraine 6-month double-blind trials (ClinTrials.gov NCT02614183 and NCT02614196) have been reported separately.^{17,18} Briefly, in both trials, adult patients with episodic migraine were to have a history of migraine of at least 1 year prior to

study screening and onset of migraine prior to age 50. Episodic migraine was defined as having between 4 and 14 MHD and at least 2 migraine attacks per month.⁵ The patients were randomized 1:1:2 and received subcutaneous injections of galcanezumab 120 mg/month (after a 240 mg initial loading dose) or 240 mg/month or placebo.^{17,18} The patients recorded headache symptoms, duration, and severity with an electronic diary. The study protocol was reviewed and approved by the appropriate institutional review board for each of the study sites. The study was conducted according to Good Clinical Practice and the Declaration of Helsinki guidelines. The patients provided written informed consent before undergoing the study procedures.

Statistical Method.—Data for the 2 trials were pooled and were the basis of the post hoc analyses. The analysis set consisted of 1739 adult patients with episodic migraine and a baseline and a Month 1 MHD value. Complete response for a given month was defined as the proportion of patients with 100% reduction from baseline in their MHD (ie, patients had no MHD during the given month). Similarly, a 75% response was defined as the proportion of patients with $\geq 75\%$ reduction from baseline in MHD in a given month. In calculating the number of MHD for each month period, if the entry period was not equal to 30 days, the number of MHD was normalized by multiplying the number of MHD by $(30/x)$ where “x” is the total number of non-missing diary days in the period. Additionally, if the daily diary entry rate for any period was less than or equal to 50%, all endpoints derived from the diary data for that period were set to missing.

Response rates for each month and response rates across all months were calculated using a generalized linear mixed model with effects for study, baseline MHD, treatment, month, and treatment-by-month interaction.¹⁹ For each month of dosing, the number of MHD was estimated and the determination that the patient met response at that month was based on either the ≥ 75 or 100% response definition. Hence, the patient had a binary response (either “yes” or “no”) at each month with non-missing number of MHD. The rates of nonresponse (no change or worsening response) for each month were also calculated similar to positive response rates. Nonresponse was defined as having a monthly MHD value that was greater than or equal to their baseline monthly MHD (ie, if their change from baseline is ≥ 0).

The models for the repeated binary outcomes included the fixed, categorical effects of study treatment, month, and treatment-by-month interaction, as well as the continuous, fixed covariate of baseline value. The patient was considered a random effect in this model and a logit link was used along with an unstructured covariance. The rates of patients achieving response for at least 1 month were summarized by treatment with pairwise comparisons between the treatments conducted via Fisher's exact tests. Similar comparisons were made for patients achieving response for at least 2, at least 3, at least 4, at least 5, and for all 6 months. For each patient, the average length (in days) of migraine headache-free periods (AMHFP) between nonconsecutive MHD was calculated as the total number of days without a migraine headache divided by the number of migraine-free "gaps" between MHD. This calculation was done both for the baseline period as well as for the entire 6-month double-blind period. The mean AMHFP was calculated for all patients as well as for patients having certain number of migraine headache-free

months (for example, patients with at least 1 month of 100% response) to help characterize the experience of those responding to galcanezumab treatment. All analyses were conducted using SAS 9.4. All assessments of statistical significance are based on 2-sided tests conducted at the 0.05 significance level.

RESULTS

Patient Disposition.—Data from 1739 adult patients with episodic migraine treated with 120 mg galcanezumab (n = 436), 240 mg galcanezumab (n = 428), or placebo (n = 875) from the 2 studies were evaluated in the analysis. The full description of patient disposition is provided in previous publications.^{17,18} Table 1 presents the baseline demographics and the disease characteristics for the 2 galcanezumab dose groups and the placebo group. Overall, more than 80% of the patients were female and more than 74% were white; the mean age was approximately 40 years, and the mean migraine disease duration was 20 years. At baseline, the mean number of migraine

Table 1.—Patient Demographics and Disease Characteristics of Galcanezumab-Treated Patients From Episodic Migraine Trials

Variables	Placebo (N = 894)	Galcanezumab ^a (N = 879)
Age, years, mean (SD)	41.9 (11.4)	40.7 (11.4)
Female, n (%)	755 (84.5)	744 (84.6)
Race, white, n (%)	681 (76.2)	652 (74.2)
Body mass index, kg/m ² mean (SD)	27.6 (5.5)	27.6 (5.5)
Migraine disease duration, years, mean (SD)	20.5 (12.5)	20.1 (12.2)
Migraine headache days (MHD)/month, mean (SD)	9.1 (3.0)	9.1 (2.9)
MHD/month with acute medication use, mean (SD)	7.5 (3.4)	7.4 (3.4)
Headache days/month, mean (SD)	10.6 (3.4)	10.7 (3.7)
Migraine headache hours/month, mean (SD)	54.5 (37.7)	55.0 (39.7)
Headache hours/month, mean (SD)	59.3 (40.1)	61.7 (51.9)
Migraine with aura, n (%)	471 (52.7)	467 (53.1)
Prior preventive treatment in past 5 years, n (%)	555 (62.1)	559 (63.6)
Failed ≥2 preventives in past 5 years, n (%)	85 (9.5)	88 (10.0)
MIDAS total, mean (SD)	33.1 (29.3)	33.1 (28.2)
MSQ RF-R, mean (SD)	52.1 (15.6)	51.1 (16.1)
MSQ RF-P, mean (SD)	67.9 (18.5)	66.7 (19.7)
MSQ EF, mean (SD)	62.1 (24.6)	59.2 (24.0)
PGI-S, mean (SD)	4.3 (1.2)	4.3 (1.2)

Abbreviations: EF = Emotional Function; MIDAS = Migraine Disability Assessment; MSQ = Migraine-Specific Quality of Life Questionnaire version 2.1; PGI-S = Patient Global Impression of Severity; RF-P = Role Function-Preventive; RF-R = Role Function-Restrictive; SD = standard deviation.

Note: One patient did not have MHD values at Month 1 and was excluded from further analyses.

^aPooled data from two 6-month trials in patients with episodic migraine and combined 120 mg/month and 240 mg/month galcanezumab-treated patient groups.

Table 2.—Baseline Migraine Headache Days and Headache Days by Number of Months With 100% Response

	At Least 1 Month (n = 171)	At Least 2 Months (n = 74)	At Least 3 Months (n = 48)	At Least 4 Months (n = 22)	At Least 5 Months (n = 6)	All 6 Months (n = 2)
Placebo (N = 872)						
Migraine headache days, mean (SD)	8.2 (3.0)	8.2 (3.0)	7.6 (2.7)	7.3 (2.8)	5.4 (1.7)	4.5 (0.7)
Headache days, mean (SD)	9.9 (3.4)	9.8 (3.4)	9.2 (3.2)	8.6 (3.2)	5.6 (1.6)	4.5 (0.7)
Galcanezumab 120 mg (N = 435)	At least 1 month (n = 169)	At least 2 months (n = 95)	At least 3 months (n = 46)	At least 4 months (n = 21)	At least 5 months (n = 12)	All 6 months (n = 3)
Migraine headache days, mean (SD)	8.2 (3.0)	8.1 (3.0)	7.8 (3.0)	7.5 (2.9)	6.6 (1.4)	7.7 (1.5)
Headache days, mean (SD)	9.7 (3.4)	9.5 (3.4)	9.1 (3.3)	8.6 (3.1)	7.9 (2.3)	7.7 (1.5)
Galcanezumab 240 mg (N = 427)	At least 1 month (n = 178)	At least 2 months (n = 91)	At least 3 months (n = 59)	At least 4 months (n = 28)	At least 5 months (n = 12)	All 6 months (n = 6)
Migraine headache days, mean (SD)	8.4 (2.9)	7.9 (2.9)	7.9 (2.9)	7.9 (2.9)	7.6 (2.3)	7.1 (2.8)
Headache days, mean (SD)	10.5 (4.0)	9.4 (3.7)	9.7 (4.0)	9.4 (3.9)	9.6 (4.7)	9.8 (6.3)

Abbreviation: SD = standard deviation.

headache days was 9.1 and number of headache days was 10.7. The completion rates for the double-blind portion of the 2 studies ranged from 83 to 87% across both galcanezumab doses.^{17,18} The baseline MHD days and headache days for the subgroup of patients with 100% response by the number of months with 100% response are shown in Table 2.

Patients With 100% Response.—The mean (standard error [SE]) monthly 100% response rate on an average month in the 6-month double-blind phase was greater for galcanezumab 120 mg (13.5 ± 1.1%) and 240 mg (14.3 ± 1.1%) groups vs placebo (5.9 ± 0.5%). The 100% response rate odds ratios were 2.5 (95% confidence interval [CI] 1.9, 3.2) for galcanezumab 120 mg and 2.6 (95% CI 2.0, 3.4) for galcanezumab 240 mg (*P* < .001 for both).

Starting at Month 1, 100% response was achieved by 9% (±1%) of the galcanezumab-treated patients compared to 2% (±0.5%) of the placebo patients (*P* < .001) and at Month 6 the rates were up to 17% (±2%) and 21% (±2%) of the patients on galcanezumab 120 mg or 240 mg treatment, respectively, vs 10% (±1%) of the placebo patients (*P* < .001) (Fig. 1). When considering the other end of the spectrum, patients with no change or worsening response, it is important to note that at every month within the 6-month period, the percentage of these patients was statistically significantly larger for placebo compared to either of the galcanezumab group. The rates ranged from 8.6% (±1%) to 17.3% (±2%) with galcanezumab treatment compared to 21.9% (±2%) to 32.9% (±2%)

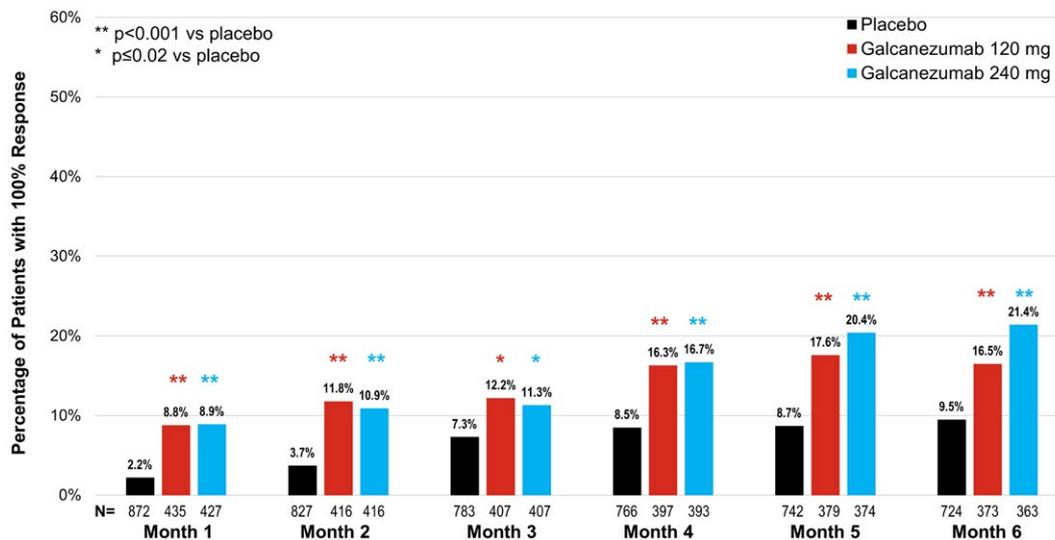


Fig. 1.—Patients with 100% response by month. N = sample size of the treatment group.

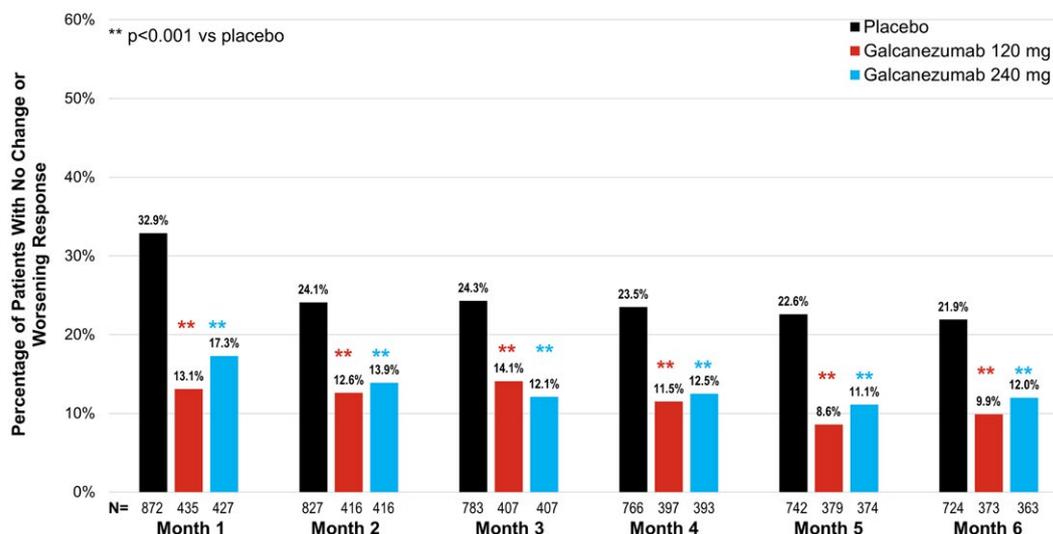


Fig. 2.—Patients with no change or worsening response by month. N = sample size of the treatment group.

of the patients with placebo treatment (Fig. 2). Taking into account the proportions of patients who achieved $\geq 75\%$ response on an average month in the 6-month period, the proportions of 36% ($\pm 2\%$) in either of the galcanezumab dose group were significantly greater than the 19% ($\pm 1\%$) of the patients in the placebo group ($P < .001$). Breaking down the proportions by month, in both the galcanezumab dose groups, 25% ($\pm 2\%$) of the patients achieved $\geq 75\%$ response at Month 1 (as shown in Fig. 3) compared to 9% ($\pm 1\%$) of the patients in the placebo group ($P < .001$). By Month 6, the proportions of patients who achieved $\geq 75\%$ response were 44% ($\pm 3\%$) in either of the galcanezumab group (Fig. 3) and greater than the 25% ($\pm 2\%$) of the placebo group ($P < .001$). The observed proportions of patients with episodic migraine with 100 or $\geq 75\%$ response, or no change or worsening response are shown by month in the online Supplemental Table 1.

Evaluation of 100% response by the number of months with 100% response is shown in Figure 4. At baseline, the mean number of MHD was 8 days for patients with at least 1 month of 100% response. The proportions of patients who achieved 100% response for at least 1 month were greater for the galcanezumab 120 mg (38.8%) and 240 mg (41.6%) dose groups compared with the placebo group (19.5%; $P < .0001$). Though very few patients had more than 4 months with 100% response, the baseline mean number of MHD was 7 days and the proportions of patients who attained this measure were generally significantly greater with galcanezumab

treatment compared with placebo ($P < .02$). The timing of achievement of 100% response occurred for more patients with at least 1, 2, or 3 months of 100% response in the last 3 months (Month 4 to Month 6) of the double-blind phase than in the first 3 months (Fig. 5).

Considering the average number days between nonconsecutive MHD across the 6-month period (not just during the times of 100% response), the mean average length (in days \pm standard deviation) of migraine headache-free periods in the galcanezumab groups was around 29 days (± 34) for those with at least 1 month of 100% response and around 55 days (± 48) for those with at least 3 months of 100% response (Fig. 6). For those with at least 1 month of 100% response, this was 6 times greater than the mean baseline gap of 5 days (± 2) and close to 11 times greater than the baseline for those who had 3 months of 100% response. The change from baseline in the average length (in days) of migraine headache-free periods in patients with 100% response with at least 1, 2, or 3 months of 100% response was similar between the galcanezumab dose groups. Breaking down the percentages on a weekly level, the percentage of galcanezumab 120 mg and 240 mg patients vs placebo patients achieving average migraine headache-free day gaps for ≥ 1 week was 68 and 67 vs 47%, respectively; for ≥ 2 weeks was 35 and 33 vs 15%, respectively; for ≥ 3 weeks was 19 and 17 vs 8%, respectively; and for ≥ 4 weeks was 11 and 12 vs 5%, respectively. After ≥ 5 weeks to ≥ 8 weeks, the percentages of patients

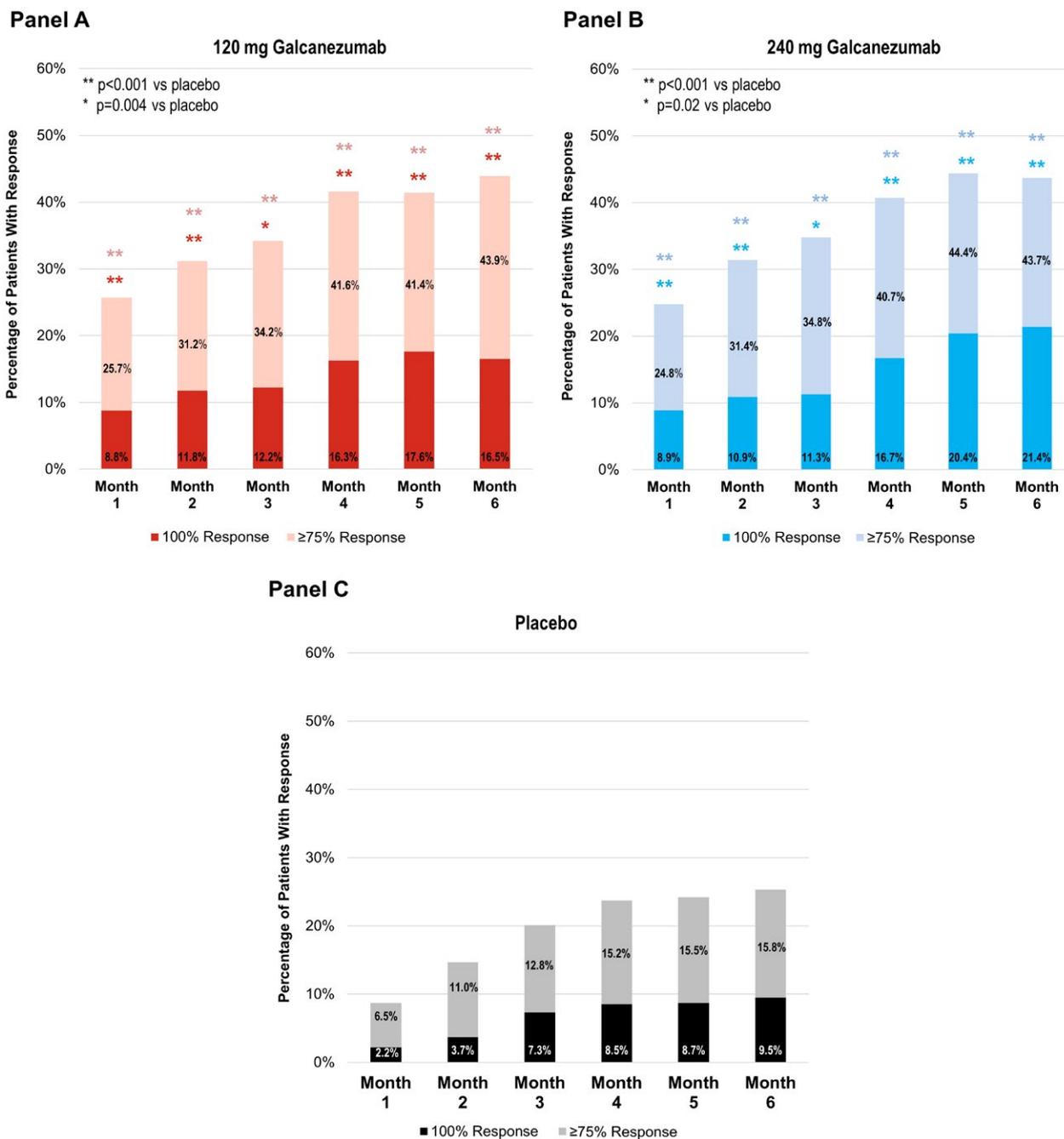


Fig. 3.—Galcanezumab-treated patients with 100 and ≥75% response by month. Illustrated here by stacked bars are patients with ≥75% response and the portion of those patients with 100% response to reflect, by month, the overall percentage of patients that met either response measure. The percentages within each bar represent only the percentage of patients with either 100 or ≥75% response and should not be added. Panel A and Panel B represent patients treated with galcanezumab 120 mg/month or 240 mg/month, respectively. Asterisks denote statistical significance compared with placebo. Panel C represents patients treated with placebo.

achieving average migraine headache-free day gaps in the galcanezumab groups ranged from 4 to 8% vs the 2 to 3% of the placebo group.

Overall, it is important to clarify that these results are specific to freedom of migraine headache days and does not infer headache-free.

DISCUSSION

Treatment with galcanezumab 120 mg or 240 mg demonstrated a greater efficacy in achieving 100% response in reduction of MHD compared with placebo in the 6-month double-blind phase. The proportions of galcanezumab patients who achieved 100%

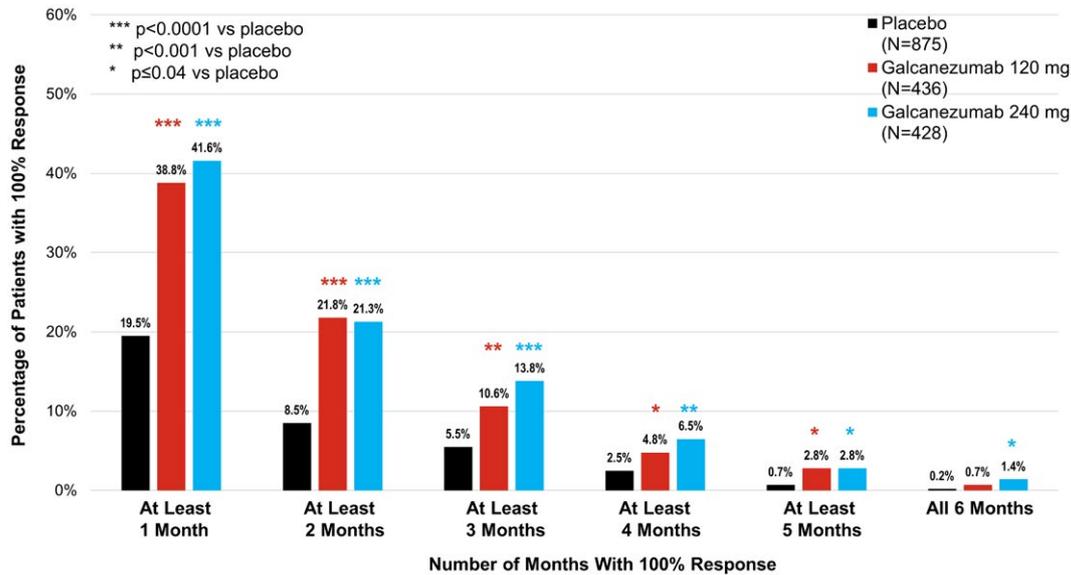


Fig. 4.—Patients with 100% response by number of months with 100% response. N = sample size of the treatment group.

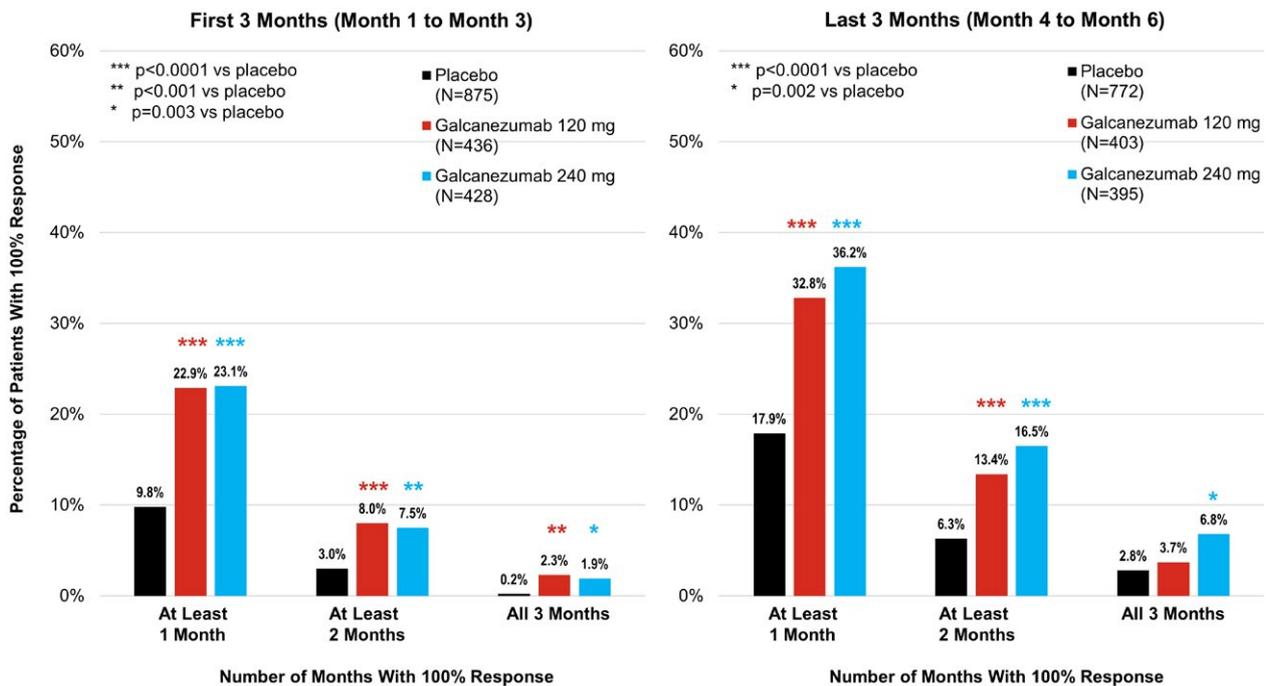


Fig. 5.—Patients with 100% response in first and last 3 months by number of months with 100% response. N = sample size of the treatment group.

response on an average month was over double that of the placebo.

At the patient level, approximately 40% of the galcanezumab-treated patients had at least 1 month of 100% response in reduction of MHD. Notably, a good number of galcanezumab-treated patients were free of migraine headache for 2 out of the 3 months on the last 3 months of the treatment. The

proportions of patients who achieved multiple months of 100% responses decreased as the number of months with response increased. It is encouraging that approximately 13% of the patients had at least 3 months of 100% response across the 6-month phase. More patients achieved at least 1 month of 100% response in the last 3 months of treatment than in the first 3 months. This suggests that the

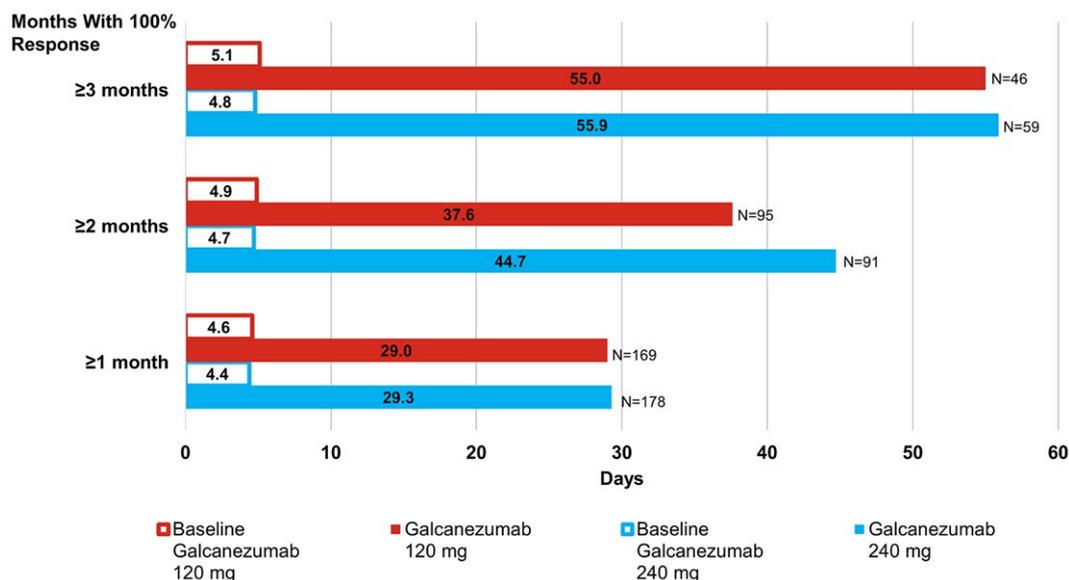


Fig. 6.—Average length (in days) of migraine headache-free periods in patients with 100% response (across Months 1-6). Illustrated are the mean baseline average lengths (in days) of migraine headache-free periods between migraine headache days (open bars) and the mean number of migraine headache-free days between migraine headache days across Months 1-6 for patients treated with galcanezumab 120 mg (red solid bar) or galcanezumab 240 mg (blue solid bar). N = sample size of the treatment group.

longer the patient remains on medication, the more likely the patient is to have at least 1 month of 100% response. However, it is important to point out that this analysis specifically evaluated freedom from *migraine* headache days and these results do not imply headache-free.

The findings from this study are relevant but must be considered in light of study limitations. The 100% response was only captured for the month between injections. If a patient had 30 or more consecutive migraine headache-free days and this occurred across a dosing cycle, this may not have been counted as having had a month of 100% reduction of MHD. Additionally, for any patient who discontinued the study early, only the daily diary data up to the date of discontinuation were used. For the analyses of the number of months with 100% response, this effectively treated any missing month as having had no response (although patients may have had 30 days with a MHD after discontinuation). Both of these limitations actually represent a potential underestimation of the percentage of patients showing 100% monthly response. Finally, as with any controlled clinical trial, the generalizability of the findings among the larger population is limited.

Complete response and no recurrence of MHD are important attributes in preventive migraine therapies. It is well understood that patients who suffer from migraine are burdened by factoring in considerations to accommodate impending migraine attacks. The disruptions to work, family, and social activities caused by migraine translate into an overall poorer quality of life.^{13,20} In this study, patients who had at least 1 month of 100% response had more freedom from their migraine headaches across the 6-month dosing period. On average, patients treated with galcanezumab with at least a month of 100% response gained 25 consecutive migraine headache-free days between the few migraine headaches they did experience. Further, patients with at least 3 out of the 6 months of 100% response averaged nearly a 2-month gap between nonconsecutive MHD. The clinical bar of a 50% reduction on an average month in baseline MHD is important and provides an estimate for what a majority of patients can expect. The higher bar of a $\geq 75\%$ reduction on an average month in baseline MHD was attained by 36% of the galcanezumab-treated patients compared with 19% of the placebo-treated patients. However, the fact that a smaller percentage of patients treated with galcanezumab can achieve a 100% reduction of

MHD coupled with longer times between nonconsecutive MHD lessens the extent to which they experience the burden of their disease.

CONCLUSIONS

Around 40% of the patients with episodic migraine treated with galcanezumab achieved 100% response for at least 1 month. The percentages of patients with 100% response increased by month in the 6-month double-blind period; very few patients (0.7 to 1.4%) achieved 100% response for all 6 months of the study. More patients had 100% monthly response in the last 3 months. For those with at least 1 month of 100% response, the average time between nonconsecutive MHD for the entire treatment period was nearly 1 month and approached 2 months for patients with 3 or more months of 100% response.

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