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Research Submission

Rapid Onset of Effect of Galcanezumab for the Prevention of Episodic Migraine: Analysis of the EVOLVE Studies

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Objective.—To evaluate onset of effect of galcanezumab in patients with episodic migraine.

Background.—Galcanezumab is a monoclonal antibody that binds to calcitonin gene-related peptide and is indicated for preventive treatment of migraine.

Design/Methods.—Data on the primary outcome measure were analyzed from 2 previously published double-blind, Phase 3 studies (EVOLVE-1 [N = 858] and EVOLVE-2 [N = 915]) wherein adult patients with episodic migraine were randomized to receive monthly subcutaneous injections of galcanezumab 120 mg (with 240-mg loading dose) or 240 mg or placebo for up to 6 months. Monthly onset of effect was defined as the earliest month at which galcanezumab achieved and subsequently maintained statistical superiority to placebo on the mean change from baseline in the number of monthly migraine headache days (MHDs). If onset occurred in Month 1, weekly onset was evaluated and defined as the earliest week at which galcanezumab statistically separated from placebo and maintained statistical separation for remaining weeks in that month. Day of onset of effect was also analyzed, as were monthly and weekly onset, for occurrence of ≥50% reduction from baseline in number of MHDs.

Results.—For both studies, change from baseline in monthly MHDs showed a statistically significant separation of galcanezumab from placebo at Month 1 and each subsequent month (each $P < .001$). Analysis of the first month for both studies indicated onset of effect in the first week, with galcanezumab-treated patients having significantly higher odds of having fewer MHDs in the first week (odds ratio [95% confidence interval] for EVOLVE-1, 2.71 [2.00, 3.66], and for EVOLVE-2, 2.88 [2.16, 3.86]; both $P < .001$) and each subsequent week compared with placebo-treated patients ($P \leq .004$). Daily analysis showed onset of effect at Day 1 (first day after injection day). Galcanezumab also demonstrated superiority to placebo on occurrence of ≥50% reduction in MHDs starting at Week 1 (percentage of patients with 50% response in galcanezumab group vs placebo group for EVOLVE-1, 54.3% vs 32.4% [$P < .001$], and for EVOLVE-2, 59.4% vs 38.0% [$P < .001$]).

Conclusion.—Rapid onset of preventive effect on the first day after injection of galcanezumab was confirmed in both studies of episodic migraine.

Key words: galcanezumab, calcitonin gene-related peptide, episodic migraine, onset of effect

Abbreviations: CGRP calcitonin gene-related peptide, MHDs migraine headache days

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INTRODUCTION

Migraine is a distinct neurological disease associated with alterations in brain biology and function[1] and is characterized by moderate to severe headache that is often accompanied by nausea, vomiting, phonophobia, and photophobia.[2] Migraine is considered to be episodic when the individual experiences up to 14 headache days per month.[2,3] Episodic migraine is often initially managed through the use of acute medication to treat the symptoms of migraine as they emerge. Even with the use of acute migraine treatment, recurrent migraine attacks are functionally disabling and can impair quality of life. Treatment guidelines suggest that patients who have 4 or more migraine headache days (MHDs) per month or who have significant impairment due to migraine should be offered preventive therapy.[3]

Although approximately 38% of people with migraine qualify to be offered preventive therapy, only an estimated 13% of people with migraine receive preventive drug therapy.[4] Among those who do receive preventive therapy, adherence is poor, with most discontinuing the therapy within 6-12 months.[5,6] One retrospective analysis of migraine preventive prescriptions in a United States claims database found a sharp decline in adherence occurring after the first 30 days.[7] There appears to be a limited window of time during which a patient will make a decision on whether to remain on their current migraine preventive medication. Having a medication with a rapid onset of effect as well as a tolerable safety profile is therefore important to support adherence and long-term patient outcomes.

Prior to the availability of the calcitonin gene-related peptide (CGRP) monoclonal antibodies, drugs used for preventive treatment of episodic migraine were typically administered orally and often involved slow dose titration.[8] Oral preventive medications for migraine have been associated with suboptimal efficacy or intolerable side effects that frequently lead to poor adherence, multiple medication switches, or discontinuation;[5,6,9] as a result, many patients rely solely on acute medications for treatment of their migraine attacks. The reliance on acute treatments exclusively, especially in those with frequent attacks, may lead to overuse of acute medications and the development of medication overuse headache and chronic migraine.[10] A recent study evaluated cycling of preventive migraine medications from a claims database and found that for patients with episodic and chronic migraine, more than

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Conflict of Interest: Doctors Detke, Millen, Samaan, and Aurora are employees and minor stockholders of Eli Lilly and Company. Dr. Zhang is a former Eli Lilly employee, current minor stockholder of Eli Lilly, and current employee of Sanofi, Bridgewater, New Jersey. Dr. Ailani has received honoraria from the following: Amgen (consulting/speaking), Alder (consulting/speaking), Allergan (consulting/speaking), Avanir (speaking), Eli Lilly and Company (consulting/speaking), Teva (consulting/speaking), Gammacore (consulting/speaking), Impel (consulting), Satsuma (consulting), Biohaven (consulting), Revance (consulting), Neurodiem (consulting), Neurology Live (speaking/writing), Medscape (consulting/writing), Avant (consulting), Alpha Sites (consulting), Miller Medical (continuing medical education [CME] content/speaking), Forefront (CME content/speaking), Peer View (speaking), and Current Pain and Headache Reports (editorial fees) and has received grants for clinical trials from the following: Allergan, Biohaven, American Registry for Migraine Research (ARMR), and Eli Lilly and Company.

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75% of patients switched or discontinued their initial preventive treatment within 12 months, leading to increased healthcare resource utilization and cost.[11]

Galcanezumab is a humanized monoclonal antibody that potently and selectively binds to the CGRP ligand[12,13] and is approved for the preventive treatment of migraine in adults.[14,15] The efficacy, safety, and tolerability of galcanezumab for migraine prevention have been established in 2 Phase 2 studies[16-18] and 3 Phase 3 studies.[19-21] In EVOLVE-1 (NCT02614183) and EVOLVE-2 (NCT02614196), patients with episodic migraine treated with monthly galcanezumab of 120-mg or 240-mg doses had a greater decrease from baseline than did placebo-treated patients in the average number of MHDs per month over the 6-month double-blind treatment period (EVOLVE-1: 4.7 days [120 mg] and 4.6 days [240 mg] vs 2.8 days [placebo; each $P < .001$] and EVOLVE-2: 4.3 days [120 mg] and 4.2 days [240 mg] vs 2.3 days [placebo; each $P < .001$]), with no statistically significant differences between the 2 galcanezumab doses in either study.[19,20] There were also no clinically meaningful differences between the 2 galcanezumab doses with respect to safety profiles.[19,20]

This paper aimed to evaluate time to onset of effect of galcanezumab, based on findings from the EVOLVE-1 and EVOLVE-2 studies.[19,20] Galcanezumab is injected subcutaneously once a month at a dose of 120 mg, with a loading dose of 240 mg (2 120-mg injections) administered the first month of therapy.[14,15] Pharmacokinetic data indicate that the use of a loading dose speeds the time to steady-state serum concentration of galcanezumab.[22] Average time to peak concentration after a single injection is 5 days.[14,15,22] Therefore, it was hypothesized that time to onset of effect could be in the first week of treatment.

METHODS

Study Design.—Analyses were based on data from 2 previously published double-blind, randomized, Phase 3 studies of identical design comparing galcanezumab vs placebo in patients with episodic migraine.[19,20] Ninety sites across North America (EVOLVE-1; United States and Canada) and 109 sites in 11 countries (EVOLVE-2; Argentina, Czech Republic, Germany, Israel, South Korea, Mexico, Netherlands, Spain, Taiwan, United States, and United Kingdom) enrolled patients from January 2016 to March 2017. The study design consisted of 4 study periods: initial screening and washout of all migraine preventive treatments (3-45 days), a 1-month prospective baseline period, a 6-month double-blind treatment period, and a 4-month post-treatment period. Patients were randomized (2:1:1) to placebo, galcanezumab 120 mg, or galcanezumab 240 mg using a computer-generated randomization sequence via an interactive web-response system. Study treatment was administered once per month for 6 months (subcutaneous injection via pre-filled syringe). All patients randomized to galcanezumab received a loading dose of 240 mg as their first dose. A daily electronic diary was used to record headache and other migraine symptoms during the 1-month baseline period and throughout the remainder of the trial.

The study protocols were reviewed and approved by the institutional review board for each of the study sites. The studies were conducted according to Good Clinical Practice and the Declaration of Helsinki guidelines. Patients provided written informed consent before undergoing study procedures.

Patient Selection.—Study participants were adults (18-65 years) diagnosed prior to 50 years of age, with a diagnosis of episodic migraine and at least a 1-year history of migraine with or without aura[23] and 4-14 MHDs per month with at least 2 migraine attacks per month on average within the past 3 months and during a 1-month prospective baseline-period, and with at least 80% diary compliance during the prospective baseline period. During the study, patients could take acute headache medication, but no migraine preventive medications were allowed.

Key exclusion criteria included history of failure to respond to an adequate trial of 3 or more classes of migraine preventive treatments as defined by the American Academy of Neurology/American Headache Society treatment guidelines Level (A) and (B) evidence[24] or including botulinum toxin a or b, prior exposure to any CGRP antibody, having taken a therapeutic antibody in the past 12 months, and receiving migraine preventive medication within 30 days of the baseline period.

Outcome Measures and Statistical Analysis.—The pre-specified primary outcome in each study was the overall mean change from baseline in the number of monthly MHDs during the double-blind treatment

period (across Months 1 through 6).[19,20] The study's pre-defined secondary objectives included identification of time (month) of onset of effect, based on the primary measure of change in MHDs for Months 1 through 6. In this paper, a further post-hoc analysis of time of onset of effect is presented, which includes weekly assessments based on the number of MHDs and daily assessments based on occurrence or absence of migraine headaches.

To determine the time of onset of effect of galcanezumab, a sequential analysis approach was used. The first step assessed the onset of effect at a monthly interval. If onset occurred at Month 1, then the onset of effect was assessed at a weekly interval (Weeks 1-4 within the first month). If onset occurred at Week 1, then the onset of effect was assessed at a daily interval within the first week. This approach was pre-specified based on clinical relevance and because it is an application of closed testing, which provides strong control of the type I error rate across the multiple tests.[25,26]

The month of onset of effect was defined as the earliest month at which galcanezumab statistically separated from placebo on mean change from baseline in monthly MHDs and maintained that statistically significant separation at each subsequent month in the treatment period. Changes from baseline in monthly MHDs at Months 1-6 were analyzed using a mixed model repeated measures approach. Statistical significance of treatment vs placebo was assessed based on two-sided tests at the 0.05 alpha level. The approach to missing diary data was to assume that the rate of MHD was the same for days with missing and non-missing diary days. In the pre-defined calculation of monthly MHDs, monthly MHDs were set to missing when diary compliance for the month was ≤50%.

The week of onset of effect within Month 1 was defined as the earliest week at which galcanezumab statistically significantly separated from placebo in the number of MHDs and maintained that statistically significant separation for each remaining week in Month 1. The galcanezumab treatment groups (120 and 240 mg) were pooled together for this analysis due to the fact that both treatment groups received 240 mg as their first monthly dose because the 120-mg group was required to have a 240-mg loading dose. The number of MHDs for each of Weeks 1 through 4 within Month 1 was analyzed with a repeated measures ordinal logistic regression. Odds ratios of having fewer MHDs for the galcanezumab group vs placebo were calculated for each week. The weekly analysis was conducted using a repeated measures ordinal logistic regression model due to the inherent limited ordinal nature of the data (ie, only possible values of 0, 1, 2, …, 7 MHDs per week), the potential for a high number of patients with 0 MHDs at any of Weeks 1 through 4, and deviation from the normality assumption of the primary model.

Nevertheless, for descriptive purposes, a post-hoc analysis of mean change from baseline in the number of weekly MHDs was also conducted to supplement the weekly repeated measures ordinal logistic analysis. In this analysis, the data from the baseline month were normalized to a 1-week baseline for comparisons with those of Weeks 1 through 4 of the post-baseline period.

Following confirmation of onset of effect of galcanezumab during the first week, onset was subsequently assessed daily by evaluating the estimated proportion of patients with presence of migraine headache (yes or no) for each of the initial 7 days of treatment. A generalized linear mixed model was used to analyze these repeated binary data.

Although the aforementioned sequential approach provided a comprehensive assessment of onset of effect for galcanezumab for the primary efficacy measure of number of MHDs, the onset of effect was also assessed for an additional pre-specified clinically meaningful measure: 50% response (ie, ≥50% reduction from baseline in number of MHDs).[27] Consistent with the sequential approach based on the primary efficacy measure, monthly (Months 1-6) proportions of patients experiencing a 50% response were assessed first, and the month of onset of response was defined as the first month at which galcanezumab separated from placebo and maintained that statistical separation for each subsequent month through Month 6. As a post-hoc analysis, if onset occurred at Month 1, then the weekly proportions of 50% responders were evaluated, and the week of onset of response was found as the first week at which galcanezumab separated from placebo and maintained that statistical separation for each subsequent week through Week 4. These weekly data were analyzed using a generalized linear mixed model for repeated binary data.

All analyses were conducted using SAS Enterprise Guide 7.1 (SAS Institute, Cary, North Carolina) and were performed separately on the EVOLVE-1 and EVOLVE-2 studies in order to provide validation of the results through replication.

RESULTS

Patient Baseline Characteristics and Diary Compliance.—A total of 1773 patients were randomized for treatment in EVOLVE-1 (n = 858) and EVOLVE-2 (n = 915) and received 120-mg or 240-mg galcanezumab (n = 879) or placebo (n = 894). Patients were predominately female (83.7% EVOLVE-1, 85.4% EVOLVE-2) and White (80.4% EVOLVE-1, 70.3% EVOLVE-2) with a mean age of approximately 41 years (40.7 years EVOLVE-1, 41.9 years EVOLVE-2) (Table 1). The geographic distribution of patients varied between the 2 studies, with 100% of patients residing in North America in EVOLVE-1 vs 48.7% in EVOLVE-2. Mean baseline number of monthly MHDs was 9.1 for both studies. On average, patients were diagnosed with migraine 20 years prior to study enrollment and had a mean baseline Migraine Disability Assessment total score of approximately 33, which represents the total number of days that migraine limited activity during the previous 3-month period and indicates severe disability.[28] A complete review of patient disposition and baseline characteristics may be found in the primary publications for the 2 studies.[19,20]

Table 1.—Demographic and Baseline Disease Characteristics

	EVOLVE-1 (n = 858)	EVOLVE-2 (n = 915)
Female, n (%)	718 (83.7)	781 (85.4)
White, n (%)	690 (80.4)	643 (70.3)
Geographic region, n (%)		
North America	858 (100)	446 (48.7)
Europe	—	241 (26.3)
Other	—	228 (24.9)
Mean age, years (SD)	40.7 (11.6)	41.9 (11.1)
Mean duration of migraine diagnosis, years (SD)	20.1 (12.4)	20.6 (12.4)
Migraine Disability Assessment, mean total score (SD)	33.2 (27.7)	33.0 (29.7)
Mean number of monthly MHDs, days (SD)	9.1 (3.0)	9.1 (2.9)
Mean number of weekly MHDs, days (SD)	2.1 (0.7)	2.1 (0.7)
Patients with ≥2 prior preventive treatment failures in previous 5 years, n (%)	42 (4.9)	130 (14.2)

MHD = migraine headache days; SD = standard deviation.

Mean diary compliance at baseline was 97% in EVOLVE-1 and 98% in EVOLVE-2. Diary compliance remained high at all subsequent months, ranging from means of 94% and 95% at Month 1 to means of 91% and 92% at Month 6 in EVOLVE-1 and EVOLVE-2, respectively.

Onset of Effect.—Onset of effect at the monthly interval occurred at Month 1 for the galcanezumab treatment groups vs placebo for each study (each month, $P < .001$ for galcanezumab) (Fig. 1a,b). At Month 1, the mean change in number of MHDs in EVOLVE-1 was −3.72 and −3.59 for the galcanezumab 120 and 240 mg groups, respectively, vs −1.67 for placebo. Corresponding data for EVOLVE-2 were −3.90 and −3.23 for galcanezumab 120 and 240 mg, respectively, vs −1.17 for placebo, with no statistically significant differences between the 2 galcanezumab doses in either study.

Because Month 1 was identified as the month of onset of effect, weekly analyses were conducted to further identify onset of effect within the first month. For both studies, Week 1 was identified as the week of onset of effect of galcanezumab (odds ratio [95% confidence interval] for EVOLVE-1, 2.71 [2.00, 3.66], and for EVOLVE-2, 2.88 [2.16, 3.86]; both $P < .001$), with significant treatment effects maintained at all subsequent weeks in the first month (all $P \leq .004$) (Table 2). In each study, patients had significantly higher odds of having fewer weekly MHDs with galcanezumab treatment compared with placebo, during each of the first 4 weeks of double-blind treatment. The larger the odds ratio, the greater the improvement in the galcanezumab treatment group compared with placebo. For instance, following a single 240-mg dose of galcanezumab, patients were almost 3 times as likely to have a significant reduction in MHDs at Week 1 compared with placebo in both studies.

To provide descriptive statistics not available with the weekly ordinal logistic regression analysis, weekly mean change analyses were performed. Figure 2a,b presents the mean change from baseline, normalized to 7 days, of each study for Weeks 1 through 4. As seen in

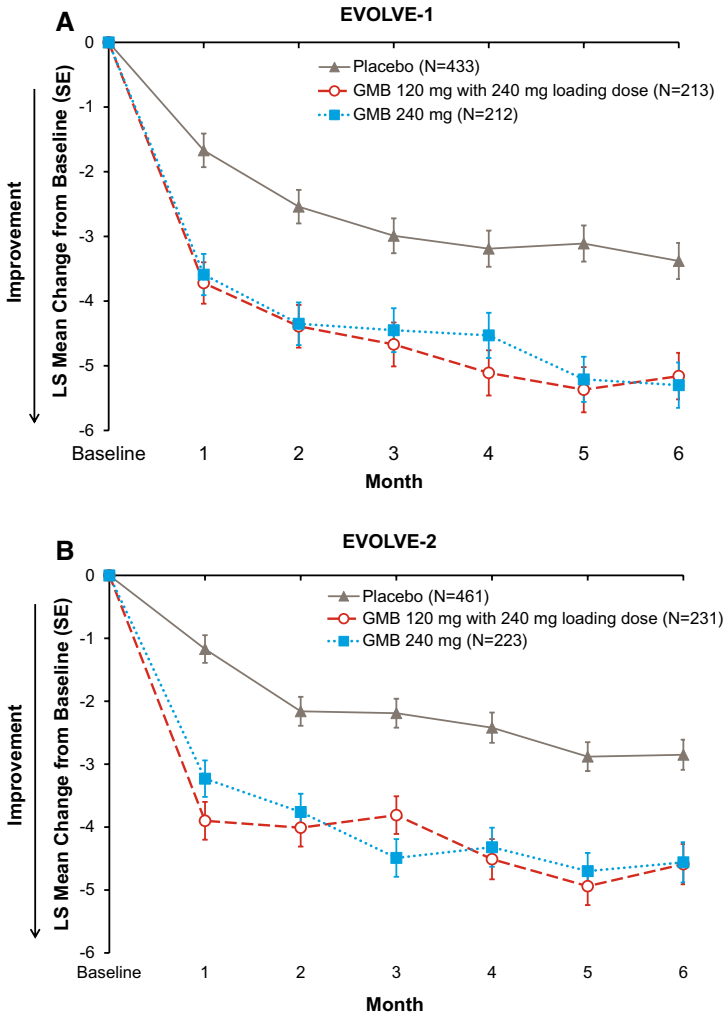

Fig. 1.—Change from baseline in number of migraine headache days (MHDs) for Months 1-6 in (A) EVOLVE-1 and (B) EVOLVE-2. All *P* values vs placebo < .001; no significant differences were observed between the two GMB doses. GMB, galcanezumab; LS, Least Squares; SE, standard error. [Color figure can be viewed at wileyonlinelibrary.com]

Table 2.—Odds of Having Fewer Migraine Headache Days if Treated With Galcanezumab vs Placebo at Weeks 1 Through 4

	Odds Ratio	95% CI	*P* Value†
Study 1 (EVOLVE-1)			
Week 1	2.71	2.00, 3.66	<.001
Week 2	3.08	2.27, 4.17	<.001
Week 3	2.11	1.55, 2.86	<.001
Week 4	1.56	1.15, 2.11	.004
Study 2 (EVOLVE-2)			
Week 1	2.88	2.16, 3.86	<.001
Week 2	2.76	2.07, 3.68	<.001
Week 3	2.41	1.80, 3.22	<.001
Week 4	2.67	1.99, 3.58	<.001

†Data analyzed using a repeated measures ordinal logistic regression.
CI = confidence interval.

Figure 2a,b, the galcanezumab groups in both studies consistently experienced a mean reduction of approximately 1 MHD per week (−0.9 to −1.09 days/week) vs less than 1 day per week in the placebo groups (−0.35 to −0.68 days/week).

Because Week 1 was identified as the onset of effect for the weekly analyses within Month 1, additional analyses for each of the first 7 days of treatment were conducted to further identify if galcanezumab provided an earlier benefit to patients. The estimated proportion of patients experiencing migraine headaches for each day of Week 1 for each study was significantly lower in the treatment group compared with placebo beginning at Day 1 post-injection (EVOLVE-1, $P = .002$; EVOLVE-2, $P = .038$), which was maintained through

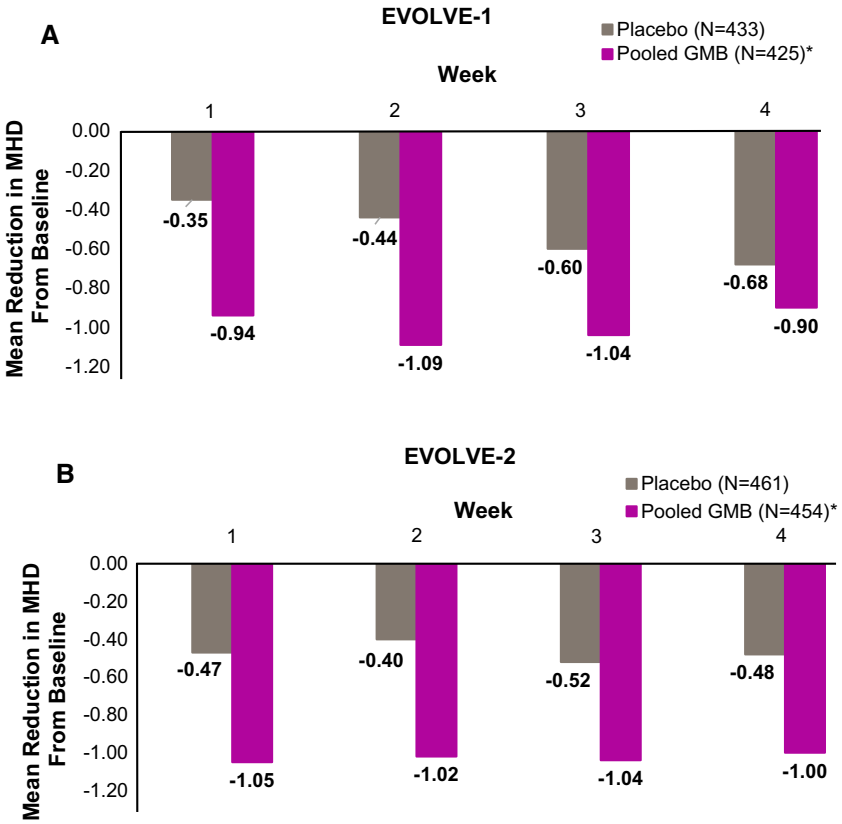

Fig. 2.—Mean change from 7-day baseline in number of migraine headache days (MHDs) for Weeks 1-4 in (A) EVOLVE-1 and (B) EVOLVE-2. Statistically significant at each week per Table 2. *Onset of effect analyses evaluated pooled GMB-treated patients vs placebo (as both GMB groups received 240 mg in the first month). GMB, galcanezumab. [Color figure can be viewed at wileyonlinelibrary.com]

the remainder of the week (Fig. 3a,b). Therefore, following the sequential approach, the onset of effect for galcanezumab was determined to occur at Day 1 post-injection (ie, the first full day on treatment).

For each study at each of Months 1-6, the proportion of patients with ≥50% reduction from baseline in MHDs were statistically significantly greater in the galcanezumab treatment groups compared with placebo (all $P < .001$) (Fig. 4a,b). The estimated proportion of ≥50% reduction from baseline for MHDs at each of Weeks 1-4 during Month 1 for each study also was significantly greater in the pooled galcanezumab treatment group compared with placebo (Week 1 percentage of patients with 50% response in galcanezumab group vs placebo group for EVOLVE-1, 54.3% vs 32.4% [$P < .001$], and for EVOLVE-2, 59.4% vs 38% [$P < .001$]) (Fig. 5a,b). Therefore, weekly assessment of onset of 50% response for galcanezumab was determined to occur at Week 1. This analysis supports the primary onset analysis based on number of MHDs.

DISCUSSION

Due to the high rates of patient nonadherence to oral migraine preventive medications, early onset of effect is an important feature to consider when prescribing a preventive treatment. The present analyses indicate that galcanezumab, a monthly injectable migraine preventive, had onset of effect beginning 1 day after injection. Moreover, this finding of rapid onset was replicated in 2 large Phase 3 clinical trials in adult patients with episodic migraine (EVOLVE-1[19] and EVOLVE-2[20]). Both doses of galcanezumab (120 and 240 mg) achieved a statistically significant reduction in the number of monthly MHDs beginning at Month 1 and continuing through Month 6, with no

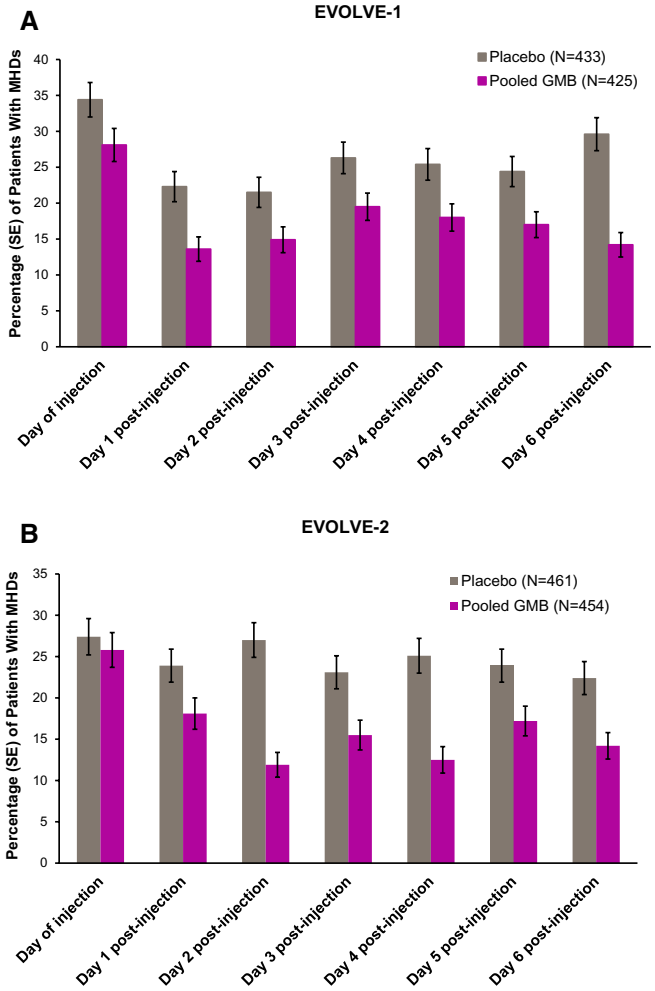

Fig. 3.—Daily estimated proportions of patients with migraine headache days (MHDs) in Week 1 in (A) EVOLVE-1 and (B) EVOLVE-2. All *P* values vs placebo < .05 except day of injection. GMB, galcanezumab; SE, standard error. [Color figure can be viewed at wileyonlinelibrary.com]

statistically significant difference between galcanezumab doses. Additional weekly analyses examining onset within the first month, after a 240-mg loading dose, showed a significant effect at Week 1, which continued throughout the remaining weeks of Month 1. Moreover, daily analyses found that the estimated proportion of patients experiencing migraine headaches was significantly lower in the galcanezumab group beginning at Day 1. Weekly onset analyses based on a 50% or greater reduction in MHDs demonstrated consistent superiority to placebo starting at Week 1. The early onset of 50% response is not only rapid but also a clinically meaningful effect.[27]

The finding of a rapid onset of effect in reduction in MHDs as early as Day 1 is consistent with the mechanism of action for galcanezumab and its known pharmacokinetic profile.[14,15] Galcanezumab works by binding to and thus neutralizing the migraine-inducing effects of CGRP.[14,15] Studies of the pharmacokinetic/pharmacodynamic properties of galcanezumab in healthy volunteers as well as in patients with migraine have found an average time to peak serum concentration of galcanezumab of 5 days.[14,15,22] The average half-life of 27 days allows for monthly administration of galcanezumab.[14,15,22] Use of the 240-mg loading dose as the first dose of a normal maintenance regimen of 120 mg/month also contributes to a faster time to onset as therapeutic steady-state concentrations of galcanezumab may be achieved following the first injection.[14,15,22]

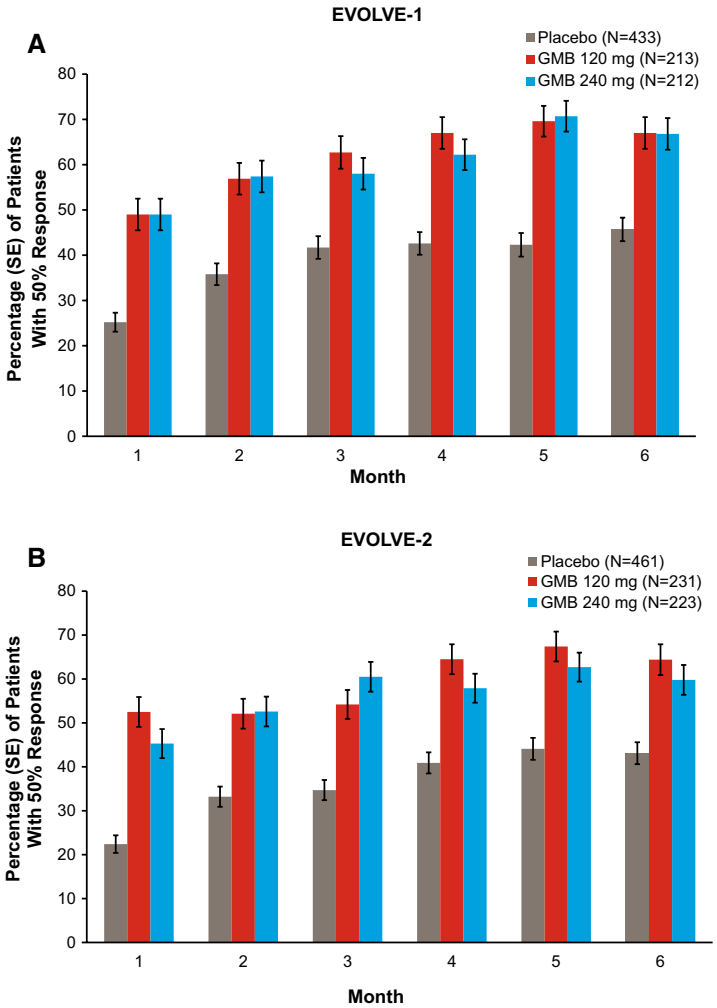

Fig. 4.—Estimated monthly proportion of 50% response for migraine headache days (MHDs) at Months 1-6 in (A) EVOLVE-1 and (B) EVOLVE-2. All *P* values for both GMB doses vs placebo < .001. GMB, galcanezumab; SE, standard error. [Color figure can be viewed at wileyonlinelibrary.com]

This represents an advantage over oral therapies, which require daily adherence and also titration schedules that may extend for months to reach an optimal therapeutic dose. Patients thus may discontinue oral treatments before they have had the opportunity to realize their full effects.

Importantly, the effect of galcanezumab appeared consistent from week to week. Although review of the odds ratios for Weeks 1 through 4 of the first month of treatment indicated some numeric lessening of these ratios at Weeks 3 and 4 primarily in the EVOLVE-1 study (Table 2), this finding appeared to be driven by variability in the placebo group. The patients in the EVOLVE-1 placebo group showed a doubling of their MHD reduction from Week 1 to Week 4, whereas patients treated with galcanezumab showed a consistent reduction of ~1 MHD each week in both studies. For both studies, the statistical significance between groups occurred at Week 1 and was maintained for all subsequent weeks through Week 4 of the first month, with $P < .001$ for all weeks in both studies except for Week 4 of EVOLVE-1, which was nevertheless still statistically significant at $P = .004$. Review of weekly data from all subsequent months showed a consistent effect for galcanezumab from week to week.[29]

There are some limitations that need to be considered when interpreting the findings presented herein. The EVOLVE studies[19,20] were conducted in patients with episodic migraine, of whom only 60 to

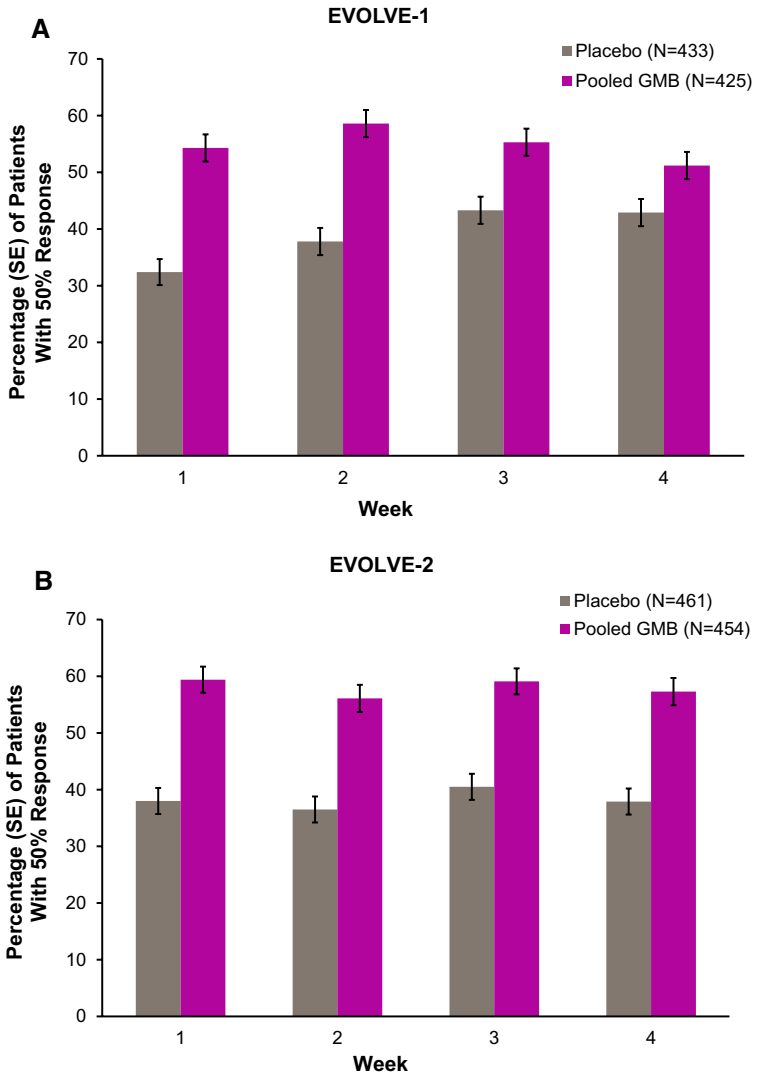

Fig. 5.—Estimated weekly proportion of 50% response for migraine headache days (MHDs) at Weeks 1-4 in (A) EVOLVE-1 and (B) EVOLVE-2. All *P* values vs placebo < .001 except Week 4 in EVOLVE-1, *P* < .05. GMB, galcanezumab; SE, standard error. [Color figure can be viewed at wileyonlinelibrary.com]

65% had had prior migraine preventive treatment in the past 5 years. Moreover, patients were primarily middle-aged, White, and female, which is typical of the migraine populations assessed in clinical trials but which may make the results less generalizable to other populations. Also, because MHDs do not occur as frequently in patients with episodic migraine, evaluation of onset of effect in an individual patient may be more difficult to assess within the first week of treatment. While early effects are encouraging and important for continued adherence, ultimate evaluation of the efficacy of galcanezumab or other monthly injectable preventives for an individual patient may require at least 3 months of treatment, according to guidelines from the American Headache Society.[30]

It should also be noted that although the studies were not prospectively powered for the complete set of onset-of-effect assessments provided in this manuscript, month of onset of effect was a predefined protocol objective in each study. The methodology employed was consistent with the methods applied to that objective and was statistically robust to false-positive findings due to the pre-specified multiple testing procedure. Since false-negative findings would result in declaring a later onset of effect

than is true, these analyses are considered conservative. Moreover, the replication of findings across 2 studies, along with convergence of evidence based on multiple analysis methods, provides confidence in the conclusions. Presentation of response rates further allows the reader to assess clinical relevance of the findings.

CONCLUSION

In summary, galcanezumab administered at 120 mg (with a 240-mg loading dose) or 240 mg subcutaneously once per month demonstrated an onset of effect 1 day after injection (Day 1 post-injection). Galcanezumab also demonstrated superiority to placebo based on a clinically meaningful measure of 50% response rate starting by Week 1, the earliest time point of assessment for this measure. This rapid onset of effect of galcanezumab makes it a promising treatment for prevention of migraine in patients with episodic migraine.

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