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ORIGINAL RESEARCH

Early Onset and Maintenance Effect of Galcanezumab in Japanese Patients with Episodic Migraine

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Purpose: This study aimed to extensively evaluate the onset and maintenance effect of galcanezumab compared with placebo for the prevention of episodic migraine in Japanese patients.

Patients and Methods: This was a post-hoc analysis of a Phase 2, multicenter, randomized, double-blind, placebo-controlled study conducted between December 2016 and January 2019 (ClinicalTrials.gov: NCT02959177). Patients aged between 18 and 65 years with episodic migraine were randomized to receive a monthly injection of galcanezumab (120 mg: N = 115, 240 mg: N = 114) or placebo (N = 230) for 6 months. Outcome measures included onset of effect at weekly and daily intervals—assessed by change from baseline in the number of migraine headache days and the proportion of patients with migraine headache —with galcanezumab versus placebo. To further confirm the onset and maintenance effect, the 50% response rate was also evaluated.

Results: The mean change from baseline in weekly migraine headache days was significantly reduced with galcanezumab (–0.97 days) compared with placebo (–0.10 days) at week 1 ($p \leq 0.0001$), which was maintained at all subsequent weeks up to week 4 (all $p \leq 0.0001$ vs placebo). A significantly smaller proportion of galcanezumab-treated patients had migraine headache compared with placebo-treated patients at day 1 after the first injection (13.6% vs 31.4%, respectively; $p \leq 0.0001$), which was also maintained at all subsequent days during the first week after the first injection. Furthermore, the 50% response rate was significantly higher with galcanezumab compared with placebo from week 1 through month 6.

Conclusion: The onset of the migraine preventive effect of galcanezumab was rapid compared with placebo, starting from day 1 after the first injection in Japanese patients with episodic migraine. The effect was maintained during the first week and first month, and throughout 6 months of monthly injections of galcanezumab. Galcanezumab is a promising preventive treatment in Japanese patients with episodic migraine.

Keywords: calcitonin gene-related peptide, galcanezumab, Japan, migraine disorders, onset of effect, maintenance effect

Introduction

Migraine is a highly prevalent neurological disease that is associated with high disability and an enormous health and economic burden to both individuals and society.[1–3] Preventive treatments, including antiepileptics, beta-blockers, calcium channel blockers, and antidepressants, are currently recommended in the Japanese treatment guideline;[4] however, usage rates of these drugs are low, with only 14.9%

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of patients receiving treatment.[5] Also, the discontinuation rate is high, mainly owing to intolerance and lack of efficacy of the existing preventive treatments.[6,7] In fact, many patients discontinue treatment within approximately 2 months,[5] possibly because many of these treatments take at least 2–3 months to establish their effects, and patients are unable to show immediate improvement.[4,8] Therefore, there is a demand for a new preventive treatment for migraine with an early onset of effect, and with improved efficacy and tolerability.

Galcanezumab is a humanized monoclonal antibody that selectively binds to calcitonin gene-related peptide (CGRP), preventing its activity that is thought to play an important role in migraine pathogenesis.[9] Galcanezumab has been shown to be efficacious, safe, and well tolerated in several phase 2 and 3 randomized controlled trials, mainly in White patients with migraine,[10–12] including those who failed to respond to 2–4 preventive treatment categories.[13] A pooled analysis of two global Phase 3 studies (EVOLVE-1 and EVOLVE-2) analyzed the onset of effect of galcanezumab in patients with episodic migraine.[14] In this analysis, the onset of the preventive effect of galcanezumab was rapid; the proportion of patients with migraine headaches was significantly reduced with galcanezumab compared with placebo, starting from day 1 after the first injection day. This preventive effect of galcanezumab was further confirmed, with galcanezumab significantly reducing the number of migraine headache days starting from week 1 and continuing throughout the treatment period (months 1–6). Furthermore, an ongoing real-world prospective cohort study in Italy showed that galcanezumab consistently decreased monthly migraine headache days in patients with high-frequency episodic migraine, with 76.5% of patients experiencing 50% reduction in monthly migraine headache days at 6 months of treatment.[15]

In a phase 2 randomized controlled study of galcanezumab in Japanese patients with episodic migraine, the primary objective was met, showing superiority of galcanezumab over placebo in the overall mean change from baseline in the number of monthly migraine headache days during the study period (months 1–6).[16] This study also reported that galcanezumab significantly reduced migraine headache days compared with placebo at each month starting from month 1 and maintained that effect at all subsequent months up to month 6, suggesting that galcanezumab has a rapid onset of effect starting from month 1. However, the earliest time of onset of effect and weekly and monthly maintenance effect after the first or previous injections of galcanezumab in Japanese patients with episodic migraine have not yet been determined.

In this post-hoc analysis of the Japanese phase 2 randomized controlled study,[16] we aimed to extensively evaluate the onset and maintenance preventive effect of galcanezumab in Japanese patients with episodic migraine.

Patients and Methods

Study Design

This was a post-hoc analysis of a phase 2, multicenter, randomized, double-blind, placebo-controlled study of galcanezumab in Japanese patients with episodic migraine (ClinicalTrials.gov: NCT02959177; Figure 1). The study was conducted at 40 sites in Japan between December 2016 and January 2019. Additional details on the study design have been described previously.[16] Briefly, this study had four study periods: a screening period for full clinical assessment and washout of migraine preventive treatments; a baseline period for assessing patient eligibility and establishing baseline data; a 6-month double-blind treatment period; and a 4-month follow-up (washout) period. The study was approved by the institutional review boards of each study site (see Supplementary Table) and was compliant with the Declaration of Helsinki, Good Clinical Practice, and the Council for International Organization of Medical Science International Ethical Guidelines. All patients provided written informed consent before participating in the study.

Study Population

The study population has been described previously.[16] Briefly, patients were included if they were aged between 18 and 65 years, with a diagnosis of migraine per the International Headache Society International Classification of Headache Disorders, 3rd edition (beta version [ICHD-3β])[17] v1.1 or v1.2 and a history of 4–14 migraine headache days and ≥2 migraine attacks per month in the past 3 months. Patients were excluded if they had ≥15 headache days per month in the past 3 months; were suspected of having chronic migraine per the ICHD-3β;[17] had a history of persistent daily headache, cluster headache, or migraine subtypes (including hemiplegic migraine, ophthalmoplegic migraine, and migraine with brainstem aura); or had a history or presence of other medical conditions, including cardiovascular diseases and psychiatric diseases. Patients who were currently taking preventive treatment for migraine or who had failed to respond to ≥3 adequately

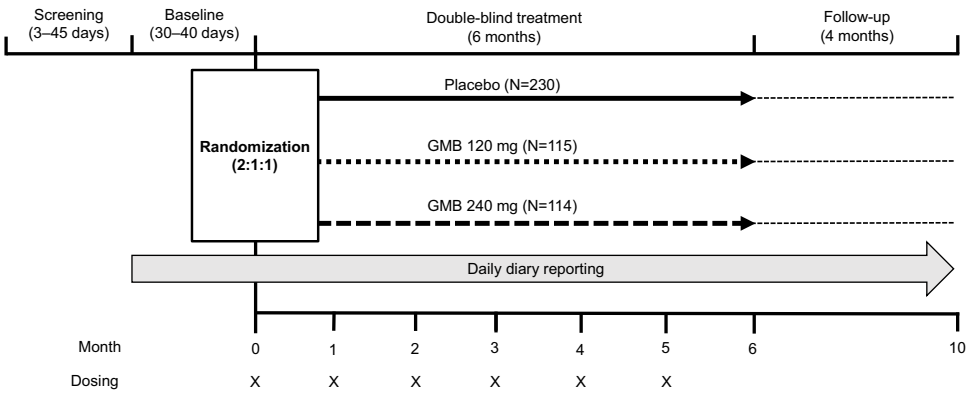

Figure 1 Study design.
Notes: Reproduced from Sakai F, Ozeki A, Sklijarevski V. Efficacy and safety of galcanezumab for prevention of migraine in Japanese patients with episodic migraine: A phase 2 randomized controlled clinical trial. *Cephalalgia Rep*. 2020; 3:1–10.[16] Patients in the galcanezumab 120-mg cohort received a 240-mg loading dose at first injection.
Abbreviation: GMB, galcanezumab.

dosed (ie, maximum tolerated dose for ≥2 months) migraine preventive treatments were also excluded. Migraine preventive treatments were defined as grade A or B Japanese guideline-recommended drugs[4] and botulinum toxin A or B. Patients had to have discontinued any preventive treatment for ≥30 days (or ≥4 months for botulinum toxin A and B) before entering the baseline period.

Treatment Protocol

Patients were randomized 2:1:1 to placebo, galcanezumab 120 mg, or galcanezumab 240 mg, respectively, which was determined by a computer-generated random sequence using an interactive web-response system stratified by baseline migraine frequency (<8 migraine headache days vs ≥8 migraine headache days) (Figure 1). Patients, study investigators, and all clinical study personnel who were involved in this study were blinded to individual treatment assignments during the study period. All patients received placebo or galcanezumab (120 mg or 240 mg) by once-monthly subcutaneous injection for 6 months, supplied as two 1-mL doses to maintain blinding. At the first injection, a loading dose of galcanezumab 240 mg was administered to patients who were randomized to galcanezumab 120 mg.

Outcome Measures

Based on the primary outcome of the phase 2 study,[16] this current post-hoc analysis determined the onset of effect at weekly intervals by assessing the change from baseline in the number of migraine headache days during the specified time period. A calendar day on which a migraine headache or a probable migraine headache occurred was defined as a migraine headache day. The onset of effect at weekly intervals was the earliest week that galcanezumab significantly improved the mean weekly migraine headache days compared with placebo and maintained that significant improvement at subsequent weeks. Following the weekly analysis, the onset of effect at daily intervals was determined by assessing the proportion of patients with migraine headache over the first 7 days after the first injection (during week 1 [ie, day 0 to day 6]). To further confirm the onset and maintenance effect, the 50% response rate, defined as the proportion of patients with ≥50% reduction from baseline in the number of migraine headache days, was analyzed each month during the treatment period (months 1–6) and each week during the first month (weeks 1–4). Patients recorded their headache information via an electronic patient-reported outcomes diary.

Statistical Analysis

The planned sample size was 451 patients, with random 2:1:1 assignment of 225 patients to placebo, and 113 patients each to galcanezumab 120 mg and 240 mg. Details of the statistical analysis of the phase 2 study have been published.[16] All analyses were conducted on an intention-to-treat (ITT) population, which included all patients who were randomized and received ≥1 dose of placebo or galcanezumab (120 mg or 240 mg). For all weekly and daily analyses conducted for month 1, the galcanezumab 120-mg and 240-mg groups were pooled, as patients in the galcanezumab 120-mg group received a 240-mg loading dose at the first injection. Least squares (LS) mean change from baseline in the number of weekly migraine headache days was analyzed using the mixed-

model repeated measures, which included the fixed categorical effects of treatment, week, and treatment-by-week interaction, and the continuous, fixed covariates of number of baseline migraine headache days and baseline-by-week interaction. Binary variables, including the proportion of patients with migraine headache and the proportion of patients with ≥50% reduction from baseline in the number of migraine headache days (ie, 50% response rate), were analyzed using the generalized linear mixed model. The generalized linear mixed model included the fixed categorical effects of treatment, time (day, week, or month for daily, weekly, or monthly analysis, respectively), and treatment-by-time interaction, and the continuous, fixed covariate of number of baseline migraine headache days. The statistical significance test between galcanezumab and placebo was conducted at a two-sided alpha level of 0.05. If the patients' monthly diary compliance was ≤50%, the monthly migraine headache day was considered to be missing in the predefined calculation of monthly migraine headache days. A migraine headache day was normalized to 30 days for the monthly analysis and 7 days for the weekly analysis. All analyses were conducted without adjustment for multiplicity. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.02.

Results

Patient Disposition

As previously reported,[16] a total of 459 patients were randomized, received ≥1 dose of placebo or galcanezumab, and were included in the ITT population (placebo: N = 230; galcanezumab 120 mg: N = 115; galcanezumab 240 mg: N = 114). Of these, 440 patients (95.9%) completed the 6-month treatment; 19 patients (4.1%) discontinued, and the main reasons for discontinuation were withdrawal (n = 5) for the placebo group, withdrawal (n = 5) or adverse events (n = 5) for the galcanezumab 120-mg group, and adverse events (n = 2) for the galcanezumab 240-mg group.

Demographic and Baseline Clinical Characteristics

Patient demographic and baseline characteristics were generally similar across the three treatment groups (Table 1). Most patients were female (placebo: 85.2%; galcanezumab 120 mg: 82.6%; galcanezumab 240 mg: 84.2%), and the mean (standard deviation) age was 44.2 (10.0) years in the placebo group, 43.2 (10.0) years in the galcanezumab 120-mg group, and 44.8 (10.2) years in the galcanezumab 240-mg group. In all treatment groups, patients were experiencing about 9 migraine headache days per month. Furthermore, no difference in the proportion of patients with migraine headache during the baseline period was observed between the placebo group and the galcanezumab group (data not shown).

Onset of Effect

The weekly analysis conducted in month 1 showed a significant reduction in the number of migraine headache days with galcanezumab compared with placebo at week 1 (Figure 2). At week 1, the LS mean (standard error [SE]) change in the number of migraine headache days was –0.97 (0.09) days for galcanezumab and –0.10 (0.09) days for placebo, with an estimated difference of –0.88 days (SE = 0.13; $p \leq 0.0001$). Significant improvement in

Table 1 Demographic and Baseline Clinical Characteristics (ITT Population)

	Placebo (N = 230)	GMB 120 mg (N = 115)	GMB 240 mg (N = 114)
Demographics			
Sex, female, n (%)	196 (85.2)	95 (82.6)	96 (84.2)
Age, years	44.2 (10.0)	43.2 (10.0)	44.8 (10.2)
BMI, kg/m^2	22.3 (3.7)	22.2 (3.5)	22.5 (3.6)
Disease characteristics			
Duration of migraine, years	21.2 (11.6)	21.1 (11.8)	22.1 (11.6)
Baseline monthly migraine headache days[a]	8.6 (3.0)	8.6 (2.8)	9.0 (3.0)
Baseline migraine headache days with acute medication use per month	7.4 (3.0)	7.3 (2.9)	7.8 (3.0)

Notes: Data show mean (SD) unless otherwise indicated. [a]Monthly migraine headache day was defined as the number of calendar days on which a migraine headache or probable migraine headache occurred in a 30-day period.

Abbreviations: BMI, body mass index; GMB, galcanezumab; ITT, intention-to-treat; SD, standard deviation.

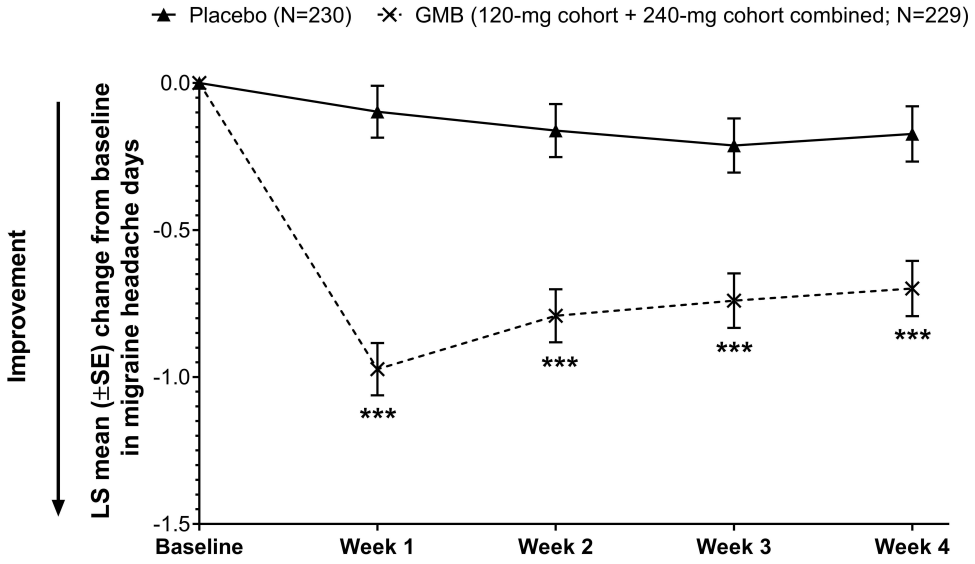

Figure 2 LS mean change from baseline in number of migraine headache days from week 1 to 4. Error bars indicate SE. ***$p \leq 0.0001$ vs placebo.
Note: The galcanezumab 120-mg and 240-mg groups were pooled during month 1 as patients in the galcanezumab 120-mg cohort received a 240-mg loading dose at first injection.
Abbreviations: GMB, galcanezumab; LS, least squares; SE, standard error.

migraine headache days was maintained at all subsequent weeks up to week 4 (all $p \leq 0.0001$ vs placebo). For the daily analysis conducted in week 1, the proportion of patients who experienced a migraine headache was significantly smaller in the galcanezumab group compared with the placebo group at day 1 after the first injection (13.6% vs 31.4%, respectively; $p \leq 0.0001$; Figure 3). The proportion of patients with a migraine headache remained lower in patients treated with galcanezumab than in those treated with placebo at all subsequent days during the first week after the first injection. Furthermore, compared with placebo, a significantly greater proportion of patients treated with galcanezumab had ≥50% response at month 1 (galcanezumab 120 mg: 50.6%; galcanezumab 240 mg:

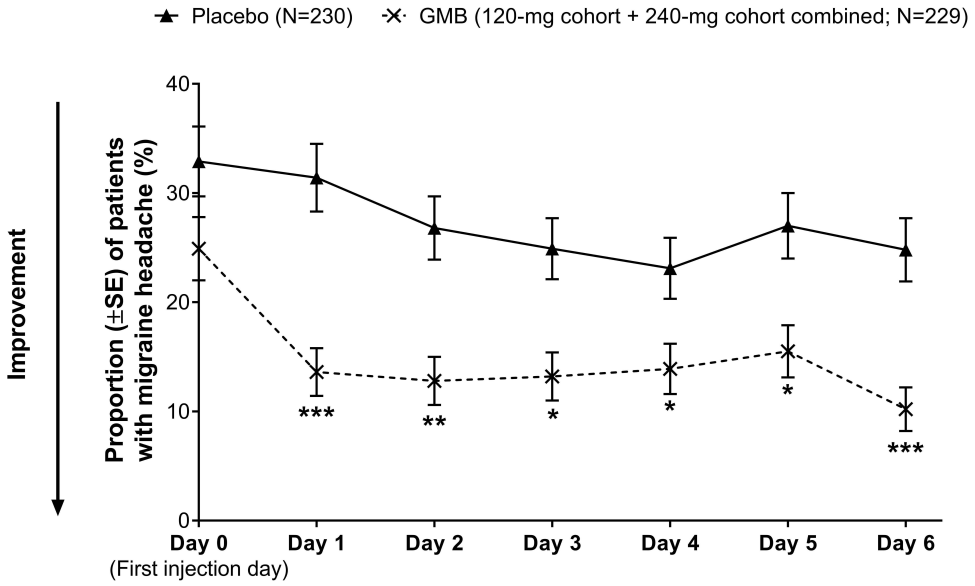

Figure 3 Daily estimated proportion of patients with migraine headache during week 1. Error bars indicate SE. *$p<0.05$, **$p<0.001$, ***$p \leq 0.0001$ vs placebo.
Note: The galcanezumab 120-mg and 240-mg groups were pooled during month 1 as patients in the galcanezumab 120-mg cohort received a 240-mg loading dose at first injection.
Abbreviations: GMB, galcanezumab; SE, standard error.

41.3%; placebo: 13.0%; $p < 0.001$, respectively), which remained significantly greater with galcanezumab (120 mg and 240 mg) compared with placebo at all subsequent months during the 6-month treatment period (Figure 4A). Weekly analysis further showed that the proportion of patients who had a ≥50% response was significantly higher with galcanezumab than with placebo at week 1 (57.0% vs 28.7%, respectively; $p < 0.0001$;

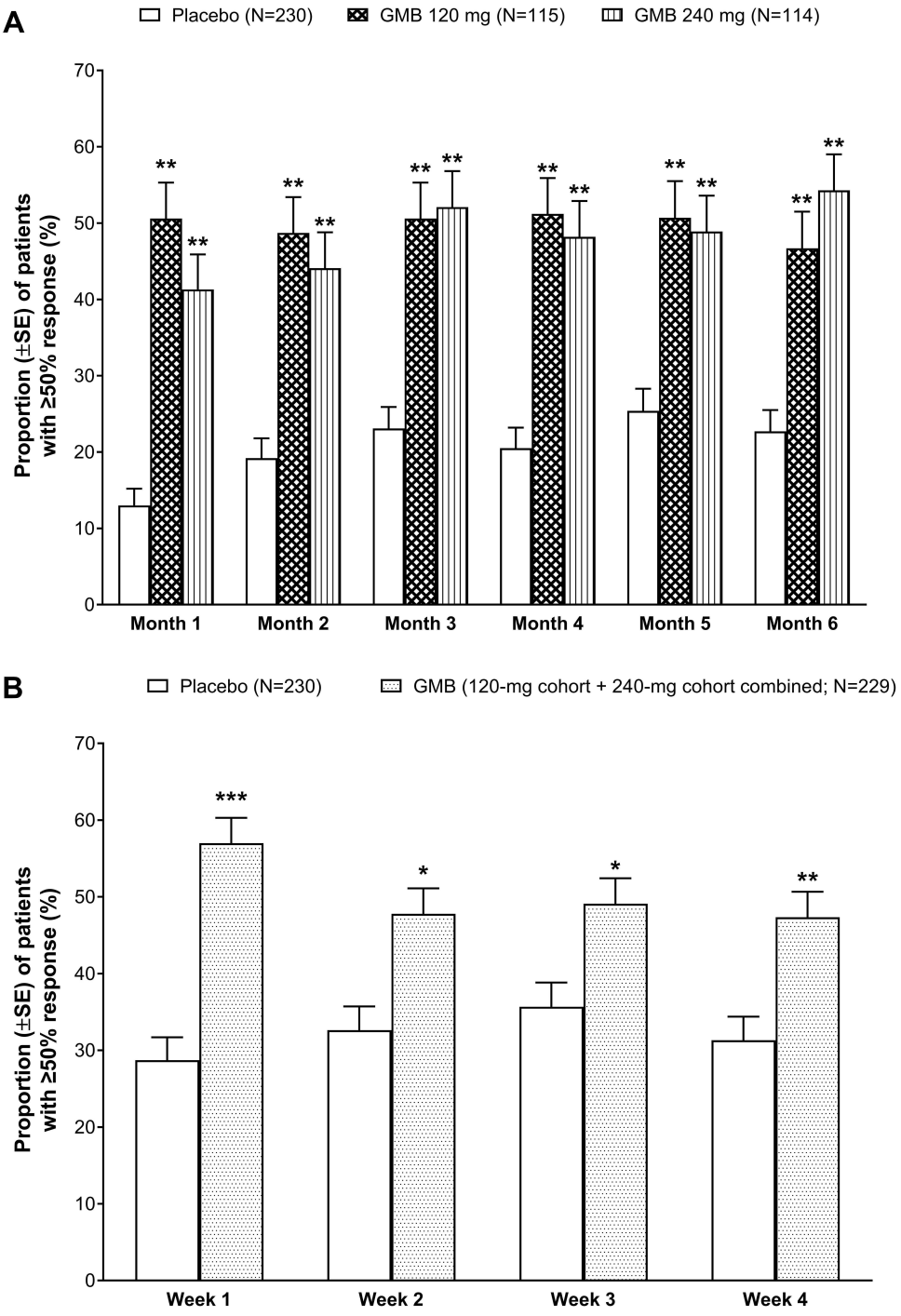

Figure 4 Estimated proportion of patients with ≥50% reduction in number of migraine headache days from (**A**) months 1–6 and (**B**) weeks 1–4. Error bars indicate SE. *p<0.05, **p<0.001, ***p≤0.0001 vs placebo.

Notes: The galcanezumab 120-mg cohort received a 240-mg loading dose at first injection. Therefore, for the monthly analysis, the results in month 1 show the effect of a 240-mg dose for both galcanezumab groups. For the weekly analysis, the galcanezumab 120-mg and 240-mg groups were pooled.

Abbreviations: GMB, galcanezumab; SE, standard error.

Figure 4B). In both treatment groups, 50% response rates remained relatively stable through week 4, with 47.4% and 31.3% of patients experiencing ≥50% response in the galcanezumab and placebo groups, respectively, at week 4 ($p = 0.0005$).

Discussion

This was the first study that extensively evaluated the onset and maintenance effect of galcanezumab for the prevention of migraine in Japanese patients with episodic migraine. In this study, galcanezumab showed a rapid onset of effect in preventing migraine compared with placebo. A significantly smaller proportion of galcanezumab-treated patients experienced a migraine headache compared with placebo-treated patients as early as day 1 after the first injection, and this was maintained during the first week. Furthermore, galcanezumab-treated patients had a significantly higher 50% response rate compared with placebo-treated patients during the first month and throughout 6 months of monthly injection. These results suggest that galcanezumab is an effective treatment option that provides an early and maintained effect in Japanese patients with episodic migraine.

In this study, less than 20% of galcanezumab-treated patients reported a migraine headache at day 1 after the first injection and each day during the first week, which was significantly lower than that reported for placebo-treated patients. As there were no differences in the proportion of patients with a migraine headache between the treatment groups during the baseline period (data not shown), it is suggested that the results observed at day 1 after the first injection are from the effect of galcanezumab and not from potential baseline differences in migraine headache between the treatment groups, and that the day of onset of effect of galcanezumab is day 1 after the first injection. A significant reduction in the number of weekly migraine headache days with galcanezumab compared with placebo was also observed at week 1 and during the first month. These results were consistent with the findings from the pooled analysis[14] of the phase 3 global randomized controlled studies, EVOLVE-1 and EVOLVE-2, in which day 1 was identified as the day of the onset of effect and week 1 as the week of the onset of effect. In this pooled analysis, galcanezumab was associated with fewer migraine headache days as early as day 1 after the first injection, and with a significantly reduced number of migraine headache days starting at week 1, compared with placebo. Therefore, findings from this current study further confirmed that galcanezumab establishes its preventive effect as early as day 1 after treatment initiation.

Similar to the results observed in this study for galcanezumab, botulinum toxin A has also demonstrated an early onset of effect in chronic migraine, significantly reducing weekly headache and migraine days starting at week 1 of treatment.[18] However, botulinum toxin A has not been demonstrated to be more efficacious than placebo for episodic migraine[19] and is only approved for the prevention of chronic migraine in the USA and Europe. The results of our study suggest that galcanezumab, a CGRP monoclonal antibody, may be more rapidly acting than many other conventional preventive treatments currently available[20,21] and may overcome the challenges associated with conventional preventive treatments, including lack of efficacy, low adherence, and high discontinuation rates.[5,6,22]

The current study showed that approximately half of the patients receiving galcanezumab experienced ≥50% response at each week from weeks 1 to 4. The monthly 50% response rate also remained stable; regardless of the dose, approximately 40–50% of patients treated with galcanezumab had a 50% response rate at all time points over the 6-month treatment period. In this study, patients were Japanese, slightly older, and had lower body mass index compared with the patients included in previous trials.[10,11] However, compared with the results from the pooled analysis of the previous randomized controlled trials,[14] the 50% response rates in the current study were generally similar over the treatment period. These results correlate with a recent cohort study, which showed no association between clinical characteristics and a 50% response rate in a small number of patients with episodic migraine,[15] suggesting that patients' baseline demographic and clinical characteristics may not affect patients' responsiveness to galcanezumab in episodic migraine.

Consistent with the results from the pooled analysis of EVOLVE-1 and EVOLVE-2,[14] the 50% response rates observed in the current study demonstrated that the rapid onset of effect of galcanezumab was maintained weekly, and then monthly, with monthly injections. These observations are also not surprising considering the pharmacokinetic (PK) and pharmacodynamic (PD) profile of galcanezumab. In a previous PK/PD study, galcanezumab was shown to reach maximum concentration after 5 days, with an elimination half-life of 27 days.[23] A PK/PD simulation also demonstrated that galcanezumab 120 mg (with a 240-mg loading dose) and 240 mg reduced free CGRP

by 97% within the first day after the first injection. This reduction in free CGRP was maintained: after 1 month of the first injection, free CGRP was still reduced by 64% with both the 120-mg (with a 240-mg loading dose) and 240-mg doses.[23] Moreover, subsequent monthly injections of galcanezumab 120 mg and 240 mg reduced free CGRP by a relatively similar extent (61% and 76%, respectively, on average).[23] Owing to the mechanism of action of galcanezumab, which selectively binds to CGRP and blocks the CGRP-mediated effects that are involved in migraine,[9] the rapid and maintained reduction in free CGRP correlates with the preventive effect of galcanezumab observed in this study. Collectively, the results of this current study further confirmed that the migraine preventive effect of galcanezumab is rapid and is maintained.

The strengths of this study include the randomized, double-blind, placebo-controlled design and the sufficiently large sample size, with a low rate of discontinuation from the study. Limitations of this study included no adjustment for multiplicity and evaluation of the maintenance effect for only 6 months. Generalizability of the study results in patients with episodic migraine may also be limited because of the strict eligibility criteria, which excluded patients with comorbidities such as cardiovascular and psychiatric diseases. Furthermore, as migraine headache days do not occur as frequently in episodic migraine compared with chronic migraine,[24] the onset of effect of galcanezumab in an individual patient within the first week of treatment is more difficult to assess. Therefore, although our study in patients with episodic migraine showed that galcanezumab has rapid migraine preventive effects, the effectiveness of galcanezumab for individual patients should be evaluated after at least 3 months of continuous treatment.[24]

Conclusion

Galcanezumab demonstrated a rapid and maintained effect in reducing migraine headache days in Japanese patients with episodic migraine, starting from day 1 after the first injection through month 6 of treatment. This study provides promising results that support the use of galcanezumab for migraine prevention in Japanese patients with episodic migraine.

Abbreviations

CGRP, calcitonin gene-related peptide; ICHD-3β, International Classification of Headache Disorders, 3rd edition (beta version); ITT, intention-to-treat; LS, least squares; PD, pharmacodynamics; PK, pharmacokinetics; SE, standard error.

Data Sharing Statement

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, agreed to the submitted journal, and agreed to be accountable for all aspects of the work.

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Disclosure

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