Neurol Ther (2024) 13:85–105
https://doi.org/10.1007/s40120-023-00562-w

ORIGINAL RESEARCH

Comparing the Efficacy and Safety of Galcanezumab Versus Rimegepant for Prevention of Episodic Migraine: Results from a Randomized, Controlled Clinical Trial

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Received: September 6, 2023 / Accepted: October 24, 2023 / Published online: November 10, 2023

ABSTRACT

Introduction: There have been no prior trials directly comparing the efficacy of different calcitonin gene-related peptide (CGRP) antagonists for migraine prevention. Reported are the results from the first head-to-head study of two CGRP antagonists, galcanezumab (monoclonal antibody) versus rimegepant (gepant), for the prevention of episodic migraine.

Methods: In this 3-month, double-blind, double-dummy study, participants were randomized (1:1) to subcutaneous (SC) galcanezumab 120 mg per month (after a 240 mg loading dose) and a placebo oral disintegrating tablet (ODT) every other day (q.o.d.) or to rimegepant 75 mg ODT q.o.d. and a monthly SC placebo. The primary endpoint was the proportion of participants with a $\geq$ 50% reduction in migraine headache days per month from baseline across the 3-month double-blind treatment period. Key secondary endpoints were overall mean change from baseline in: migraine headache days per month across 3 months and at month 3, 2, and 1; migraine headache days per month with acute migraine medication use; Migraine-Specific Quality of Life Questionnaire Role Function-Restrictive domain score at month 3; and a $\geq$ 75% and 100% reduction from baseline in migraine headache days per month across 3 months.

Results: Of 580 randomized participants (galcanezumab: 287, rimegepant: 293; mean age: 42 years), 83% were female and 81% Caucasian. Galcanezumab was not superior to rimegepant in achieving a $\geq$ 50% reduction from baseline in migraine headache days per month (62% versus 61% respectively; $P = 0.70$). Given the pre-specified multiple testing procedure, key secondary endpoints cannot be considered statistically significant. Overall, treatment-emergent adverse events were reported by 21% of

Prior Presentation: Data, in part, were presented as an oral presentation at the XXVI World Congress of Neurology, October 15–19, 2023, Montreal, Canada.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40120-023-00562-w.

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participants, with no significant differences between study intervention groups.
Conclusions: Galcanezumab was not superior to rimegepant for the primary endpoint; however, both interventions demonstrated efficacy as preventive treatments in participants with episodic migraine. The efficacy and safety profiles observed in galcanezumab-treated participants were consistent with previous studies.
Trial registration: ClinTrials.gov—NCT05127486 (I5Q-MC-CGBD).

PLAIN LANGUAGE SUMMARY

Galcanezumab and rimegepant are preventive treatments for episodic migraine. The goal of this study was to compare the efficacy of galcanezumab and rimegepant in reducing the number of monthly migraine headaches and to determine if galcanezumab was better than rimegepant. The study provides important information to doctors and their patients when making treatment decisions.

People with episodic migraine were assigned to the galcanezumab (given as an injection under the skin) or rimegepant (given as a tablet that dissolves in the mouth) group and treated for 3 months. The doctor and the patient did not know which group they were assigned to, and to keep it unknown to both, people in the galcanezumab group got an injection with real medicine and a fake tablet, and people in the rimegepant group got a tablet with real medicine and a fake injection. The researchers wanted to know how many people in each group had at least a 50% reduction in their monthly migraine headaches.

Of the 580 people in the study, 287 were assigned to galcanezumab and 293 to rimegepant. In both groups, most were female and white. After 3 months of treatment, 62% of the people in the galcanezumab group and 61% of people in the rimegepant group had at least a 50% reduction in monthly migraine headaches. Both treatments were effective, but galcanezumab was not better than rimegepant. About 20% of the people in each treatment group had a side effect from the medication, and most were mild or moderate in severity.

Keywords: Calcitonin gene-related peptide (CGRP); CGRP antagonist; Galcanezumab; Gepant; Head-to-head; Migraine; Prevention; Rimegepant; Clinical study; Comparative efficacy

Key Summary Points

Why carry out this study?

CGRP antagonists, the first medications designed specifically for migraine prevention, advanced the armamentarium of treatment options for migraine.

There have been few head-to-head studies directly comparing the efficacy of migraine preventive treatments, and none between CGRP antagonists.

Head-to-head studies comparing the efficacy of CGRP antagonists are needed to help clinicians and patients make informed treatment decisions.

What was learned from the study?

Both galcanezumab and rimegepant demonstrated efficacy as preventive treatments in participants with episodic migraine, though the difference in the primary outcome between the two treatment groups was not statistically significant.

INTRODUCTION

There have been only a few head-to-head clinical trials comparing treatments for the prevention of migraine [1–3]. We report the first head-to-head study of calcitonin gene-related peptide (CGRP) antagonist class medications—galcanezumab (a monoclonal antibody [mAb]

that binds to CGRP ligand and blocks its binding to the CGRP receptor) versus rimegepant (a CGRP receptor antagonist)—in the prevention of episodic migraine. This study compared the efficacy of galcanezumab and rimegepant, with the aim of providing important information to clinicians and patients when making treatment decisions.

The validation of the CGRP receptor as a target for acute [4–9] and preventive treatment [10] of migraine was initially established with oral small molecule receptor antagonists or "gepants." However, some of the early oral molecules did not advance in development due to concerns over hepatotoxicity [5, 7] or other reasons [4, 6]. Monoclonal antibodies (mAbs) targeting the CGRP receptor or CGRP ligand were then developed and shown to be efficacious in reducing the frequency of migraine, leading to regulatory body approval for the preventive treatment of migraine (erenumab, fremanezumab, galcanezumab, and eptinezumab) [11]. Approval of the mAbs was followed by the approval of oral gepants for acute treatment and then preventive migraine treatment [11].

The efficacy and safety of galcanezumab as a preventive treatment for episodic and chronic migraine have been established in multiple clinical trials, including two placebo-controlled, phase 3 clinical trials for preventive treatment in episodic migraine [12–17]. Galcanezumab is a humanized IgG4 monoclonal antibody administered subcutaneously (SC) that binds CGRP ligand and prevents its biological activity without blocking the CGRP receptor [18]. Rimegepant, an oral CGRP receptor antagonist (gepant), was the first oral gepant to receive marketing approval in the United States for episodic migraine prevention [19], and has also received marketing approval for acute treatment of migraine [20, 21].

There have been no clinical trials directly comparing the efficacy of CGRP antagonists, including gepants or mAbs. A head-to-head comparison of erenumab (a CGRP mAb) versus topiramate, with the primary endpoint of discontinuation due to adverse events and the secondary endpoint of efficacy, demonstrated the superiority of erenumab [3]. Given the lack of prior comparative efficacy studies of CGRP antagonists, the objective of this study was to directly compare galcanezumab with rimegepant, hereafter referred to as CGRP antagonists, and to generate study results that would be useful to healthcare providers and their patients when making informed decisions regarding their migraine-preventive treatment. Reported here are the results of the first head-to-head study comparing two CGRP antagonists, galcanezumab versus rimegepant.

METHODS

Study Design

This was a phase 4, randomized, 3-month double-blind, double-dummy, parallel-group study of galcanezumab and rimegepant in participants with episodic migraine, with or without aura (Fig. 1). The study was conducted between December 2021 and May 2023 at 75 sites in the United States among investigators who were neurologists, headache specialists, or other physicians with experience in headache clinical trials and diagnosing and treating migraine. The study was registered with ClinicalTrials.gov (NCT05127486) and was funded by Eli Lilly and Company (Indianapolis, IN, USA).

Study period I included a clinical assessment and washout of excluded medications. In study period II, participants prospectively recorded their daily headache data in an electronic diary (hereafter referred to as the electronic patient-reported outcome [ePRO] diary). Study period III was a 3-month double-blind treatment phase in which participants continued their daily recording of headache data in the ePRO diary. Protocol-specified acute migraine headache medications (acetaminophen; non-steroidal anti-inflammatory drugs; triptans; ergotamine and derivatives; aspirin, caffeine, and acetaminophen combination; or combinations thereof), as needed, were permitted during all study periods. Gepants, including rimegepant, were not allowed to be used for acute migraine treatment. Opioid and barbiturates were limited to 4 days per month, and acetaminophen was limited to 3 g/day maximal dose from all

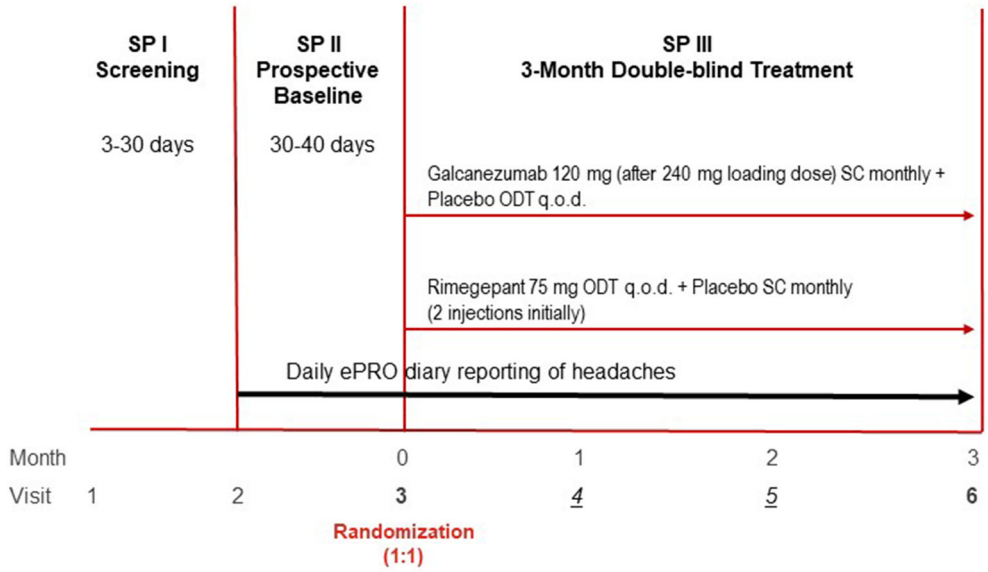

Fig. 1 Study design. All participants received SC injections using a prefilled syringe and ODT. Visits 1, 2, 3 (randomization) and 6 were conducted in the office. Visits 4 and 5 were telephone visits. At visit 3, participants randomized to galcanezumab 120 mg received a 240-mg loading dose (two injections) and one ODT placebo, and participants randomized to rimegepant received one rimegepant 75 mg ODT and two placebo injections. *ePRO* electronic patient-reported outcome, *ODT* orally disintegrating tablet, *QOD* every other day, *SC* subcutaneous, *SP* study period

acetaminophen-containing products. A single dose of injectable steroids was allowed once during the study in an emergency setting.

The study protocol was reviewed and approved by the Advara, Inc. Institutional Review Board (Columbia, MD) and utilized by all participating study investigative sites (Table S1 in the electronic supplementary material). The study was conducted according to Good Clinical Practice and the Declaration of Helsinki guidelines. Participants provided written informed consent before undergoing study procedures. Investigators at each study site evaluated and confirmed eligibility, obtained consent, and enrolled the participants.

Inclusion and Exclusion Criteria

Enrolled participants were between 18 and 75 years (inclusive) of age at the time of consent, had migraine with and/or without aura as defined by the International Classification of Headache Disorders-3 (ICHD-3) [22], and had migraine (onset prior to age 50 years) for at least 1 year prior to first visit. During the prospective baseline period, a frequency of 4 to 14 migraine headache days and at least two migraine attacks per month and an 80% compliance rate in using ePRO diary were required for enrollment. Women of childbearing potential agreed to use an acceptable method of birth control during the study and for 5 months after the last dose. All participants agreed to refrain from posting any personal medical data or protocol information related to the study on any website or social media platform until after the trial was completed.

Concomitant use of strong or moderate cytochrome P450 (CYP) 3A4 inhibitors, strong or moderate CYP3A inducers or inhibitors of P-glycoprotein (P-gp) and breast cancer-resistant protein (BCRP) were excluded during the study due to potential drug interactions with rimegepant. Participants with any prior exposure or current use of a CGRP antagonist (mAb or gepant) and those with known hypersensitivity to rimegepant or galcanezumab were excluded. Further exclusion criteria included

preventive migraine therapy within 5 days prior to the prospective baseline and during the study, use of botulinum toxin A or B in the head or neck area within the last 3 months, or nerve block or neuromodulation device use in the head or neck area within 30 days of the prospective baseline. Potential participants with acute cardiovascular events and/or a serious cardiovascular risk based on electrocardiogram at the screening visit, or a history of myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft or stroke within 6 months before screening, hepatic disease based on liver tests, or the presence of significant active psychiatric disease or other medical illness that would preclude study participation were excluded. Diagnostic exclusions included any history of new daily persistent headache, cluster headache, hemiplegic (sporadic or familial) migraine, retinal migraine, and migraine with brainstem aura (basilar-type migraine) defined by ICHD-3 [22]. Further, a report of a headache other than migraine or tension-type headache in the past 3 months, a history of 15 or more headache days per month on average, or chronic migraine as defined by ICHD-3 [22] were also excluded. The full listing of inclusion and exclusion criteria can be found in Table S2 in the electronic supplementary material.

Randomization and Blinding and Study Interventions

The randomization was a double-blinded, double-dummy scheme with participants randomized 1:1 to receive either galcanezumab or rimegepant. Participants randomized to the galcanezumab group received a loading dose of 240 mg administered as two galcanezumab 120 mg subcutaneous (SC) injections and a placebo orally disintegrating tablet (ODT). Participants randomized to the rimegepant group received 75 mg ODT and two placebo SC injections. Following the initial dosing, participants in the galcanezumab group received galcanezumab 120 mg SC monthly + placebo ODT every other day, and participants in the rimegepant group received rimegepant 75 mg ODT every other day + SC monthly placebo injection.

The first dose (at randomization) was administered in the office, whereas all subsequent doses of study intervention were self- or caregiver administered at home. Participants or their caregiver received training at the randomization visit on the use of the prefilled syringe used for SC injections (either galcanezumab verum or SC placebo injections) and ODT (either rimegepant verum or oral placebo ODT). Post-randomization, participants completed two monthly study visits by telephone. During the telephone visit, dosing was confirmed to be in accordance with the schedule of events and the use of concomitant medications and reports of any adverse events were collected. The final study visit was an office visit to complete final study procedures and assessments.

The clinical trial investigational materials used in this trial were blinded through established processes to control bias in the trial. The SC injections (galcanezumab and SC placebo) were packaged in cartons, and the oral disintegrating tablet ODT (rimegepant and placebo ODT) were packaged in blister packs. The packaging was identical in size, shape, and labeling for each type of intervention (SC injection or ODT). Rimegepant and placebo ODT tablets were slightly different in appearance; therefore, to further control bias, the study used designated, unblinded site personnel for all handling of study interventions (SC injections and ODT) including receipt, storage, dosing, dispensing and return. Commercially available rimegepant and non-commercial Zydis ODT were sourced and procured in the United States via established processes through the sponsor's Clinical Trial Commercial Product Group.

Randomization was stratified by baseline migraine frequency into < 8 migraine headache days per month versus ≥ 8 migraine days per month and was accomplished by a computer-generated randomization sequence using an interactive web-response system.

Objective and Endpoints

The efficacy analyses were performed in the intent-to-treat (ITT) population and included all randomized participants who had received at least one dose of both study interventions (injections and ODT). When change from baseline was assessed, the analysis included the ITT population with a baseline and at least one post-baseline measurement (full analysis set). The primary objective of the study was to assess whether galcanezumab was superior to rimegepant in the prevention of episodic migraine. The primary endpoint was the percentage of participants with a $\geq$ 50% reduction from baseline in monthly migraine headache days ($\geq$ 50% response rate) across the 3 month double-blind treatment period. Key secondary endpoints, presented in order of planned analyses, were (1) the mean change from baseline in number of monthly migraine headache days across the 3-month double-blind period; (2) the percentage of participants with $\geq$ 75% response rate (defined as a $\geq$ 75% reduction from baseline in monthly migraine headache days) across the 3-month double-blind treatment period; (3) the mean change from baseline in number of monthly migraine headache days at month 3, month 2, and month 1; (4) the mean change from baseline in number of monthly migraine headache days requiring acute treatment across the 3-month double-blind treatment period; (5) the mean change in Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ) Role Function-Restrictive (RF-R) domain score at month 3; and (6) the percentage of participants with a 100% response rate (defined as a 100% reduction from baseline in monthly migraine headache days) across the 3-month double-blind treatment period.

Other secondary efficacy endpoints, not controlled for multiplicity, included change from baseline to month 3 in the Migraine Disability Assessment (MIDAS) total score, the MSQ v2.1 total score, and the domain scores of Role Function-Preventive (RF-P) and Emotional Function (EF).

Pre-specified exploratory endpoints included assessments at month 3 and across the 3-month double-blind treatment period, as well as assessments of timing of onset of action and sustained response. Change from baseline to month 3 in the Patient Global Impression of Severity (PGI-S) was assessed. Endpoints assessed across the 3-month double-blind treatment period included: mean change from baseline in number of monthly moderate-to-severe headache days; mean change from baseline in number of monthly moderate-to-severe monthly migraine headache days; $\geq$ 50% reduction from baseline in monthly moderate-to-severe monthly migraine headache days; and mean change from baseline in the number of days with acute headache medication use. Onset of action and sustained response endpoints included: mean change from baseline in the number of weekly migraine headache days in the months that galcanezumab was superior to rimegepant; $\geq$ 50% reduction from baseline in monthly migraine headache days at month 3, month 2, and month 1; $\geq$ 50% reduction from baseline in weekly migraine headache days at weeks 4, 3, 2, and 1 in the months that galcanezumab was superior to rimegepant; and the initial month that galcanezumab was superior to rimegepant and the superiority was sustained at all subsequent months through month 3.

Safety analyses were conducted on all randomized participants who were exposed to the study intervention (either injection or ODT). Safety endpoints included treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), discontinuation reasons and rate, discontinuations due to an adverse event, vital signs, and laboratory measures.

Assessments

All efficacy assessments conducted during the study were self-reported by the participant. The ePRO daily diary was used to record headache occurrence, headache intensity (rated as a 1 = mild, 2 = moderate, or 3 = severe) and features, and if any acute headache medication was taken (yes/no). The details of acute medication use were reported separately in a headache medication log. A migraine headache day was defined as a calendar day on which a migraine or probable migraine headache occurred

[14, 16]. A migraine headache was defined as a headache lasting at least 30 min, with both features of A (at least two of the following: unilateral location, pulsatile quality, moderate or severe pain intensity, and aggravation by or causing avoidance of routine physical activity) and B (at least one of the following during headache: nausea and/or vomiting and/or photophobia and phonophobia) of the ICHD-3 criteria for [22]. A probable migraine headache was defined the same as a migraine headache but was missing one of the migraine features in the ICHD-3 criteria (e.g., either two A and zero B criteria or one A and at least one B criterion).

Other self-reported assessments were collected at baseline (prior to study intervention) and at month 3. The MSQ v2.1 assesses the emotional and physical impact of migraine on functioning over a 4-week recall period [23]. The MIDAS quantifies headache-related disability over a 3-month recall period and provides categorical grades of disability ranging from little or no disability (0 to 5) to mild (6 to 10), moderate (11 to 20), and severe (21 and above) disability [24]. The PGI-S was used to measure migraine illness severity [25].

Statistical methods

The primary estimand of interest was the overall mean monthly 50% response rate across the 3-month double-blind period under the treatment condition (galcanezumab or rimegepant), regardless of the initiation of new preventive migraine medication (protocol violation), the use of acute medication to treat a migraine headache, and the discontinuation of treatment for any reason. The population included participants who (1) met ICHD-3 criteria for a diagnosis of migraine with or without aura; (2) had an episodic frequency of 4 to 14 migraine headache days per month; and (3) fulfilled the inclusion and exclusion criteria of the study, with the variable (or endpoint) as the percentage of participants with a $\geq$ 50% reduction from baseline in monthly migraine headache days across the 3-month double-blind treatment period. All available monthly migraine headache data were included in the analysis provided that the baseline monthly migraine headache day values were available. Any migraine headache day data collected after study intervention discontinuation, but within the double-blind period (e.g., up to study disposition for the participant), were included in the analysis.

The number of migraine headache days for each period was adjusted for a 30-day period by multiplying the number of migraine headache days by $(30/x)$, where x is the total number of non-missing ePRO diary days in the period. This approach to missing ePRO diary data assumes that (1) the rate of migraine headaches per day is the same with missing and non-missing ePRO diary days and (2) it is missing at random. The same approach was applied to secondary and exploratory measures that were derived from the ePRO diary data. If the ePRO diary compliance rate for a monthly interval is $\leq$ 50%, then all endpoints derived from the ePRO diary data for that 1-month period were considered missing. For a participant who discontinued treatment early in the double-blind treatment phase, the compliance rate for the last month of that study period was calculated with the maximum denominator of 30 and the total number of calendar days in that month.

The primary efficacy analysis was performed for the full analysis set within the ITT population. The primary endpoint (50% responder) is a binary variable with repeated measures and was analyzed using a generalized linear mixed model (GLIMMIX) as a pseudo-likelihood-based mixed-effects repeated measures analysis. The GLIMMIX procedure included the fixed, categorical effects of treatment, month, and treatment-by-month interaction, as well as the baseline monthly migraine headache days value, which was treated as a continuous, fixed covariate. Binary distribution and logit link were used. An unstructured covariance structure was used to model the within-participant errors. The Newton–Raphson method with ridging was used for nonlinear optimization and the Kenward–Roger approximation was used to estimate denominator degrees of freedom [26].

The secondary efficacy analyses were performed for the full analysis set within the ITT population, and the estimand employed was

similar to the estimand used for the primary analysis. In other words, the estimand of interest was based on the overall mean monthly estimates across/within the double-blind period, based on all available data during that period (even if collected after study intervention discontinuation but prior to study disposition for the participant), and required that a baseline value was available.

The analysis of the key binary secondary endpoints (proportions of participants with $\geq$ 75% and 100% reductions from baseline in monthly migraine headache days across the 3-month double-blind treatment period) was performed using the GLIMMIX as a pseudo-likelihood-based mixed effects repeated-measures analysis, as was done for the primary endpoint. The continuous efficacy variables with repeated measures were analyzed using a restricted maximum likelihood (REML)-based mixed-models repeated measures (MMRM) technique and included the fixed, categorical effects of treatment, month, and treatment-by-month interaction as well as the continuous fixed covariates of baseline number of migraine headache days and baseline-by-month interaction. Further, for continuous efficacy variables without repeated measures, an analysis of covariance (ANCOVA) was conducted, which included the main effects of treatment and the continuous fixed covariate of baseline. Type III sum of squares for the least-squares mean (LSMean) was used for the statistical comparisons.

The statistical comparisons for the primary efficacy endpoint and the key secondary endpoints were carried out in hierarchical order (primary, then ranked key secondary variables). A step-down procedure was used to preserve the overall alpha level of 0.05, and each comparison was tested at a significance level of 0.05. In this manner, type I error due to multiple comparisons for the primary and key secondary objectives was controlled using a sequential gating procedure [27–29].

Sample size

The protocol included a sample size re-estimation approach. Study sites were blinded to the details. The planned enrollment was a minimum of 575 participants, with an opportunity to increase to a maximum of 850 based on a pre-defined sample size re-estimation which provided a power ranging between 71 and 85% for assumed effect sizes between 0.10 and 0.12 to detect a significant difference between rimegepant and galcanezumab at a one-sided $\alpha = 0.025$. Study sample size and power were calculated by leveraging R software (version 4.1.2) for simulated multiple collections of trials with monthly benefits in patient response of galcanezumab versus rimegepant of 8 to 12% (with an appropriate patient correlation of response between months). Monte Carlo estimates of study operating characteristics were calculated from these simulated trials.

One interim analysis was performed for sample size re-estimation. The interim analysis was conducted by an independent Statistical Analysis Center (SAC) external to the study team and internal to the sponsor. The interim analysis included 325 randomized participants who had received at least one dose and who contributed data for primary analysis; of these, 223 had the opportunity to complete the 3-month double-blind treatment period. Based on the pre-specified criteria, the SAC recommended that the sample size remain at 575.

RESULTS

Participant Disposition

A total of 1467 participants were screened, of whom 849 (57.9%) were screen failures and 38 were lost to follow-up prior to randomization. The remaining 580 participants were randomized to galcanezumab (n = 287) or rimegepant (n = 293). The primary reasons for screen failures were that participants did not meet the inclusion criteria for minimum migraine headache days and migraine attacks (17.2%) or failed to maintain > 80% ePRO diary compliance (9.5%) (Table S2 in the electronic supplementary material; inclusion #4 and #5, respectively). Overall, 90.9% of participants (527/580) completed the study; completion rates were nearly identical between groups (90.9% for galcanezumab and 90.8% for rimegepant). Of the

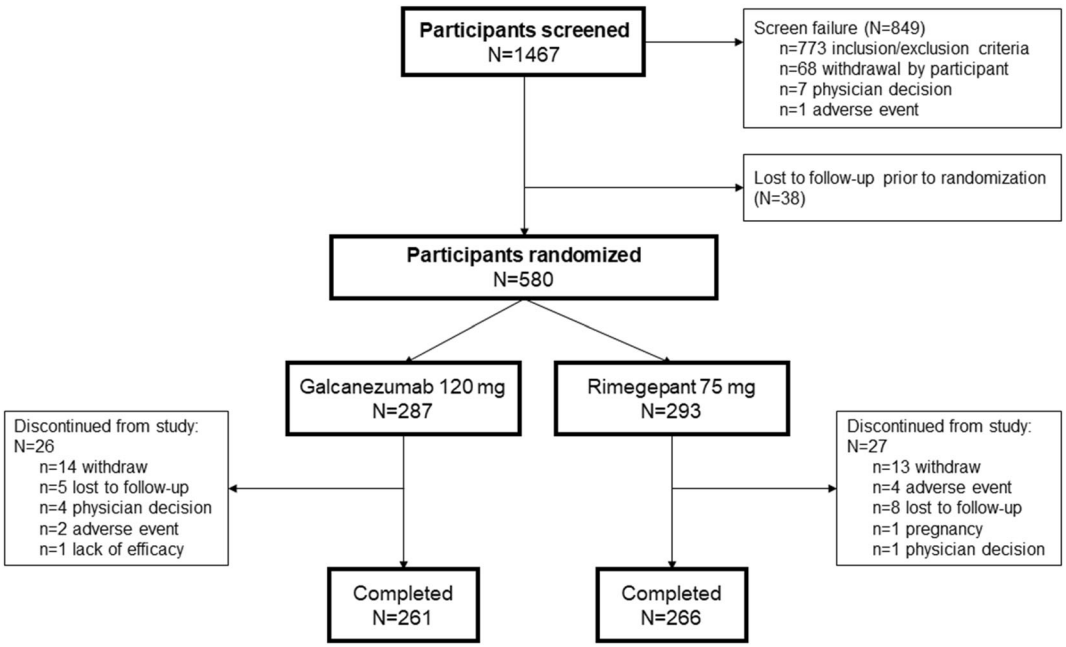

Fig. 2 Participant study disposition

9.1% of participants who discontinued early from the study, the primary reason was withdrawal by participant; 4.9% in the galcanezumab group and 4.4% in the rimegepant group. Overall, 6 (1.0%) participants discontinued the study due to an adverse event(s): 2 (0.7%) in the galcanezumab group and 4 (1.4%) in the rimegepant group. One additional participant randomized to rimegepant discontinued treatment early due to an adverse event, but this subject continued in the study, completing all study procedures. Discontinuations from study or treatment for any reason were balanced between the intervention groups. The study disposition of participants is illustrated in Fig. 2.

Across the double-blind period, the mean ePRO diary compliance was 89.4% in the galcanezumab group and 89.1% in the rimegepant group; there were no significant differences between groups ($P = 0.66$). Across the 3-month double-blind period, treatment compliance was 99.8% in the galcanezumab group and 100.8% in the rimegepant group (note: participants were dispensed additional ODT doses to cover the ± 2-day visit window; some participants took extra doses); there were no significant differences between groups ($P = 0.17$).

Baseline and clinical characteristics of the ITT population shown by study intervention group are summarized in Table 1. In the overall population, the mean (standard deviation [SD]) age of participants was 42.0 (12.0) years, and the majority were female (83.1%) and white (81.1%). The mean duration of migraine disease was 19.1 years, and the mean number of migraine headache days per month was 8.4 (2.9), similar to the median of 8.0. The participant population was primarily preventive treatment naïve (84.1%), with 86.4% in the galcanezumab group and 81.9% in the rimegepant group. Sixty-four (11.0%) participants had failed at least one previous preventive treatment: 25 (8.7%) in the galcanezumab group and 39 (13.3%) in the rimegepant group. Topiramate ($n = 30$), propranolol/metoprolol ($n = 10$), and amitriptyline/nortriptyline/imipramine ($n = 13$) were the most common previous preventive treatment failures; all other preventives were reported by four or fewer participants. Demographic and clinical characteristics were balanced between groups.

Table 1 Participant demographics and clinical characteristics at baseline

Category	Galcanezumab 120 mg *N* = 287	Rimegepant 75 mg *N* = 293	Total *N* = 580
Age, years, mean (SD)	41.7 (12.6)	42.3 (11.3)	42.0 (12.0)
Sex (female), *n* (%)	244 (85.0)	238 (81.2)	482 (83.1)
Race, *n* (%)			
White	236 (83.1)	232 (79.2)	468 (81.1)
Black	34 (12.0)	44 (15.0)	78 (13.5)
Asian	8 (2.8)	11 (3.8)	19 (3.3)
Other[a]	6 (2.1)	6 (2.0)	12 (2.1)
BMI, kg/m^2, mean (SD)	28.9 (5.8)	28.1 (5.2)	28.5 (5.5)
Ethnicity, non-Hispanic, *n* (%)	219 (76.3)	223 (76.1)	442 (76.2)
Disease characteristics			
Time since migraine diagnosis, years (SD)	19.3 (12.8)	18.8 (12.4)	19.1 (12.6)
Migraine headache day per month, mean (SD)	8.5 (2.9)	8.3 (2.9)	8.4 (2.9)
Frequency of migraine headache days per month, n (%)			
$<$ 8 days/month	128 (44.6)	136 (46.4)	264 (45.5)
$\geq$ 8 days/month	159 (55.4)	157 (53.6)	316 (54.5)
Moderate-to-severe headache days per month, mean (SD)	7.0 (2.7)	6.9 (2.9)	6.9 (2.8)
Migraine headache days with aura per month, mean (SD)	2.7 (3.3)	2.5 (3.0)	2.6 (3.1)
Number of headache days per month, mean (SD)	9.8 (3.6)	9.5 (3.4)	9.6 (3.5)
Migraine headache days with acute medication use per month, mean (SD)	6.1 (3.2)	6.3 (3.2)	6.2 (3.2)
Acute medication use days per month[b], mean (SD)	6.8 (4.0)	6.9 (3.7)	6.9 (3.8)
Prior migraine preventive treatments, *n* (%)			
No prior preventive treatment	248 (86.4)	240 (81.9)	488 (84.1)
Prior treatment and failed $\geq$ 1 medication	25 (8.7)	39 (13.3)	64 (11.0)
	n = 271[c]	*n* = 269[c]	*n* = 540[c]
MSQ RF-R, mean (SD)	49.3 (17.0)	48.8 (17.8)	49.1 (17.4)
MSQ RF-P, mean (SD)	64.8 (21.3)	63.9 (21.0)	64.4 (21.2)
MSQ RF-EF, mean (SD)	60.3 (24.1)	58.4 (25.6)	59.4 (24.9)

Table 1 continued

Category	Galcanezumab 120 mg *N* = 287	Rimegepant 75 mg *N* = 293	Total *N* = 580
MIDAS, mean (SD)	39.1 (32.3)	37.7 (30.4)	38.4 (31.4)
PGI-S, mean (SD)	4.2 (0.9)	4.2 (1.1)	4.2 (1.0)

All disease-related baseline data are from the headache diary data from the prospective baseline period with the exception of data for the time since migraine diagnosis, number of prior preventive migraine treatments collected at visit 1, and the baseline scores for the MSQ, MIDAS, PGI-S collected at visit 3 prior to dosing

MIDAS Migraine Disability Assessment, *MSQ-RF-EF* Migraine-Specific Quality of Life Questionnaire—Emotional Function, *MSQ-RF-P* Migraine-Specific Quality of Life Questionnaire—Role Function-Preventative, *MSQ-RF-R* Migraine-Specific Quality of Life Questionnaire—Role Function-Restrictive, *PGI-S* Patient Global Impression of Severity, *SD* standard deviation

[a]American Indian or Alaska native, native Hawaiian or other Pacific Islander, or multiple

[b]Regardless of any headache occurrence

[c]"*n*" denotes the number of participants with baseline and post-baseline assessments

Efficacy Outcomes

Table 2 summarizes the primary and key secondary outcomes. The primary objective was not met. The proportion of participants with at least a 50% reduction in monthly migraine headache days (≥ 50% response rate) from baseline across 3 months of the double-blind phase was 62.0% in the galcanezumab group and 61.0% in the rimegepant group, with no statistically significant difference between groups, odds ratio 1.1 (95% confidence intervals 0.8, 1.4; $P = 0.70$). The sensitivity analyses (data not shown) were consistent with the primary efficacy analysis.

In accordance with the pre-specified multiple testing procedure, the key secondary endpoints cannot be considered statistically significant. Shown in Table 2 are the key secondary endpoint outcomes, without multiplicity adjustment, along with the primary endpoint. The LSMean reduction from baseline (standard error [SE]) in monthly migraine headache days across 3 months for participants in the galcanezumab group was – 4.8 (0.2) and – 4.4 (0.2) for the rimegepant group. Reductions in monthly migraine headache days were observed at each month for both intervention groups: – 4.3 (0.2) at month 1 in the galcanezumab group versus – 3.8 (0.2) in the rimegepant group; at months 2 and 3, both study intervention groups showed a continued reduction in monthly migraine headache days, with the greatest reduction occurring at month 3 (– 5.1 [0.2] for galcanezumab and – 4.9 [0.2] for rimegepant). The number of monthly migraine headache days requiring acute medication use decreased across the double-blind treatment phase (galcanezumab group – 4.0 [0.1] versus rimegepant – 3.5 [0.1]). The MSQ-RF-R domain score improvement from baseline to month 3 was 31.9 points in the galcanezumab group compared to 26.7 points in the rimegepant group. The percentages of participants in the galcanezumab and rimegepant groups who achieved a 75% response were 37.0% and 33.0%, respectively, while 18.0% and 15.0%, respectively, achieved a 100% response.

Table 3 summarizes the additional secondary endpoints. Improvements in both study intervention groups were observed in the MSQ Total score (galcanezumab 28.9 and rimegepant 24.5), RF-P domain (galcanezumab 24.6 and rimegepant: 20.7), and the EF domain score (galcanezumab 27.8 and rimegepant: 24.6) from baseline to month 3. Similarly, the MIDAS total score improvement from baseline to month 3 was – 22.5 for galcanezumab and –20.1 for rimegepant. Exploratory endpoints are summarized in Table 4.

Table 2 Primary and key secondary outcomes

Endpoint	Treatment[a]	*N*	% response rate (SE)/ LSMean change from baseline (SE)	Odds ratio/LSMean change difference (95% CI)[b]
Primary endpoint: ≥ 50% response[c]	Galcanezumab	269	62.0 (2.0)	1.1 (0.8, 1.4)[d]
	Rimegepant	284	61.0 (2.0)	
Key secondary endpoints[e]				
Number of monthly migraine headache days[f]	Galcanezumab	269	− 4.8 (0.17)	− 0.4 (− 0.8, 0.1)
	Rimegepant	284	− 4.4 (0.16)	
≥ 75% response[c]	Galcanezumab	269	37.0 (2.0)	1.2 (0.9, 1.6)
	Rimegepant	284	33.0 (2.0)	
Number of monthly migraine headache days at month 3[g]	Galcanezumab	249	− 5.1 (0.2)	− 0.2 (− 0.7, 0.4)
	Rimegepant	259	− 4.9 (0.2)	
Number of monthly migraine headache days at month 2[g]	Galcanezumab	256	− 4.8 (0.2)	− 0.4 (− 0.9, 0.2)
	Rimegepant	268	− 4.4 (0.2)	
Number of monthly migraine headache days at month 1[g]	Galcanezumab	266	− 4.3 (0.2)	− 0.6 (− 1.1, 0)
	Rimegepant	275	− 3.8 (0.2)	
Number of monthly migraine headache days with acute medication use[f]	Galcanezumab	269	− 4.0 (0.1)	− 0.5 (− 0.9, − 0.1)
	Rimegepant	284	− 3.5 (0.1)	
MSQ-RF-R score at month 3[g]	Galcanezumab	271	31.9 (1.2)	5.2 (1.9, 8.6)
	Rimegepant	269	26.7 (1.2)	
100% response[c]	Galcanezumab	269	18.0 (2.0)	1.3 (0.9, 1.8)
	Rimegepant	284	15.0 (2.0)	

CI confidence interval, *LSMean* least squares mean, *MSQ-RF-R* Migraine-Specific Quality of Life Questionnaire—Role Function-Restrictive, *ODT* orally disintegrating tablet, *SC* subcutaneous, *SE* standard error

[a]Participants in the galcanezumab group received galcanezumab 120 mg and placebo ODT; participants in the rimegepant group received 75 mg rimegepant and SC placebo injection

[b]Odds ratio is provided for response measures. For the other measures, the LSMean change difference is provided

[c]Proportions of participants with the percentage reduction in monthly migraine headache days from baseline across the 3-month double-blind period

[d]$P = 0.70$

[e]Outcomes presented in order of pre-defined multiple testing procedure

[f]LSMean change from baseline across the 3-month double-blind period

[g]LSMean change from baseline to specified timepoint

Table 3 Additional secondary outcomes

Endpoint	Treatment[a]	*N*	% response rate (SE)/LSMean change from baseline (SE)	LSMean change difference (95% CI)
Additional secondary endpoints[b]				
MSQ Total score	Galcanezumab	271	28.92 (1.07)	4.39 (1.42, 7.37)
	Rimegepant	269	24.53 (1.07)	
MSQ-RF-P	Galcanezumab	271	24.62 (1.02)	3.88 (1.06, 6.71)
	Rimegepant	269	20.74 (1.02)	
MSQ-EF	Galcanezumab	271	27.76 (1.17)	3.18 (−0.08, 6.44)
	Rimegepant	269	24.58 (1.17)	
MIDAS Total score	Galcanezumab	271	-22.54 (1.63)	−2.43 (−6.94, 2.08)
	Rimegepant	269	-20.11 (1.63)	

CI confidence interval, *LSMean* least squares mean, *MIDAS* Migraine Disability Assessment, *MSQ-EF* Migraine-Specific Quality of Life (v2.1)-Questionnaire—Emotional Function, *MSQ-RF-P* Migraine-Specific Quality of Life Questionnaire (v2.1)—Role Function-Preventive, *ODT* orally disintegrating tablet, *SC* subcutaneous, *SE* standard error

[a]Participants in the galcanezumab group received galcanezumab 120 mg and placebo ODT; participants in the rimegepant group received 75 mg rimegepant and SC placebo injection

[b]LSMean change from baseline to month 3

Safety

The mean exposure duration during the double-blind period was 85.8 (14.6) days (67.4 person years) for galcanezumab and 87.9 (12.0) days (64.0 person years) for rimegepant. No deaths were reported in either study intervention group. No SAEs occurred in the galcanezumab group. One SAE, in the rimegepant group, was a pulmonary embolism in a participant who had a history of pulmonary embolism that was undisclosed at baseline. The participant recovered from the event and discontinued the study. The event was considered by the investigator to be related to the blinded study intervention. A pregnancy was reported for one participant in the rimegepant group, which led to discontinuation from the study.

Six participants (1.0%) discontinued the study due to an adverse event: 2 (0.7%) in the galcanezumab group for reasons of a depressed level of consciousness and injection site pain and 4 (1.4%) in the rimegepant group for reasons of fatigue, migraine, pulmonary embolism, and somnolence. Of the six events, two were rated as severe (pulmonary embolism and injection site pain), one was rated as moderate (fatigue), and the remaining were rated as mild intensity. All events were noted as resolved. One additional participant in the rimegepant group discontinued treatment due to nausea but remained in the study to completion.

The number of participants who reported at least one TEAE was equal for the galcanezumab (60; 20.9%) and rimegepant (60; 20.5%) groups (Table 5). The most common TEAE overall (in at least 3%) was COVID-19, which was not significantly different between study intervention groups. To assess if there was a difference in respiratory infections or other infections, the system organ classes of "Infections and Infestations" and "Respiratory, Thoracic and Mediastinal Disorders" were further inspected to look for differences between groups; there were also no statistically significant differences between groups. Of note, one participant discontinued

Table 4 Exploratory outcomes

Endpoint	Treatment[a]	*N*	% response rate (SE)/ LSMean change from baseline (SE)	Odds ratio/LSMean change difference (95% CI)[b]
PGI-S at month 3	Galcanezumab	271	– 0.7 (0.1)	– 0.2 (– 0.4, 0.0)
	Rimegepant	269	– 0.5 (0.1)	
Endpoints assessed across the 3-month double-blind treatment period				
Number of monthly moderate-to-severe headache days[c]	Galcanezumab	269	– 4.2 (0.1)	– 0.4 (– 0.8, 0.0)
	Rimegepant	284	– 3.8 (0.1)	
Number of moderate-to-severe monthly migraine headache days[c]	Galcanezumab	269	– 4.2 (0.1)	– 0.4 (– 0.8, 0.0)
	Rimegepant	284	– 3.9 (0.1)	
≥ 50% response in moderate-to-severe monthly migraine headache days[d]	Galcanezumab	269	68.0 (2.0)	1.2 (0.9, 1.5)
	Rimegepant	284	65.0 (2.0)	
Number of days with acute medication use[c]	Galcanezumab	269	– 4.0 (0.2)	– 0.5 (– 0.9, 0.0)
	Rimegepant	284	– 3.6 (0.2)	
Onset of action and sustained response endpoints				
≥ 50% response in monthly migraine headache days at month 3[e]	Galcanezumab	249	66.0 (3.0)	0.9 (0.6, 1.3)
	Rimegepant	259	69.0 (3.0)	
≥ 50% response in monthly migraine headache days at month 2[e]	Galcanezumab	256	63.0 (3.0)	1.0 (0.7, 1.5)
	Rimegepant	268	63.0 (3.0)	
≥ 50% response in monthly migraine headache days at month 1[e]	Galcanezumab	266	56.0 (3.0)	1.3 (0.9, 1.8)
	Rimegepant	275	50.0 (3.0)	
Number of weekly migraine headache days in the months that galcanezumab was superior to rimegepant[f]			ND	ND
≥ 50% response in weekly migraine headache days at weeks 4, 3, 2, 1 in the months that galcanezumab was superior to rimegepant[f]			ND	ND

Table 4 continued

Endpoint	Treatment[a]	*N*	% response rate (SE)/ LSMean change from baseline (SE)	Odds ratio/LSMean change difference (95% CI)[b]
The initial month that galcanezumab was superior to rimegepant in the percentage of participants meeting ≥ 50% response in monthly migraine headache days and the superiority was sustained at all subsequent months through month 3[g]			ND	ND

CI confidence interval, *LSMean* least squares mean, *ND* analysis not performed, *PGI-S* Patient Global Impression of Severity, *ODT* orally disintegrating tablet, *SC* subcutaneous, *SE* standard error

[a]Participants in the galcanezumab group received galcanezumab 120 mg and placebo ODT; participants in the rimegepant group received 75 mg rimegepant and SC placebo injection

[b]The odds ratio is provided for response measures. For the other measures, the LSMean change difference is provided

[c]LSMean change from baseline across the 3-month double-blind period

[d]Proportions of participants with the percentage reduction from baseline across the 3-month double-blind period

[e]Proportions of participants with the percentage reduction from baseline to the specified timepoint

[f]Per the pre-specified analysis plan, the analysis was not performed, as galcanezumab was not superior to rimegepant at any month

[g]Per the pre-specified analysis plan, the analysis was not performed, as galcanezumab was not superior to rimegepant at month 1

treatment due to nausea but elected to remain in the study to completion. Nausea was reported in 7 (1.2%) participants: 3 (1.0%) in the galcanezumab group and 4 (1.4%) in the rimegepant group. All reports of nausea indicated mild or moderate nausea; there was no report of severe nausea. The TEAE of migraine occurred in 4 (1.4%) participants in the rimegepant group only and was reported as "worsening of migraine" (n = 3) or "severe migraine" (n = 1). Injection-site TEAEs were reported by a total of 12 (2.1%) participants: 7 (2.4%) in the galcanezumab group and 5 (1.7%) in the rimegepant group. All other TEAEs occurred in ≤ 1.0% of the overall study population.

There were no clinically meaningful differences between study intervention groups in vital signs or laboratory parameters. No participant experienced clinically meaningful liver enzyme elevations (defined as ≥ 3 times the upper limit of normal [ULN] of alanine transaminase or aspartate aminotransferase, ≥ 2 times ULN of alkaline phosphatase, or ≥ 2 times ULN of total bilirubin).

DISCUSSION

This 3-month, phase 4 study was the first randomized, double-blind, double-dummy head-to-head study of two CGRP antagonists, galcanezumab and rimegepant, for the prevention of episodic migraine. Just over 60% of the participants in each study intervention group achieved a ≥ 50% response rate across the 3-month double-blind treatment period; however, the study did not meet the primary objective of galcanezumab: to demonstrate statistically significant superiority over rimegepant in this outcome. The ≥ 50% response rate for the galcanezumab group is consistent with prior phase 3 galcanezumab studies (EVOLVE-1 and EVOLVE-2) in the prevention of episodic migraine [14, 16]; whereas the ≥ 50% response rate for the rimegepant group for monthly migraine headache days (61%) and moderate-to-severe monthly migraine headache days (68%) is higher than the 49% response rate previously reported for rimegepant in moderate-to-severe migraine days [19]. One key

Table 5 Serious adverse events and treatment-emergent adverse events

Variable, *n* (%)	Galcanezumab[a] 120 mg, *N* = 287	Rimegepant[b] 75 mg, *N* = 293
Serious adverse events	0	1 (0.3)
Participants with ≥ 1 TEAE	60 (20.9)	60 (20.5)
Discontinuation from study due to an AE	2 (0.7)	4 (1.4)
TEAEs occurring in three or more participants (overall)		
COVID-19	12 (4.2)	5 (1.7)
Nausea	3 (1.0)	4 (1.4)
Fatigue	2 (0.7)	4 (1.4)
Injection-site pain	2 (0.7)	4 (1.4)
Nasopharyngitis	1 (0.3)	5 (1.7)
Influenza	3 (1.0)	2 (0.7)
Anemia	3 (1.0)	1 (0.3)
Migraine	0	4 (1.4)
Sinusitis	1 (0.3)	3 (1.0)
Constipation	3 (1.0)	0
Diarrhea	2 (0.7)	1 (0.3)
Hypertension	1 (0.3)	2 (0.7)
Upper respiratory tract infection	1 (0.3)	2 (0.7)
Vertigo	2 (0.7)	1 (0.3)

AE adverse event, *COVID* coronary virus disease, *ODT* orally disintegrating tablet, *SC* subcutaneous, *TEAE* treatment-emergent adverse event

[a]Participants received galcanezumab 120 mg and placebo ODT

[b]Participants received 75 mg rimegepant and SC placebo injection

difference is that, in the present study, all participants received SC injections and ODT, whereas in the prior rimegepant study, participants only received ODT. More invasive therapies, such as injections, are reported to have a higher placebo response than oral medications [30].

Another important consideration for the study result, with a substantial lesson for future trial design in studies of migraine preventives, is the proportion of the study population who were preventive naïve. While the study was not designed specifically to enrich for preventive-treatment-naïve participants, most of the participants (84%) in this study were preventive treatment naïve, with 11% having failed at least one prior migraine preventive. This contrasts with the head-to-head study of erenumab versus topiramate, where approximately 25% fewer participants were preventive treatment naïve and 31% reported a prior migraine preventive treatment failure, specifically with propranolol/metoprolol, amitriptyline, or flunarizine [3]. It is conceivable that the percentage of participants who had failed a prior preventive in that study would have been higher if all preventives

had been considered, as was done in this study. It has been shown in both episodic [31] and chronic [32] migraine studies of erenumab versus placebo that participants who have never failed a preventive include a threefold-higher percentage of participants with a ≥ 50% reduction in migraine days in the placebo arm when compared to those who have failed one to two preventives. In comparing the placebo responses in the phase 3 studies of galcanezumab [14, 16] and the study of galcanezumab in participants who had failed two to four previous preventives [17], there is a threefold inflation of the placebo response rate in the phase 3 studies where the majority of participants had not failed a prior preventive. Given that phase 3 studies with both CGRP mAbs [33–35] and gepants [36, 37] are consistent with a ceiling effect of about 60%, inflating the floor (placebo responses) confounds the optimal study design when comparing active treatments. Taken together—data from the current study, along with these observations on placebo response in migraine clinical trials—comparing groups with a history of previous preventive treatment failures, for example 2 to 4, may be a better method for detecting any potential differences between active treatments that are associated with response rates approaching the potential ceiling of 60%. Although such a design would not provide information on the comparative effectiveness of medications when used for first-line or second-line treatment, the design would be completely consistent with the principle of exploring unmet need amongst a patient population who have demonstrated treatment refractoriness.

Participants in this study at baseline had an average of 8.4 migraine headache days per month, with 54% of participants having ≥ 8 migraine headache days per month at baseline. Participants reported considerable functional impairment and severe disability at baseline, as shown by the MSQ Total (55.7) and MIDAS (38.4) scores. Conversely, in the EVOLVE-1 and EVOLVE-2 studies, participants reported a higher baseline frequency (9.1) of monthly migraine headache days [38], and a higher percentage (63%) of participants were in the ≥ 8 monthly migraine headache days stratum [39]. This difference in migraine burden may be attributed to the predominant use, in the present study, of primary care investigative sites and a lower percentage of secondary care sites that typically see more severely impacted patients. Additionally, in this study, insurance coverage was not required, and some study sites recruited primarily from an underserved and/or uninsured population.

The mean number of monthly migraine headache days was reduced by half for both study intervention groups across the 3 months of double-blind treatment. The reduction in the galcanezumab group was similar to the reduction reported across 6 months of double-blind treatment in EVOLVE-1 and EVOLVE-2 [14, 16]. However, the reduction in the rimegepant group in this study was greater than that observed in the previous rimegepant prevention study when assessed in the last month of treatment and across 3 months of double-blind treatment [19].

Across the remaining key secondary, other secondary, and exploratory outcomes, both study intervention groups demonstrated substantial within-group improvements, demonstrating the efficacy of both galcanezumab and rimegepant.

In the present study, there were no new safety findings for the galcanezumab group. The safety and tolerability profiles of galcanezumab were consistent with those previously reported [14–16]. Treatment-emergent adverse events related to the injection site have been identified as the most common adverse reaction for galcanezumab [40]. In this study, the frequency of injection site reactions was similar between the galcanezumab and the placebo injection received in the rimegepant group; and furthermore, the frequency was lower than previously reported [14–16]. One event of injection site reaction in the galcanezumab group was rated as severe and led to discontinuation. Likewise, the TEAE of nausea, most commonly reported with rimegepant [41], was similar between treatment interventions and was of mild or moderate severity. Migraine was reported as an adverse event in four participants in the rimegepant group only, and rated as “worsening of migraine” or “severe migraine.”

An interesting outcome was that the frequency of TEAEs in both study intervention groups was lower than previously reported [14–16, 19]. This observation may be related to participants being less likely to report adverse events during the telephone visits compared to in-person office visits. Another possibility is that participants knew they were taking a medication with marketing approval, even though the sponsor recruitment materials and informed consent documents did not mention the brand/trade name of either galcanezumab or rimegepant and did not refer to either study intervention having marketing approval.

The high rates of study completion (90%) and low rates of discontinuation due to AEs (< 1%) for the galcanezumab-treated participants suggest that galcanezumab was well tolerated and that the dosing regimen did not appear to deter participation in the study. Further, these results were consistent with previous findings in the episodic migraine studies. There were no clinically meaningful differences between the study intervention groups with respect to changes in laboratory parameters or vital signs.

LIMITATIONS

This study was rigorously designed, but the results are still limited by several factors. The screen failure rate in this study was 58%. While some may consider this high, the rate was within the range of screen failure rates (36% to 71%) reported in the phase 3 episodic migraine prevention studies evaluating CGRP antagonists [15, 16, 21, 33, 34, 37]. Another factor is that the placebo response likely remained despite the complexity of constructing the double-dummy blind as participants were aware they would receive an active treatment.

The study included several exclusion criteria that may have inadvertently limited the results. Prior or current CGRP use for any indication was excluded to mitigate bias resulting from anticipation of effect. For example, if the participant had previously responded to their CGRP treatment, they might have remembered the time to onset, the level of efficacy, and the side effects experienced. Conversely, if a participant previously did not respond to a particular CGRP treatment, they may have anticipated the lack of efficacy and side effects based on their previous experience. The concurrent use of other preventive migraine therapies was not permitted, as the study was specifically designed as a head-to-head comparison study and limits the generalizability to patients taking more than one preventive medication. As noted earlier, the study was not intentionally designed to enrich for treatment-naïve participants. However, the availability of multiple approved preventive treatments, including the two study interventions, likely led to enrichment for the preventive-naïve population and thereby limited the extrapolation of these results to the preventive-experienced population. Further limiting the generalizability was the diversity of patients of various geographies, as enrollment was restricted to the United States.

CONCLUSIONS

This head-to-head study of galcanezumab and rimegepant (CGRP antagonists) demonstrated that both treatments were efficacious in participants with episodic migraine. In participants treated with galcanezumab, no new safety findings were observed. While the TEAE frequency was lower for both treatments than previously reported, the types of events for galcanezumab were consistent with previous galcanezumab studies.

ACKNOWLEDGEMENTS

Eli Lilly and Company would like to thank the clinical trial participants and their caregivers, without whom this work would not be possible. The authors thank Dustin Ruff (Eli Lilly and Company, Indianapolis, IN) for his statistical contribution and review of the manuscript, and Millie Hollandbeck (Synchrogenix, Wilmington, DE) for medical writing support.

Medical Writing/Editorial Assistance Medical writing support was provided by Millie Hollandbeck (Synchrogenix, Wilmington, DE) and editorial support was provided by Synchrogenix (Wilmington, DE); both were funded by Eli Lilly and Company, Indianapolis, IN, USA.

Author Contributions. Tina M. Myers Oakes, James M. Martinez, Bert B. Vargas, Hitendra Pandey, Eric M. Pearlman, Diane R. Richardson, Oralee J. Varnado, and Michael Cobas Meyer contributed to the study conception and design. Statistical analysis was performed by Hitendra Pandey. The first draft of the manuscript was written by Tina M. Myers Oakes, and all authors (Todd J. Schwedt, Tina M. Myers Oakes, James M. Martinez, Bert B. Vargas, Hitendra Pandey, Eric M. Pearlman, Diane R. Richardson, Oralee J. Varnado, Michael Cobas Meyer, and Peter J. Goadsby) commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding. This study and the journal fee were funded by Eli Lilly and Company, Indianapolis, IN, USA.

Data Availability. Lilly makes patient-level data available from Lilly-sponsored studies on marketed drugs for approved uses following acceptance for publication. Lilly provides this access through the Vivli Center for Global Clinical Research Data website (https://vivli.org/). Qualified researchers can submit research proposals and request anonymized data to test new hypotheses. Lilly's data-sharing policies are provided on Vivli's Members page (https://vivli.org/ourmember/lilly/).

Declarations

Conflict of Interest. Todd Schwedt has received compensation for *consulting* for Abbvie, Allergan, Axsome, Collegium, Eli Lilly, Linpharma, Lundbeck, Satsuma, and Theranica; *research funding* from Amgen, Mayo Clinic, National Institutes of Health, Patient Centered Outcomes Research Institute, SPARK Neuro, and the United States Department of Defense; *stock options* in Aural Analytics and Nocira; and is on the *board of directors* for the American Headache Society and the American Migraine Foundation. Peter Goadsby reports, over the last 36 months, a *grant* from Celgene; *personal fees* from Aeon Biopharma, Abbvie, Amgen, CoolTech LLC, Dr Reddys, Eli Lilly and Company, Epalex, Lundbeck, Novartis, Pfizer, Praxis, Sanofi, Satsuma, Shiratronics, Teva Pharmaceuticals, and Tremeau; *personal fees for advice* through Gerson Lehrman Group, Guidepoint, SAI Med Partners, and Vector Metric; *fees for educational materials* from CME Outfitters; *publishing royalties or fees* from Massachusetts Medical Society, Oxford University Press, UptoDate, and Wolters Kluwer; and a *patent* for magnetic stimulation for headache (no. WO2016090333 A1) assigned to eNeura without fee. James Martinez, Michael Cobas Meyer, Tina Myers Oakes, Hitendra Pandey, Eric Pearlman, Diane Richardson, Bert Vargas, and Oralee Varnado are employees of Eli Lilly and Company, Indianapolis, IN, USA.

Ethical Approval. The study was approved by all institutions and the Advara, Inc. Institutional Review Board (Columbia, MD) utilized by all investigative sites that participated in the study (Table S2 in the electronic supplementary material). The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All participants provided informed consent to participate in the study.

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