

Galcanezumab in migraine prevention: a systematic review and meta-analysis of randomized controlled trials

Panagiotis Gklinos^{ID} and Dimos D. Mitsikostas

Ther Adv Neurol Disord

2020, Vol. 13: 1–11

DOI: 10.1177/
1756286420918088

© The Author(s), 2020.
Article reuse guidelines:
sagepub.com/journals-
permissions

Abstract

Background: Galcanezumab, along with three other monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) pathway, represents the latest disease-specific and mechanism-based treatment for the prophylaxis of migraine. Galcanezumab shares data also for the prophylaxis of cluster headache.

Objective: To provide a pooled safety and efficacy analysis of all phase III randomized controlled trials of galcanezumab in the preventive therapy of migraine.

Methods: A computer-based literature search was conducted on MEDLINE and the US National Institutes of Health Clinical Trials Registry for phase III randomized controlled trials of galcanezumab in migraine prevention. The primary outcome was the mean change in monthly migraine days (MMDs). The proportions of patients who reported at least one adverse event (AE), at least one serious adverse event (SAE) or withdrew from the study were used as safety outcomes.

Results: Two trials were included in the efficacy meta-analysis and three in the safety meta-analysis. Migraine preventive treatment with subcutaneous galcanezumab, at both 120 mg and 240 mg dosages, was associated with a significantly greater reduction in the mean number of MMDs *versus* placebo (120 mg, MD = -1.98, 95% CI = -2.33 to -1.63; $p < 0.0001$) or (240 mg, MD = -1.86, 95% CI = -2.20 to -1.53; $p < 0.0001$). Galcanezumab was found to be more efficacious in all key secondary outcomes as well. Regarding safety, most of the adverse events were mild to moderate, while drop-out rates and serious adverse events were low.

Conclusions: Galcanezumab is an efficacious and well-tolerated preventive treatment for migraine. Larger clinical trials with longer follow-up periods need to be conducted in order to provide more safety data of the above-mentioned drug.

Keywords: CGRP, galcanezumab, meta-analysis, migraine, monoclonal antibodies, preventive therapy

Received: 10 December 2019; revised manuscript accepted: 19 March 2020.

Introduction

Migraine is found to be the second leading cause of years lived with disability (YLDs) with an enormous economic burden.^{1,2} Yet, no disease-specific, nor mechanism-based prophylactic treatment was available until the recent development of four monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) pathway. CGRP is a proinflammatory and vasodilating neuropeptide involved in peripheral and central sensitization,³

with adequate documentation regarding its involvement in migraine pathophysiology. It remarkably increases during migraine attacks,⁴ while intravenous infusion of CGRP induces migraine-like attacks in migraine patients.⁵

Galcanezumab is a fully humanized monoclonal antibody, targeting the CGRP ligand, studied and developed for migraine prophylaxis. In addition, it is the only one among the four monoclonal

Correspondence to:
Dimos D. Mitsikostas
First Neurology
Department, Aeginition
Hospital, Medical School,
National and Kapodistrian
University of Athens, 74
V. Sofia's Avenue, Athens
11528, Greece
dmitsikostas@med.uoa.gr
Panagiotis Gklinos
Neurology Department,
KAT General Hospital,
Athens, Greece

antibodies targeting the CGRP pathway that exerts efficacy in the prevention of cluster headache as well,⁶ thus attracting even more interest. A number of studies and reviews have been published so far, but none of them is reliable due to poor inclusion criteria. In some cases, phase II trials in which galcanezumab was tested in different doses and most importantly in different treatment periods were included. Consequently, that led to high inconsistency across trials and has probably biased the final outcome. The purpose of this systematic review and meta-analysis is to assess the efficacy of galcanezumab in the pooled phase III data of the randomized trials for episodic migraine prophylaxis and its safety in the pooled phase III data of the randomized trials for episodic or chronic migraine prophylaxis. A separate meta-analysis of galcanezumab efficacy in chronic migraine as well as its efficacy and safety in cluster headache prophylaxis should be performed, when a greater number of phase III trials will be published.

Methods

Search strategy

A computer-based literature search was conducted on MEDLINE (accessed by PubMed) and the US National Institutes of Health Clinical Trials Registry (<http://www.clinicaltrials.gov>) using ‘migraine’, ‘treatment’ and ‘placebo’ as key words and electronic publication date from 1 January 2010 to 1 September 2019, randomized controlled trials and English language as limitations. The search followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.⁷

Eligibility criteria

The following inclusion criteria were applied to the 220 articles retrieved by the search. Studies were eligible if they were randomized, double-blinded, placebo controlled, parallel group, phase III studies with active and control groups receiving galcanezumab and matched placebo, respectively. Phase II studies were not included, because they tested different dosages of the drug for different treatment periods, thus they could not be synthesized in the meta-analysis. Participants had to meet the following criteria: any sex, any ethnicity, age (≥ 18 years), history of episodic migraine for the efficacy meta-analysis and history of episodic or chronic migraine for the safety meta-analysis, with

or without aura, according to the criteria of the International Headache Society.^{8,9}

Quality assessment

The Jadad scale was used to assess the quality of the included studies. The Jadad scale scores three parameters: randomization, blindness (of the patients, caregivers, investigators) and adequate documentation of withdrawals and drop-outs, and is considered to be the most reliable.^{10,11}

Outcome measures safety: tolerability

The primary outcome was the overall mean change from baseline in the number of monthly migraine days (MMDs) during the 6-month treatment phase. The key secondary outcome measures were the following: the mean proportion of patients with reduction from baseline of 50%, 75%, and 100% in MMDs during the 6-month double-blind treatment phase; the mean change from baseline in the Role Function–Restrictive (RF-R) domain score of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1),¹² as an average of months 4–6; the overall mean change from baseline in the number of monthly acute migraine-specific medication days (MSMDs) during the 6-month double-blind treatment phase; and the mean change from baseline in the Patient Global Impression of Severity (PGI-S) rating (average of months 4–6).¹³ The safety and tolerability outcomes included the proportion of participants who experienced any adverse event (AE), any serious adverse event (SAE) and who withdrew from treatment for AEs.

Study selection, data extraction, and assessment of the risk of bias

Trials were assessed for inclusion and the following data were extracted from the included studies: main study author; age of publication; methodology and trial design (methods of randomization, allocation concealment and blinding, duration of baseline and treatment periods, dose/s of galcanezumab tested); number, demographics, and clinical characteristics of participants (age, sex, ethnic origin, age at migraine onset, disease duration, previous preventive history, MMDs, and monthly acute MSMDs during the baseline phase); number of participants experiencing each outcome; and changes in baseline frequency for each endpoint per randomized group. In the

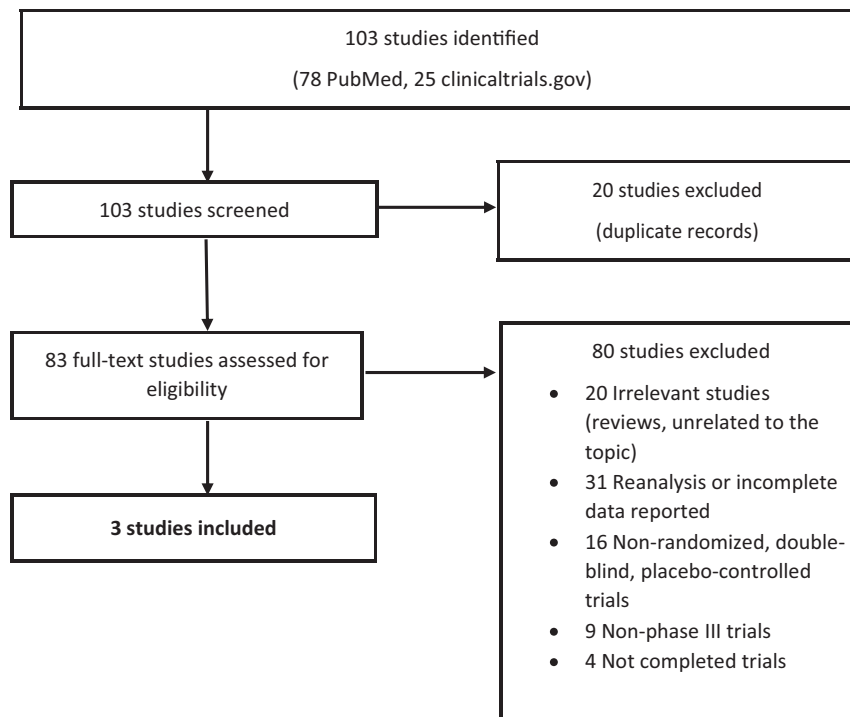


Figure 1. Article selection flow diagram.

current systematic review and meta-analysis only data for the dosages of 120 mg and 240 mg were considered.

Statistical analysis

Meta-analysis was carried out using the StatsDirect statistical software (www.statsdirect.com). The heterogeneity within trials was tested by Cochran's Q-test based on inverse variance weights.¹⁴ The I^2 statistic was also used to quantify the extent of inconsistency in outcomes across studies. Provided no significant heterogeneity was present ($p > 0.05$), results were synthesized using a fixed effect model; if the probability value was ≤ 0.05 , heterogeneity determined the choice of a fixed or random effects model for $I^2 < 40\%$ or $\geq 40\%$, respectively.^{15,16} The mean difference (MD) and risk ratio (RR) with their 95% confidence intervals (CIs) were the measures of associations between treatment and continuous/dichotomous outcomes.

Results

Literature search and study characteristics

The results of our search are summarized in Figure 1. After repeated filtering, from the 220

articles retrieved, only two were included in the efficacy meta-analysis (two studies for episodic migraine – see Appendix 1) and three studies were included in the safety meta-analysis (two studies for episodic migraine and one study for chronic migraine – see Appendix 1). These studies published in 2018 involved 2886 patients, 1434 of whom were treated with galcanezumab (722 with 120 mg and 712 with 240 mg) and 1452 with placebo. Baseline patient demographics and disease characteristics for both active and placebo-treated groups are summarized in Table 1.

Monthly migraine days and monthly acute migraine-specific medication days

The reduction in baseline monthly migraine days (MMDs) was significantly greater among patients treated with galcanezumab at either the monthly dose of 120 mg [Mean difference (MD): -1.95 (95% CI = -2.34 to -1.56), $p < 0.0001$] or 240 mg [MD: -1.85 (95% CI = -2.22 to -1.48), $p < 0.0001$] than with placebo (Figure 2A, B). Both dosing regimens of galcanezumab were superior to placebo in the reduction of monthly acute migraine specific medication days (MSMDs) [galcanezumab 120 mg: MD: -1.80 (95% CI = -2.15 to -1.45), $p < 0.0001$; galcanezumab

Table 1. Patient demographics and baseline disease characteristics of studies included in the meta-analysis.

	EVOLVE-1			EVOLVE-2			REGAIN		
Demographics	Placebo	120 mg	240 mg	Placebo	120 mg	240 mg	Placebo	120 mg	240 mg
Patient number (n)	433	213	212	461	231	223	558	278	277
Age mean, (SD)	41.3 (11.4)	40.9 (11.9)	39.1 (11.5)	42.3 (11.3)	40.9 (11.2)	41.9 (10.8)	41.6 (12.1)	39.7 (11.9)	41.1 (12.4)
Female n, (%)	362 (83.6)	181 (85.0)	175 (82.6)	393 (85.3)	197 (85.3)	191 (85.7)	483 (87)	237 (85)	226 (82)
White race n, (%)	356 (82.2)	169 (79.3)	165 (77.8)	325 (70.5)	166 (71.9)	152 (68.2)	432 (77)	223 (80)	224 (81)
Disease characteristics	///	///	///	///	///	///	///	///	///
Disease duration, mean (SD)	19.9 (12.3)	21.1 (13)	19.3 (11.9)	21.2 (12.8)	19.93 (11.7)	20.01 (12.1)	21.9 (12.9)	20.4 (12.7)	20.1 (12.7)
MMDs, mean (SD)	9.1 (3.0)	9.2 (3.1)	9.1 (2.9)	9.2 (3.0)	9.07 (2.9)	9.06 (2.9)	19.6 (4.6)	19.4 (4.3)	19.2 (4.6)
Monthly acute MSMDs	7.4 (3.5)	7.4 (3.7)	7.3 (3.3)	7.6 (3.4)	7.47 (3.3)	7.47 (3.3)	15.5 (6.6)	15.1 (6.3)	14.5 (6.3)
Prior preventive treatment, n (%)	257 (59.4)	133 (62.4)	125 (59.0)	298 (64.6)	157 (68.0)	151 (64.6)	435 (78.0)	211 (76.0)	220 (79.0)
MSQ RF-R score, mean (SD)	52.9 (15.4)	51.4 (16.2)	48.8 (16.8)	51.4 (15.7)	52.5 (14.8)	51.7 (16.3)	38.4 (17.2)	39.3 (17.3)	38.9 (17.3)
PGI-S, mean (SD)	4.2 (1.1)	4.4 (1.1)	4.5 (1.1)	4.3 (1.2)	4.1 (1.2)	4.2 (1.2)	4.9 (1.2)	4.8 (1.2)	4.9 (1.3)
MIDAS total score, mean (SD)	31.8 (27.3)	32.9 (28.2)	36.1 (27.8)	34.3 (31.0)	30.9 (27.9)	32.8 (28.8)	68.7 (57.4)	62.5 (49.5)	69.2 (64.1)

MIDAS, Migraine Disability Assessment; MMDs, monthly migraine days; MSMDs, migraine-specific medication days; MSQ, Migraine-Specific Quality of Life Questionnaire version 2.1; PGI-S, Patient Global Impression-Severity of Illness; RF-R, Role Function-Restrictive.

240 mg: MD: -1.70 (95% CI = -2.05 to -1.35), $p < 0.0001$] (Figure 3A, B).

Other key secondary outcomes

Galcanzumab treated patients were more likely to achieve at least 50% reduction in baseline MMDs either at the dose of 120 mg [RR: 1.55 (95% CI = 1.39–1.73) $p < 0.0001$ or 240 mg RR: 1.50 (95% CI = 1.34–1.68) $p < 0.0001$] (Table 2A). Also, patients treated with galcanzumab were more likely to have at least 75% reduction in baseline MMDs in both dose regimens [(120 mg RR: 1.89 (95% CI = 1.57–2.27) $p < 0.0001$, 240 mg RR: 1.91 (95% CI = 1.59–2.30) $p < 0.0001$] (Table 2B). Furthermore, galcanzumab-treated patients were more likely to achieve a 100% reduction in MMDs than placebo-treated patients [120 mg RR: 2.28 (95% CI = 1.60–3.23) $p < 0.0001$, 240 mg RR: 2.37 (95% CI = 1.67–3.36) $p < 0.0001$] (Table 3C). Galcanzumab treatment significantly improved MSQ RF-R scores compared to placebo

during treatment [120 mg MD: 8.26 (95% CI = 6.48–10.05), $p < 0.0001$ and 240 mg MD: 7.35 (95% CI = 5.53–9.17), $p < 0.0001$]. Both galcanzumab groups showed a greater improvement in patients' global impression of severity of their disease as assessed by PGI-S rating than placebo [120 mg MD: -0.30 (95% CI = -0.44 to -0.16) $p < 0.0001$ and 240 mg MD: -0.24 (95% CI = -0.38 to -0.11) $p < 0.0001$].

Adverse events and treatment withdrawals

Across the trials, AEs were reported by 913 (64%) and 827 (57%) patients treated with galcanzumab and placebo, respectively; the overall RR to develop any AE during galcanzumab treatment was 1.12 (95% CI = 1.05–1.18) $p = 0.0002$. SAEs occurred in 24 (1.7%) and 14 (1%) patients treated with galcanzumab and placebo, respectively; RR: 1.74 (95% CI = 0.90–3.34) $p = 0.0989$. Treatment was discontinued in 36 (2.5%) and 23 (1.6%) cases in the galcanzumab and placebo groups,

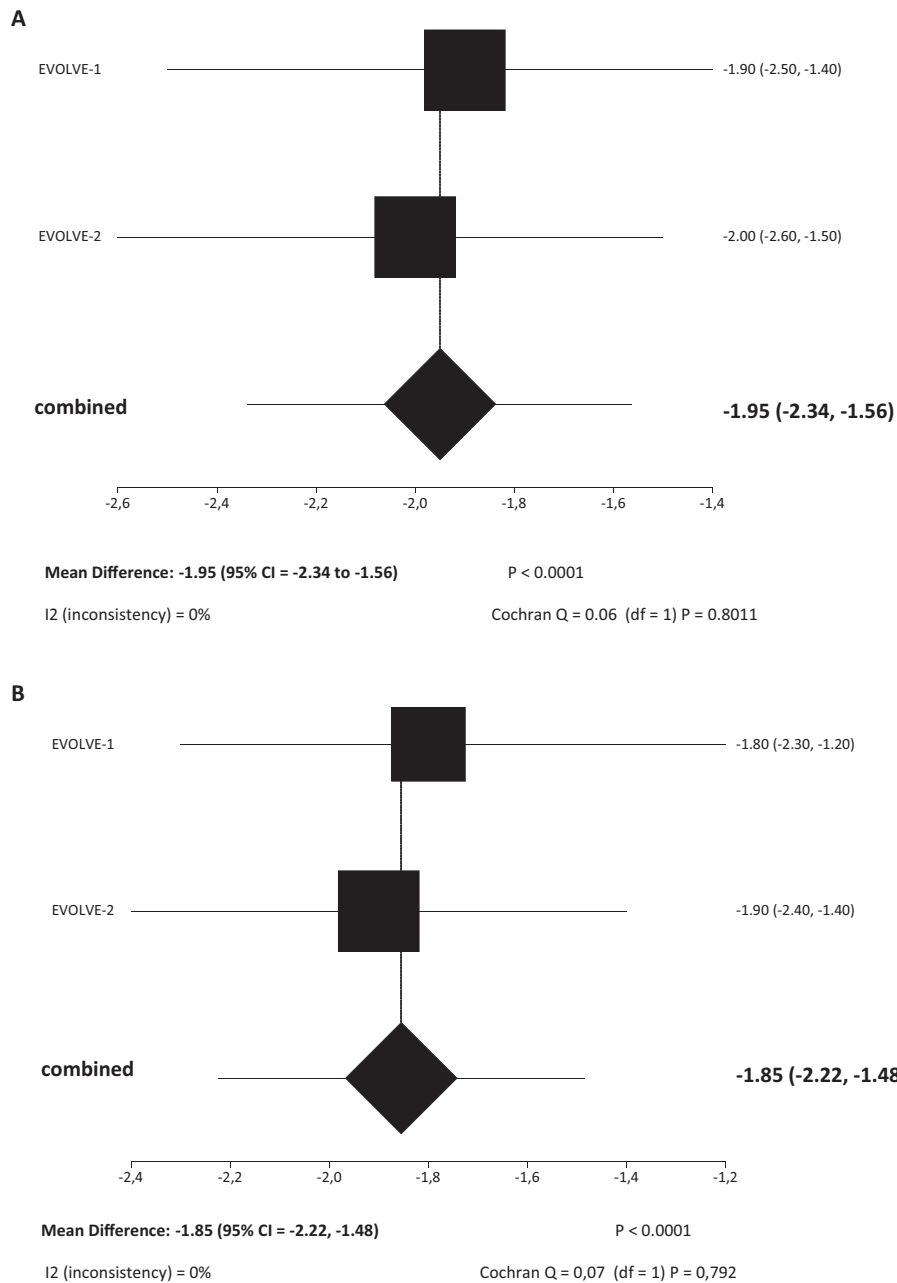


Figure 2. Meta-analysis forest plots. (A) Meta-analysis of mean difference of change in monthly migraine days of galcanezumab 120 mg *versus* placebo and (B) meta-analysis of mean difference of change in monthly migraine days of galcanezumab 240 mg *versus* placebo.

(A) Change in monthly migraine days – mean difference of galcanezumab 120 mg *versus* placebo.
 (B) Change in monthly migraine days – mean difference of galcanezumab 240 mg *versus* placebo.

respectively; the corresponding RR was 1.59 (95% CI = 0.95–2.66) $p = 0.0808$. The incidence rates of the most common AEs in the galcanezumab *versus* placebo-treated patients were as follows: injection site pain 10.9% *versus* 9.5% ($p = 0.2157$); injection site erythema 3.4% *versus* 1.4% ($p = 0.0005$); injection site pruritus 2.7% *versus* 0.1% ($p < 0.0001$);

injection site reaction (localized skin reactions that occur at the injection site besides pain, erythema and pruritus) 4.7% *versus* 1% ($p = 0.0159$); nasopharyngitis 5.8% *versus* 6.5% ($p = 0.4402$); upper respiratory tract infections 3.7% *versus* 2.4% ($p = 0.0465$). Safety results are summarized in Table 4. No statistically significant and clinically

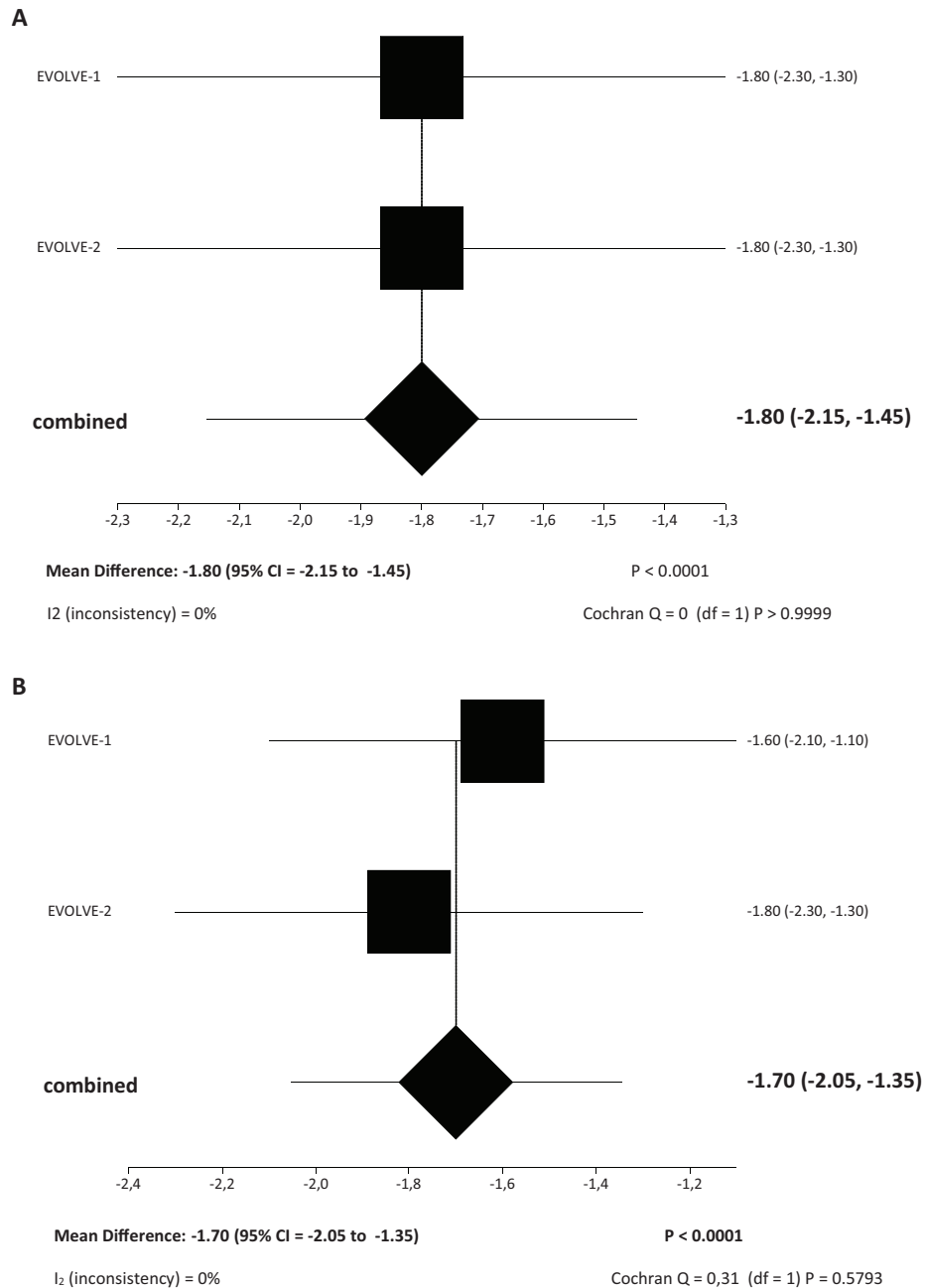


Figure 3. Meta-analysis forest plots. (A) Meta-analysis of mean difference of change in baseline monthly acute migraine-specific medication days of galcanezumab 120 mg *versus* placebo and (B) meta-analysis of mean difference of change in baseline monthly acute migraine-specific medication days of galcanezumab 240 mg *versus* placebo.

(A) Change in baseline monthly acute migraine-specific medication days – Mean difference of galcanezumab 120 mg *versus* placebo.

(B) Change in baseline monthly acute migraine-specific medication days – Mean difference of galcanezumab 240 mg *versus* placebo.

meaningful differences were observed between galcanezumab and placebo in laboratory values, vital signs, weight, or quantitative or qualitative electrocardiograms (ECGs).

Discussion

Galcanezumab is a fully humanized monoclonal antibody specifically developed and studied to prevent migraine by targeting the CGRP pathway

Table 2. (A) 50% or greater reduction in baseline monthly migraine days for galcanezumab *versus* placebo; (B) 75% or greater reduction in baseline monthly migraine days for galcanezumab *versus* placebo; and (C) 100% reduction in baseline monthly migraine days for galcanezumab *versus* placebo.

Subgroup	Number of pooled events/participants		I^2	Risk ratio (95% CI)	p value
	Galcanezumab	Placebo			
A					
Galcanezumab 120 mg	268/441	347/886	0%	1.55 (95% CI = 1.39–1.73)	<0.0001
Galcanezumab 240 mg	253/431	347/886	0%	1.50 (95% CI = 1.34–1.68)	<0.0001
B					
Galcanezumab 120 mg	158/441	168/886	0%	1.89 (95% CI = 1.57–2.27)	<0.0001
Galcanezumab 240 mg	156/431	168/886	0%	1.91 (95% CI = 1.59–2.3)	<0.0001
C					
Galcanezumab 120 mg	60/441	53/886	0%	2.28 (95% CI = 1.6 to 3.23)	<0.0001
Galcanezumab 240 mg	61/431	53/886	0%	2.37 (95% CI = 1.67–3.36)	<0.0001
CI, confidence interval.					

Table 3. (A) Changes in baseline migraine specific quality of life questionnaire, version 2.1, role-function restrictive (**MSQ R-FR**) for galcanezumab *versus* placebo and (B) changes in baseline patient global impression-severity (**PGI-S**) for galcanezumab *versus* placebo.

Subgroup	Galcanezumab <i>versus</i> placebo mean difference (95% CI)	I^2	p value
A MSQ R-FR			
Galcanezumab 120 mg	8.26 (95% CI = 6.48–10.05)	0%	<0.0001
Galcanezumab 240 mg	7.35 (95% CI = 5.53–9.17)	0%	<0.0001
B PGI-S			
Galcanezumab 120 mg	–0.30 (95% CI = –0.44 to –0.16)	0%	<0.0001
Galcanezumab 240 mg	–0.24 (95% CI = –0.38 to –0.11)	0%	=0.0003
CI, confidence interval.			

and trigeminal pain system along with erenumab, eptinezumab, and fremanezumab. It is also the only one found to be effective in cluster headache prophylaxis.⁶ Unfortunately, a meta-analysis of galcanezumab efficacy in chronic migraine prophylaxis as well as its efficacy and safety in cluster headache prophylaxis cannot be performed at this time due to the small number of published studies.

In the two studies analyzed for episodic migraine (EVOLVE-1, EVOLVE-2), preventive treatment with subcutaneous galcanezumab, at both 120 mg and 240 mg dosages, was associated with a significantly greater reduction in the mean number of MMDs *versus* placebo. Moreover, a greater reduction in the number of monthly acute MSMDs during the 6-month double-blind treatment phase was shown, further supporting the efficacy of

Table 4. Adverse events for galcanezumab *versus* placebo.

Subgroup	Number of pooled events/participants		I ²	Risk ratio (95% CI)	p value
	Galcanezumab	Placebo			
Any AE	913/1435	827/1451	0%	1.12 (95% CI = 1.05–1.18)	0.0002
Any SAE	24/1435	14/1451	0%	1.74 (95% CI = 0.9–3.34)	0.0989
Discontinuation due to AEs	36/1435	23/1451	0%	1.59 (95% CI = 0.95–2.66)	0.0808
Injection site pain	156/1435	138/1451	0%	1.14 (95% CI = 0.92–1.42)	0.2157
Injection site erythema	49/1435	20/1451	0%	2.48 (95% CI = 1.48–4.15)	0.0005
Injection site pruritus	39/1435	2/1451	0%	15.99 (95% CI = 4.47–57.3)	<00001
Injection site reaction	67/1435	14/1451	68.9%	4.98 (95% CI = 1.35–18.38)	0.0159
Nasopharyngitis	83/1435	94/1451	0%	0.89 (95% CI = 0.67–1.19)	0.4402
Upper respiratory tract infection	53/1435	35/1451	0%	1.53 (95% CI = 1.01 –2.33)	0.0465
Back pain	23/1435	20/1451	54.6%	1.21 (95% CI = 0.48–3.03)	0.686
Urinary tract infection	10/1435	7/1451	0%	1.43 (95% CI = 0.83–2.44)	0.1965
Abdominal pain	10/1435	9/1451	0%	1.12 (95% CI = 0.46–2.73)	0.8079
Fatigue	23/1435	22/1451	0%	1.06 (95% CI = 0.59–1.88)	0.8523
Diarrhea	19/1435	20/1451	0%	0.96 (95% CI = 0.52–1.79)	0.8982
Dizziness	26/1435	21/1451	0%	1.26 (95% CI = 0.71–2.22)	0.4305
Migraine	16/1435	9/1451	0%	1.79 (95% CI = 0.8–4.04)	0.1582
Influenza	31/1435	22/1451	24.8%	1.43 (95% CI = 0.83–2.45)	0.1973
Injection site bruising	6/1435	6/1451	0%	1.01 (95% CI = 0.33–3.12)	0.9805
Neck pain	14/1435	12/1451	0%	1.18 (95% CI = 0.55–2.53)	0.3849
Nausea	13/1435	15/1451	0%	0.88 (95% CI = 0.42–1.82)	0.729

AE, adverse event; CI, confidence interval; SAE, serious adverse event.

galcanezumab as migraine preventive therapy. This meta-analysis also shows that patients treated with galcanezumab 120 mg or 240 mg had a greater improvement in quality of life than did placebo-treated patients, as measured in the MSQ role-function restrictive domain at month 6. Similarly, a significant improvement in patients' global impression of severity of their disease measured by the Patient Global Impression of Severity (PGI-S) score was detected in comparison with placebo at the end of the 6-month double-blind treatment phase. Furthermore, the clinical benefit

of galcanezumab is supported by the statistically greater proportion of galcanezumab-treated patients *versus* placebo-treated patients that achieved 50% or greater, 75% or greater and 100% reduction from baseline in the mean number of MMDs at both dose regimens. However, it has to be mentioned that in EVOLVE-2 the authors stated that: 'response rate was defined as the percentages of patients meeting predefined thresholds (i.e. 50%, 75%, and 100%) in the reduction from baseline in the number of MMDs for each month, and the overall percentages of

patients meeting these thresholds averaged over months 1 through 6 were analyzed'. Thus, the proportion reported in these trials refers to the mean proportion of patients who achieved the thresholds for 1-month treatment and not within the entire treatment phase (6 months). This approach may have increased the presented response rates.

Regarding the safety profile of the drug, galcanezumab seems to be well tolerated as indicated by the comparable rates of AEs between the active and placebo-treated groups of the trials analyzed (EVOLVE-1, EVOLVE-2, REGAIN). Most of the AEs were mild to moderate, while the incidence of patients who withdrew from the studies due to AEs was not significant, especially when compared to other non-specific preventive migraine therapies such as topiramate.^{17,18} Moreover, injection site reactions were low and SAEs due to galcanezumab were below 2%.

A probable explanation for the low drop-out rates of galcanezumab could be the greater specificity of action and the greater half-life time (25–30 days), which allows the drug to be administered once a month. Monthly dosing instead of daily intake of oral preventive drugs seems to be more convenient for patients and may improve treatment adherence.¹⁹ Therefore, the effectiveness of the treatment may increase. In addition, the high efficacy of galcanezumab should lead to lower indirect costs (visits to emergency departments, missing work due to migraine or children missing school due to parent's migraine). Finally, the cardiovascular safety of galcanezumab is crucial and needs to be determined through randomized controlled trials (RCTs). The CGRP and its receptors are distributed not only in the central and peripheral nervous system but also in the cardiovascular system, both in blood vessels and in the heart. Under normal conditions, CGRP has important vasodilating effects and is thought to protect organs from ischemia.²⁰ Existing data from a double-blind clinical trial for erenumab showed that it did not impair the total exercise time in a treadmill test in high-risk cardiovascular patients, indicating that CGRP pathway inhibition does not increase the risk of myocardial ischemia.²¹

This study has a number of limitations that should be acknowledged while interpreting the findings. Firstly, only two studies in the efficacy meta-analysis and only three in the safety

meta-analysis met the inclusion criteria. All of them were funded by the manufacturing pharmaceutical companies. Moreover, the long-term safety profile of galcanezumab should be studied through real-world evidence, trials with larger numbers of patients and longer follow-up periods. Finally, it must be recognized that our findings have been calculated in phase III clinical trials and cannot be readily generalized to clinical practice.

Conclusion

Galcanezumab is an efficacious and well-tolerated preventive treatment for migraine in adults. The low drop-out rate during the clinical trials may be a good indicator of better treatment adherence, thus more effective therapy for migraine patients. The monthly subcutaneous dosing instead of daily oral intake seems to be preferred by migraine patients while injection site reactions do not differ significantly between galcanezumab and placebo. Studies with longer follow-up periods and real-world data need to be conducted.

Article highlights

- Galcanezumab is an efficacious and well-tolerated preventive treatment for migraine.
- The low drop-out rate during the clinical trials may be a good indicator to better treatment adherence, thus more effective therapy for migraine patients.
- Larger clinical trials with longer follow-up periods need to be conducted in order to provide more safety data of the above-mentioned drug.

Author contributions

PG contributed to study design, data collection, statistical analysis, data interpretation and drafted the manuscript.

DDM conceived the study, participated in the design, data collection and interpretation and drafted the manuscript.

Both authors discussed the results and approved the final manuscript.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest

P. Gklinos declares that there is no conflict of interest. D.D. Mitsikostas has received honoraria, research and travel grants from Allergan, Amgen, Biogen, Cefaly, Eli Lilly, Electrocore, Mertz, Novartis, Roche, Sanofi, Specifar and Teva.

ORCID iD

Panagiotis Gklinos  <https://orcid.org/0000-0001-5022-6460>

References

1. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the global burden of disease study 2016. *Lancet* 2017; 390: 1211–1259.
2. Linde M, Gustavsson A, Stovner LJ, *et al.* The cost of headache disorders in Europe: the Eurolight project. *Eur J Neurol* 2012; 19: 703–711.
3. Ho TW, Edvinsson L and Goadsby PJ. CGRP and its receptors provide new insights into migraine pathophysiology. *Nat Rev Neurol* 2010; 6: 573–582.
4. Lassen LH, Jacobsen VB, Haderslev PA, *et al.* Involvement of calcitonin gene-related peptide in migraine: regional cerebral blood flow and blood flow velocity in migraine patients. *J Headache Pain* 2008; 9: 151–157.
5. Hansen JM, Hauge AW, Olesen J, *et al.* Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. *Cephalalgia* 2010; 30: 1179–1186.
6. Goadsby PJ, Dodick DW, Leone M, *et al.* Trial of galcanezumab in prevention of episodic cluster headache. *N Engl J Med* 2019; 381: 132–141.
7. Moher D, Liberati A, Tetzlaff J, *et al.*; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151: 264–269.
8. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders: 2nd edition. *Cephalalgia* 2004; 24 (Suppl. 1): 9–160.
9. Headache Classification Committee of the International Headache Society. The international classification of headache disorders, 3rd edition (beta version). *Cephalalgia* 2013; 33: 629–808.
10. Olivo SA, Macedo LG, Gadotti IC, *et al.* Scales to assess the quality of randomized controlled trials: a systematic review. *Phys Ther* 2008; 88: 156–175.
11. Jadad AR, Moore RA, Carroll D, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1–12.
12. Cole JC, Lin P and Rupnow MF. Validation of the migraine-specific quality of life questionnaire version 2.1 (MSQ v. 2.1) for patients undergoing prophylactic migraine treatment. *Qual Life Res* 2007; 16: 1231–1237.
13. Guy W. *ECDEU assessment manual for psychopharmacology, revised*. Rockville: National Institute of Mental Health, Psychopharmacology Research Branch, 1976, pp. 217–222.
14. Deeks JJ. Systematic reviews of evaluations of diagnostic and screening tests. In: Egger M, Smith GD and Altman DG (eds) *Systematic reviews in health care: meta-analysis in context*. London: BMJ Books, 2001.
15. Higgins JPT and Green S (eds). *Cochrane handbook for systematic reviews of interventions*, Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. <http://handbook-5-1.cochrane.org> (2011; accessed 26 March 2020).
16. Higgins JP and Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539–1558.
17. Silberstein SD, Neto W, Schmitt J, *et al.*; MIGR-001 Study Group. Topiramate in migraine prevention: results of a large controlled trial. *Arch Neurol* 2004; 61: 490–495.
18. Brandes JL, Saper JR, Diamond M, *et al.*; MIGR-002 Study Group. Topiramate for migraine prevention: a randomized controlled trial. *JAMA* 2004; 291: 965–973.
19. Seng EK, Rains JA, Nicholson RA, *et al.* Improving medication adherence in migraine treatment. *Curr Pain Headache Rep* 2015; 19: 24.
20. Favoni V, Giani L, Al-Hasany L, *et al.* CGRP and migraine from a cardiovascular point of view: what do we expect from blocking CGRP? *J Headache Pain* 2019; 20: 27.
21. Depre C, Antalik L, Starling A, *et al.* A randomized, double-blind, placebo-controlled study to evaluate the effect of erenumab on exercise time during a treadmill test in patients with stable angina. *Headache* 2018; 58: 715–723.

Appendix 1: Studies included in the meta-analysis

1. Stauffer VL, Dodick DW, Zhang Q, *et al.* Evaluation of galcanezumab for the prevention of episodic migraine: the EVOLVE-1 randomized clinical trial. *JAMA Neurol* 2018; 75: 1080–1088.
2. Skljarevski V, Matharu M, Millen BA, *et al.* Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 phase 3 randomized controlled clinical trial. *Cephalalgia* 2018; 38: 1442–1454.
3. Detke HC, Goadsby PJ, Wang S, *et al.* Galcanezumab in chronic migraine: the randomized, double-blind, placebo-controlled REGAIN study. *Neurology* 2018; 91: e2211–e2221.

Visit SAGE journals online
[journals.sagepub.com/
home/tan](http://journals.sagepub.com/home/tan)

 SAGE journals