Received: 2 May 2025 | Accepted: 23 October 2025

DOI: 10.1111/head.70003

REVIEW ARTICLE

Real-world effectiveness and safety of galcanezumab for the treatment of migraine: A systematic review and meta-analysis

Jaime Fernández-Bravo-Rodrigo PharmD[1,2] | Carlos Pascual-Morena PhD[3,4] | Alicia Saz-Lara PhD[1] | Irene Martínez-García PhD[1,4] | Carla Geovanna Lever-Megina MSc[1] | Silvana Patiño-Cardona MSc[3] | Amparo Flor-García PharmD[5] | Iván Cavero-Redondo PhD[1]

[1]CarVasCare Research Group, Faculty of Nursing, University of Castilla–La Mancha, Cuenca, Spain

[2]Pharmacy Service, Hospital Virgen del Castillo, Yecla, Murcia, Spain

[3]Health and Social Research Center, University of Castilla–La Mancha, Cuenca, Spain

[4]Facultad de Enfermería de Albacete, University of Castilla–La Mancha, Albacete, Spain

[5]Pharmacy Service, Hospital Virgen de la Luz, Cuenca, Spain

Correspondence
Carlos Pascual-Morena, Health and Social Research Center, University of Castilla–La Mancha, Cuenca 16071, Spain.
Email: carlos.pascual@uclm.es

Funding information
Junta de Comunidades de Castilla-La Mancha, Grant/Award Number: 2025-PRED-22671; Universidad de Castilla-La Mancha; Ministerio de Ciencia, Innovación y Universidades, Grant/Award Number: FPU21/06866

Abstract

Objective: This study aimed to summarize and pool real-world evidence on the clinical effectiveness and safety of galcanezumab.

Background: Migraine is a disabling primary headache disorder. Several drugs that target calcitonin gene-related peptide, such as galcanezumab, have recently been developed. However, real-world effects have not been well studied.

Methods: A systematic search of PubMed, Scopus, and Web of Science was conducted from inception to February 2025. Studies that estimated the real-world effects of galcanezumab on monthly migraine days (MMDs), monthly headache days (MHDs), Headache Impact Test, Migraine Disability Assessment Scale, number of days in medication, acute monthly intake (AMI), pain intensity, and safety outcomes were included. Meta-analyses of proportions or mean differences were performed.

Results: Thirty-six studies were included, with an agreement of 0.93 [95% confidence interval (CI): 0.90, 0.96]. One month after the first injection, the reduction effects were −6.93 days (95% CI: −7.88, −5.99) for MMD, −8.55 days (95% CI: −11.32, −5.78) for MHD, and −7.96 points (95% CI: −8.93, −6.99) for Headache Impact Test. Over 60% of patients achieved a reduction in MMD/MHD of at least 50% within 3 months. The effect increased gradually and slightly up to 12 months. The adverse event rates were 0.25 (95% CI: 0.14, 0.38) and 0.35 (95% CI: 0.27, 0.45) at 6 and 12 months, respectively, with constipation being the most common.

Conclusion: Galcanezumab appears to be associated with clinically meaningful improvements in migraine and favorable safety outcomes, although the evidence certainty is limited by heterogeneity.

Abbreviations: 95% CI, 95% confidence interval; AMI, acute monthly intake; CGRP, calcitonin gene-related peptide; CM, chronic migraine; EM, episodic migraine; HIT-6, Headache Impact Test; MD, mean difference; MIDAS, Migraine Disability Assessment Scale; MHD, monthly headache days; MMD, monthly migraine days; PD, proportion change difference; RCT, randomized clinical trial; RR, response rates.

Plain Language Summary

Galcanezumab is a calcitonin gene-related peptide-targeting agent that has shown high efficacy in the treatment of migraine under controlled conditions, such as in randomized clinical trials. In order to assess its usefulness in the real world, we reviewed a large number of published studies from real-world clinical settings to assess the effectiveness and safety of galcanezumab in these conditions. Our study showed statistically and clinically significant reductions in monthly migraine or headache days, rescue medication use and medication days, and pain scores, which support the evidence from randomized clinical trials and help guide physicians in the management of patients with migraine.

KEYWORDS
headache, migraine, monoclonal antibodies, neurology, pharmacology, quality of life

INTRODUCTION

Migraine is a common and disabling neurological disorder that affects more than 1 billion people worldwide. It is characterized by complex neurobiology involving interactions between genetic and environmental factors and various triggers.[1–3] A recent review reported a 14% increase in prevalence,[4] and most studies indicate a significant predominance in females of nearly 2:1.[3] Consequently, young females experience the greatest disability throughout their lives because of the significant impact of migraine on their personal well-being.[2,3] Diagnostic criteria distinguish episodic migraine (EM) from chronic migraine (CM).[5]

Treatment is complex and individualized, with a wide range of acute, rescue, and preventive options available. Preventive migraine treatment is considered successful if it reduces the frequency of migraine attacks by at least 50% within 3 months. Historically, preventive treatments have included drugs developed for other conditions, such as tricyclic antidepressants, beta-blockers, calcium channel blockers, and anticonvulsants. However, these treatments only have moderate effectiveness.[6,7] OnabotulinumtoxinA was approved by the U.S. Food and Drug Administration in 2010 as the first specific preventive treatment for CM. Triptans are the preferred treatment for moderate attacks, but they are often overused, which can lead to symptom exacerbation.[8] In recent years, the role of calcitonin gene-related peptide (CGRP) in migraine pathophysiology has been identified, leading to the development of new targeted drugs that have improved migraine prevention. These include monoclonal antibodies (mAbs) targeting the CGRP peptide, such as subcutaneous fremanezumab and galcanezumab, and intravenous eptinezumab, as well as antibodies targeting the CGRP receptor, such as subcutaneous erenumab.[9,10]

Several randomized controlled trials (RCTs) on EM and CM have been published demonstrating the efficacy of galcanezumab in preventing migraine. These trials revealed significant reductions in overall and patient-reported monthly headache days (MHD), acute migraine-specific medication days (NDM), and Migraine Disability Assessment Scale (MIDAS) scores. Additionally, the incidence of treatment-emergent adverse events was low.[11–14] However, real-world effectiveness and safety may differ from the estimates in RCTs.[15] In addition, the effectiveness of some outcomes, such as monthly migraine days (MMDs), response rates (RRs) for MMD and MHD, Headache Impact Test (HIT-6) scores, acute monthly intake (AMI), and pain intensity (PI), remains unclear. Therefore, the objective of this systematic review and meta-analysis of real-world evidence was to summarize and pool data on the clinical effectiveness of galcanezumab in patients with migraine, assessed by key outcomes such as MMD, MHD and their RRs, HIT-6 and MIDAS scores, NDM, AMI, and PI, as well as the drug's safety profile.

METHODS

This systematic review and meta-analysis was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, as well as the recommendations of the Cochrane Collaboration Handbook.[16–18] It is registered in the International Prospective Register of Systematic Reviews (CRD42021266322) and has a published protocol elsewhere.[19]

Search strategy

We conducted a systematic search of the Medline (via PubMed), Web of Science, and Scopus databases from their inception until February 2025. Gray literature searches were also conducted via OpenGray, Google Scholar, and the Networked Digital Library of Theses and Dissertations databases, as well as ClinicalTrials.gov and EudraCT. The reference lists of the included articles were also screened. Mendeley software was used to manage the references and remove duplicates. The authors of the included studies were contacted when necessary. The search strategy is detailed in Appendix S1.

The systematic search was conducted by two authors, and disagreements were resolved by consensus or by a third author. Kappa statistics were applied to interrater agreement metrics.[20]

Inclusion/exclusion criteria

The inclusion criteria were as follows: (1) population—adult patients (aged ≥18 years) with chronic and/or episodic migraine; (2) intervention—treatment with galcanezumab; (3) outcomes—MMD, MHD, HIT-6, MIDAS, NDM, AMI, and PI (the latter four were added to the protocol); and (4) study design—any real-world study (i.e., prospective, retrospective, or cross-sectional observational studies conducted in real-world settings). Studies written in English or Spanish were included.

The exclusion criteria were as follows: (1) intervention—follow-up shorter than 1 month; (2) outcomes—incomplete baseline or posttreatment data (both central value and dispersion), which could not be obtained even after the study authors were contacted. Additionally, studies with missing data for specific outcomes or time points were excluded from the corresponding analyses; and (3) concomitant treatments—prior or concomitant gepant use. Study selection was conducted by two authors, and disagreements were resolved by consensus or by a third author.

Data extraction

An ad hoc table was created to extract the following data from the included studies: (1) reference (author and year); (2) country in which the data were collected; (3) study design; and (4) sample characteristics (sample size, age, sex, and EM/CM distribution). Baseline characteristics were also extracted, including medication overuse; migraine duration; previous failed and/or concomitant use of onabotulinumtoxinA; and baseline values of MMD, MHD, HIT-6, MIDAS, NDM, AMI, and PI (when studies included more than one mAb and baseline data were reported for the overall population). Intervention characteristics, including design, duration, and treatment switching, were also collected.

Data extraction was performed independently by two authors, and disagreements were solved by consensus or by a third author.

Risk of bias assessment

The risk of bias was assessed using the Quality Assessment Tool for Quantitative Studies for nonrandomized experimental and single-arm pre–post studies. This tool includes seven domains of bias, each rated as strong, moderate, or weak. Using this framework, the overall risk of bias for each study was categorized as low (no high/weak ratings), moderate (one high/weak rating), or high (two or more high/weak ratings). In addition, the Newcastle–Ottawa Scale (NOS) was used to complement the aforementioned tool. This scale assigns "stars" to each study on three domains (i.e., selection, comparability, and exposure) and classifies the risk of bias as high (<5 points), moderate (5 to 7 points), or low (8 to 9 points).[21]

The quality assessment was performed independently by two authors, and disagreements were solved by consensus or by a third author.

Data synthesis

Continuous variables (i.e., MMD, MHD, HIT-6, MIDAS, NDM, AMI, and PI) were expressed as the mean differences (MDs), whereas dichotomous variables (i.e., the proportion change difference [PD] of adverse events and the RR for MHD and MMD) were expressed as proportions ranging from 0 to 1, with 95% confidence intervals (CIs).

The Hartung–Knapp–Sidik–Jonkman random effects model was used to estimate pooled MD scores for the effects of galcanezumab on MMD, MHD, NDM, AMI, PI, HIT-6, and MIDAS.[22] The MDs were estimated at 1, 3, 6, 9, and 12 months for the different outcomes, except for the MIDAS at 1 month, due to the retrospective nature of its questions (covering the previous 3 months).

A meta-analysis of the proportionate change in adverse events at 3, 6, and 12 months was also performed, combining events when the same adverse event was reported across studies. In addition, a meta-analysis was conducted for RRs (50%, 75%, and 100%) for MHD and MMD at 1, 3, 6, and 12 months. RRs were calculated using the initial number of randomized or enrolled participants as the denominator. The Freeman–Tukey double arcsine transformation method was applied to stabilize the variance of the raw proportions.[23] Time points with insufficient data were excluded from the meta-analysis. To avoid the exclusion of potentially eligible studies that presented data as medians and ranges or in graphical form, appropriate tools (e.g., WebPlotDigitizer) were used to extract and estimate values.[24]

Heterogeneity was assessed using the I^2 statistic, which ranges from 0% to 100%. According to the I^2 value, heterogeneity was considered not important (<30%), moderate (30% to 50%), substantial (50% to 75%), or considerable (75% to 100%).[18] Statistically significant heterogeneity was considered to be present when $p < 0.100$. Publication bias was evaluated using Egger's regression asymmetry test, with $p < 0.100$ indicating potential bias.[25] The trim-and-fill method was additionally applied to estimate the potential impact of unpublished studies.[26]

Secondary analyses

Meta-regression analyses were conducted to assess whether the effectiveness and safety of galcanezumab were influenced by the following continuous variables: age, baseline outcome levels, EM, medication overuse, and percentage of females. In addition, interactions between covariates were examined (age × sex and baseline values × medication overuse). Subgroup analyses were performed to explore potential sources of heterogeneity according to study

design (retrospective vs. prospective), geographic region (European vs. non-European populations), and migraine type (EM + CM vs. CM only).

Sensitivity analyses were performed to assess the robustness of the summary estimates (i.e., systematic reanalysis by removing studies one at a time). Furthermore, sensitivity analyses were performed on studies with a high risk of bias and on studies that used any tool.

All the statistical analyses were performed with Stata SE version 18.0 (StataCorp, College Station, TX, USA). Unless otherwise specified, the statistical tests were two-tailed and considered significant at $p < 0.050$.

RESULTS

Systematic search and baseline characteristics of the included studies

The search strategy identified 5807 potential studies for inclusion. Of these, 36 were included in both the systematic review and the meta-analysis (Tables S1 and S2),[27–62] whereas 55 were excluded for justified reasons (Figure 1, Table S3).

Among the included studies, 19 were prospective, 16 were retrospective, and one was cross-sectional. Twenty-three studies were conducted in European countries (Italy and Spain), nine in Asian countries, two in Brazil, one in Australia, and one in the United States. All studies were published between 2020 and 2025 and included a total of 3859 participants treated with galcanezumab. The mean age of the participants ranged from 35.5 to 69.8 years. Based on the available data, 80.17% of participants had CM, 81.4% were female, and 60.9% had a history of medication overuse. Baseline outcome levels were as follows: MMD ranged from 8.0 to 27.4 days, MHD from 11.0 to 30.0 days, HIT-6 from 63.4 to 70.8, MIDAS from 30.0 to 128.0, AMI from 12.0 to 41.96, NDM from 9.7 to 26.9, and PI from 6.5 to 9.0. The main demographic characteristics are presented in Tables S1 and S2. Finally, the kappa statistic showed an agreement of 0.93 (95% CI, 0.90, 0.96).

Quality assessment and risk of bias

According to the Quality Assessment Tool for Quantitative Studies, 31 of the 36 studies (86.1%) were classified as having a moderate risk of bias, whereas five of the 36 studies (13.9%) were classified as having a high risk of bias (Table S4). The most affected domain was researcher blinding: All studies were rated as weak because pre–post studies without a control group were not blinded, and the study design was rated as fair in almost all cases. Some studies also showed weaknesses related to participant withdrawal and dropout. Moreover, according to the NOS, four of the 36 studies (11.1%) were classified as having a low risk of bias, 30 (83.3%) as having a moderate risk of bias, and two (5.5%) as having a high risk of bias (Table S5). The NOS identified comparability as the most critical domain because of the lack of a control group, a common limitation in real-world studies. The two studies rated as having a high risk of bias according to the NOS were also rated as such by the Quality Assessment Tool for Quantitative Studies; both had substantial losses to follow-up and participant withdrawals.

Meta-analysis

MHDs, MMDs, and HIT-6

The MDs for the effect of galcanezumab on MHD were −8.55 (95% CI: −11.32, −5.78) at 1 month, −10.58 (95% CI: −12.72, −8.44) at 3 months, −10.61 (95% CI: −13.02, −8.20) at 6 months, and −10.97 (95% CI: −12.81, −9.13) at 12 months (Figure 2). For MMD, the MDs were −6.93 (95% CI: −7.88, −5.99), −8.63 (95% CI: −9.55, −7.70), −9.89 (95% CI: −10.88, −8.90), −10.69 (95% CI: −12.40, −8.99), and −10.90 (95% CI: −12.07, −9.74) at 1, 3, 6, 9, and 12 months, respectively (Figure 3). Finally, the MDs on the HIT-6 were −7.96 (95% CI: −8.93, −6.99), −10.03 (95% CI: −11.32, −8.73), −10.33 (95% CI: −12.52, −8.13), −11.49 (95% CI: −13.25, −9.73), and −11.97 (95% CI: −14.29, −9.64) at 1, 3, 6, 9, and 12 months, respectively (Figure 4). The outcomes of the MDs are summarized in Table 1.

Migraine Disability Assessment, number of days in medication, acute monthly intake and pain intensity

The MDs for the effect of galcanezumab on the MIDAS were −42.61 (95% CI: −50.09, −35.13), −55.17 (95% CI: −62.98, −47.35), −50.52 (95% CI: −61.31, −39.74), and −53.45 (95% CI: −62.10, −44.80) at 3, 6, 9, and 12 months, respectively (Figure S1). The MDs on the NDM were −6.79 (95% CI: −10.86, −2.72), −9.95 (95% CI: −13.05, −6.86), −10.46 (95% CI: −13.06, −7.86), −11.99 (95% CI: −14.76, −9.22), and −13.01 (95% CI: −17.24, −8.77) at 1, 3, 6, 9, and 12 months, respectively (Figure S2). For AMI, the MDs were −11.85 (95% CI: −12.91, −10.79), −16.26 (95% CI: −20.34, −12.18), −16.33 (95% CI: −20.20, −12.46), −19.35 (95% CI: −29.56, −9.15), and −17.78 (95% CI: −24.27, −11.30) at 1, 3, 6, 9, and 12 months, respectively (Figure S3). The MDs on the PI were −2.04 (95% CI: −2.58, −1.51), −1.67 (95% CI: −1.96, −1.38), −1.96 (95% CI: −2.21, −1.71), −2.29 (95% CI: −3.19, −1.39), and −2.09 (95% CI: −2.58, −1.59) at 1, 3, 6, 9, and 12 months, respectively (Figure S4). The outcome MDs are summarized in Table S6.

RRs

The RRs of PD for galcanezumab at 3, 6, and 12 months for MMD and MHD are described in Table 2. The results revealed that the PD prevalence for RRs >50% MHD was 0.60 (95% CI: 0.53, 0.66) at 3 months and 0.45 (95% CI: 0.22, 0.69) at 12 months; for RRs >75%

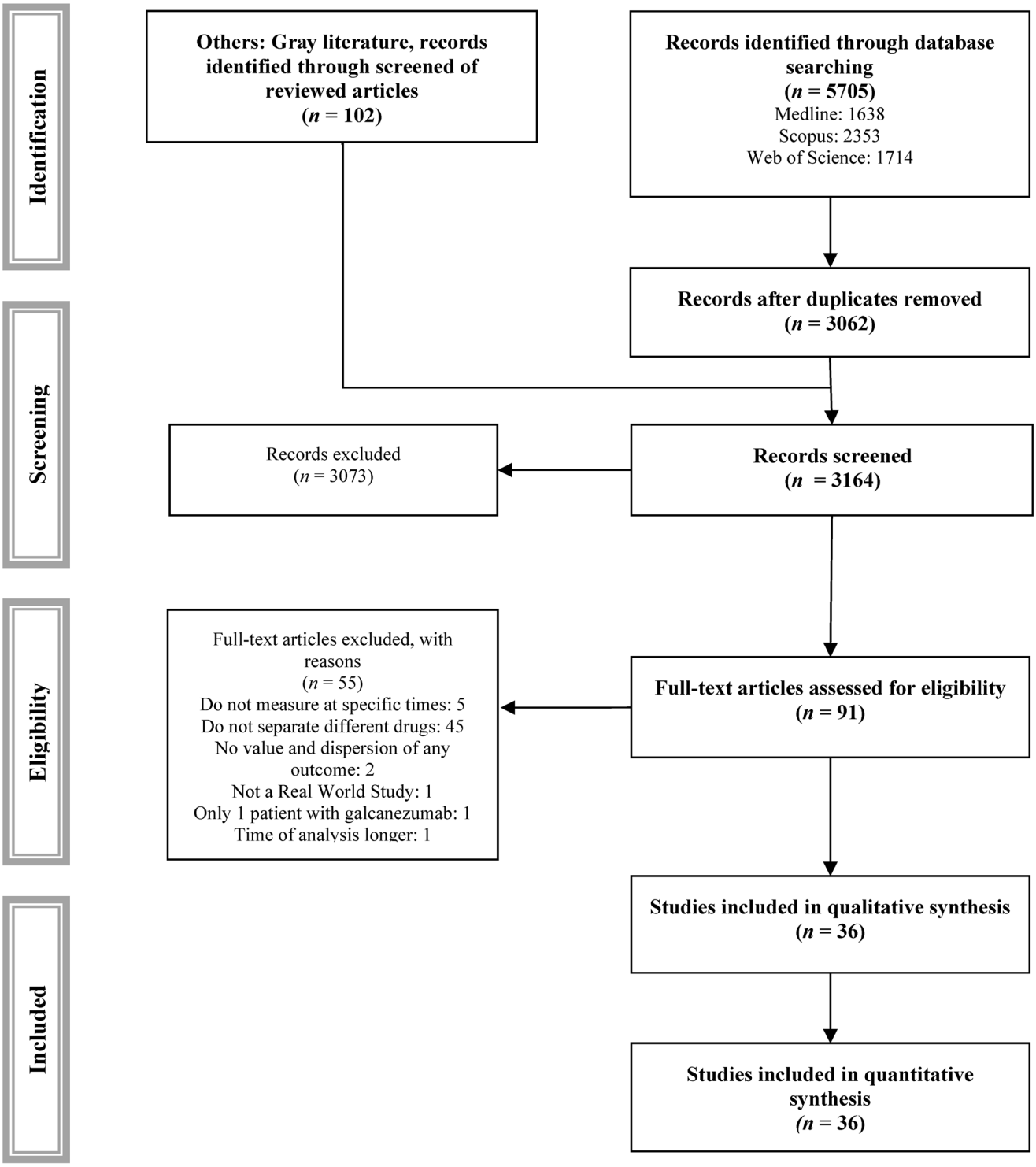

FIGURE 1 PRISMA flowchart of study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

MHD, it was between 0.30 and 0.33 at 3, 6, and 12 months; for RRs 100% MHD, it was 0.02 (95% CI: 0.01, 0.05) at 3 months; and for RRs >50% MMD, the lower prevalence was 0.50 (95% CI: 0.42, 0.59) at 1 month, increasing to 0.63 at 3 months and 6 months. For RR >75% MMD, it was 0.24 (95% CI: 0.17, 0.32) at 1 month, increasing to 0.35 (95% CI: 0.30, 0.44) at 6 months. For an RR of 100%, the MMD was between 0.03 and 0.07 at 1 and 6 months, respectively.

Safety profile

The results of the PD analysis of the safety profile of galcanezumab at 3 and 6 months for the most commonly reported adverse events (constipation, injection-site reactions, fatigue and asthenia, nausea, and dizziness/vertigo), and at 12 months for all adverse events, are presented in Table 3. The main results were that for any adverse

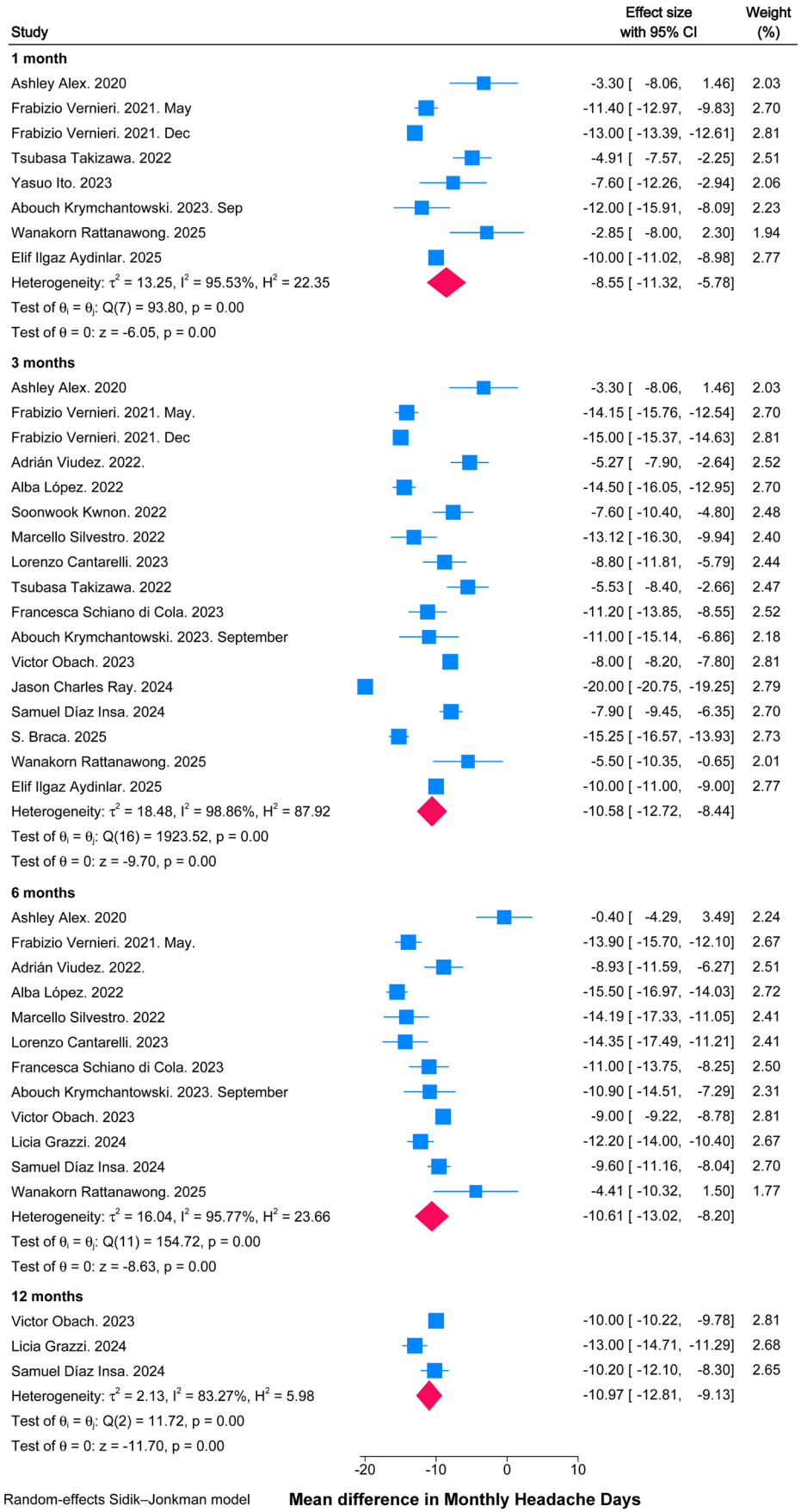

FIGURE 2 Pooled estimate of the effect of galcanezumab on monthly headache days at 1, 3, 6, and 12 months, measured as the mean difference and 95% confidence interval. [Color figure can be viewed at wileyonlinelibrary.com]

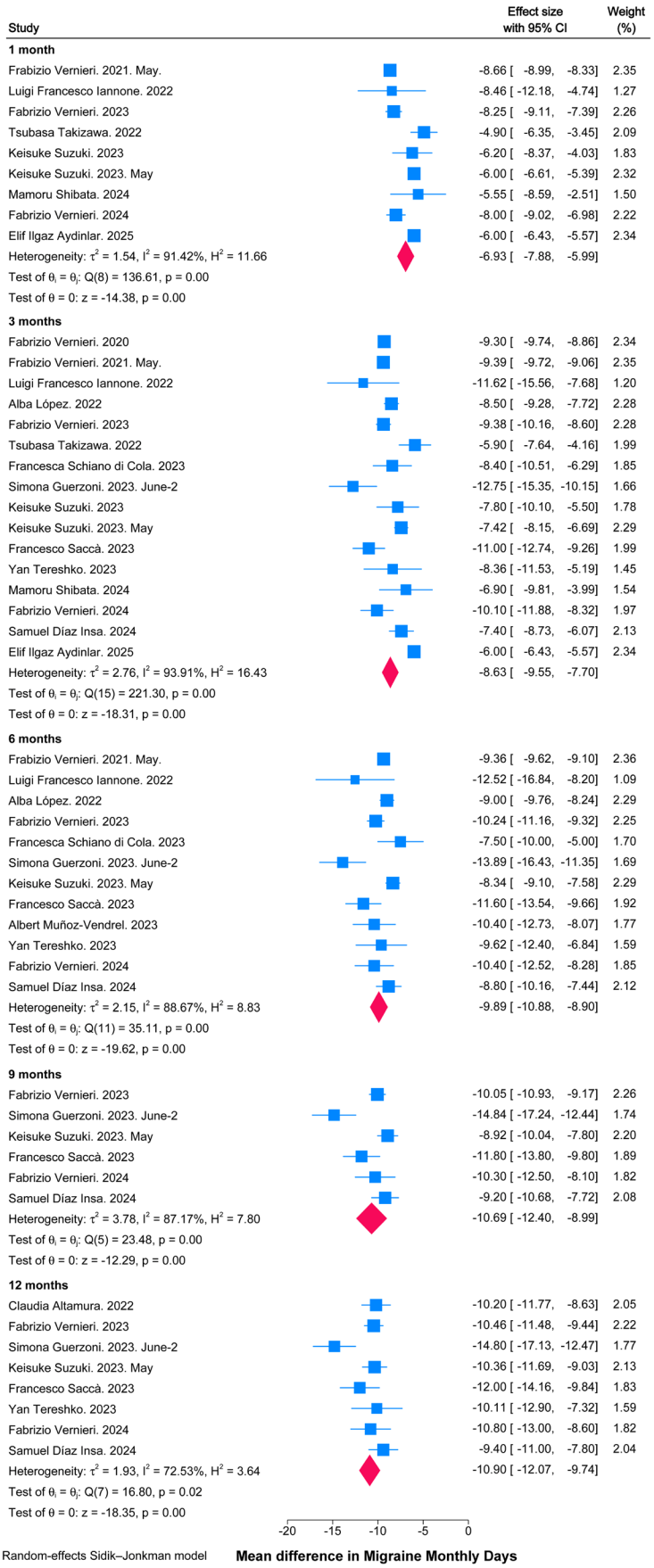

FIGURE 3 Pooled estimate of the effect of galcanezumab on migraine monthly days at 1, 3, 6, 9, and 12 months, measured as the mean difference and 95% confidence interval. [Color figure can be viewed at wileyonlinelibrary.com]

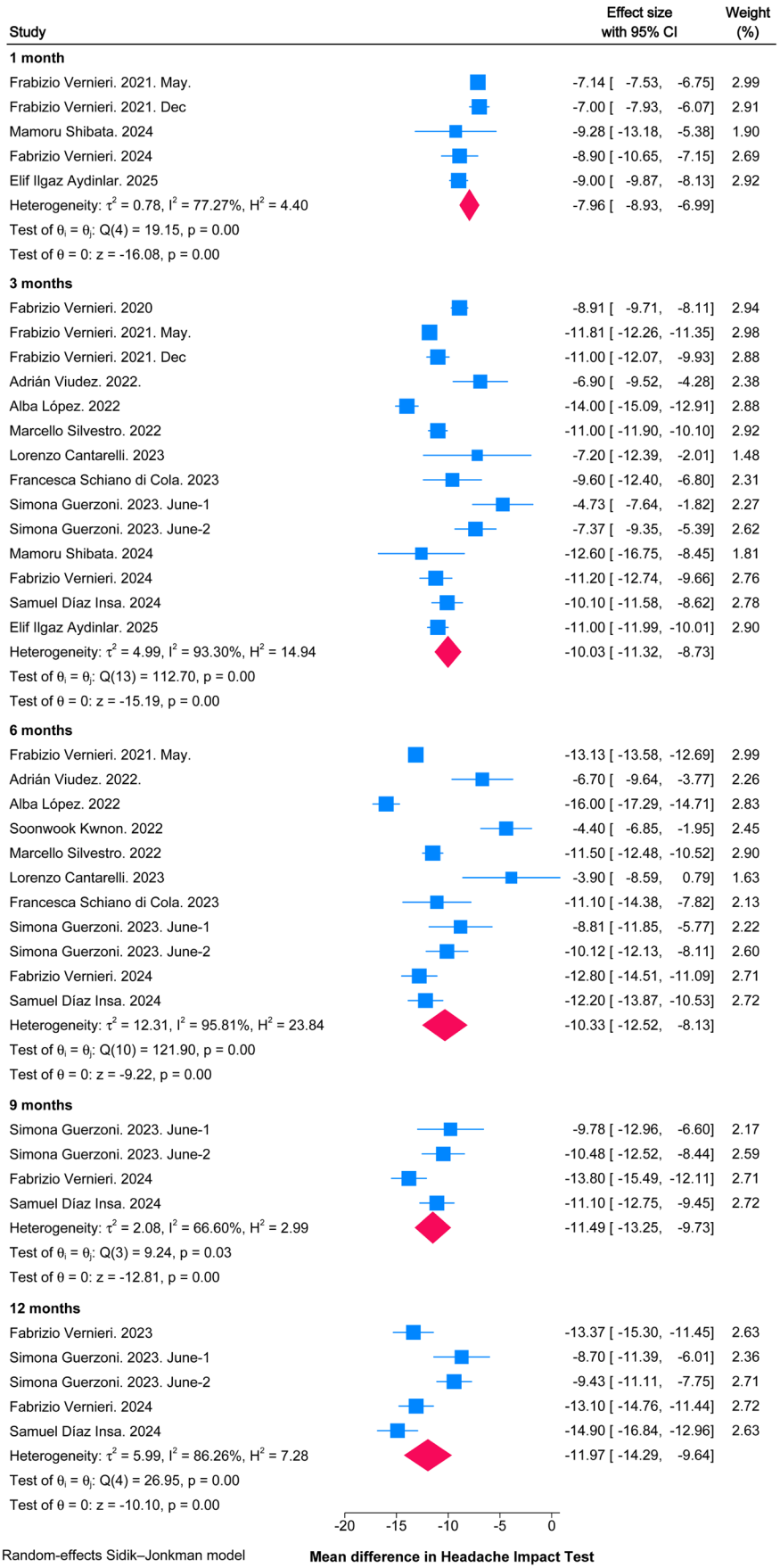

FIGURE 4 Pooled estimate of the effect of galcanezumab in Headache Impact Test at 1, 3, 6, 9, and 12 months, measured as the mean difference and 95% confidence interval. [Color figure can be viewed at wileyonlinelibrary.com]

event, the PD prevalence (0 to 1) was 0.23 (95% CI: 0.07, 0.44), 0.25 (95% CI: 0.14, 0.38), and 0.35 (95% CI: 0.27, 0.45) at 3, 6, and 12 months, respectively. The most common adverse event was constipation, with a PD prevalence of 0.06 (95% CI: 0.02, 0.11) and 0.16 (95% CI: 0.06, 0.29) at 3 and 6 months, respectively. The adverse event profile is low and mild.

Overall, heterogeneity was considerable and frequently statistically significant, although a few outcomes exhibited only moderate or substantial but nonsignificant heterogeneity. Several secondary analyses were performed to explore potential sources of heterogeneity.

Assessment of publication bias showed no evidence of bias for most effectiveness outcomes across the evaluated time points. However, some exceptions were identified. Egger's test suggested possible publication bias for HIT-6 at 3 and 6 months, MIDAS at 9 and 12 months, AMI at 6 months, and injection site–related outcomes at 3 months (Figure S5). The trim-and-fill analysis indicated that unpublished studies could have influenced the results for the following outcomes: MMD at 6 months; HIT-6 at 1 and 9 months; MIDAS and NDM at 6 months; AMI at 1 month; PI at 9 and 12 months; RR >50% MMD at 1 and 3 months; RR >75% MMD at 6 months; RR of 100% for MHD at 1 and 3 months; RR of 100% for MMD at 6 months; any adverse event at 12 months; fatigue/asthenia at 3 months; and injection-site reactions at 6 months (Table S7). Importantly, publication bias was detected by both methods for MHD at 1 month, MIDAS at 9 and 12 months, NDM at 1 month, and constipation at 6 months (Figure S5, Table S7).

TABLE 1 Mean differences in MHD, MMD, and HIT-6 scores.

Outcome	*n*	Mean difference (95% CI)	I^2	*p*-value
MHD 1 months	8	−8.55 (−11.32 to −5.78)	95.5	<0.001
MHD 3 months	17	−10.58 (−12.72 to −8.44)	98.9	<0.001
MHD 6 months	12	−10.61 (−13.02 to −8.20)	95.8	<0.001
MHD 9 months	Insufficients observations			
MHD 12 months	3	−10.97 (−12.81 to −9.13)	83.3	<0.001
MMD 1 months	9	−6.93 (−7.88 to −5.99)	91.4	<0.001
MMD 3 months	16	−8.63 (−9.55 to −7.70)	93.9	<0.001
MMD 6 months	12	−9.89 (−10.88 to −8.90)	88.7	<0.001
MMD 9 months	6	−10.69 (−12.40 to −8.99)	87.2	<0.001
MMD 12 months	8	−10.90 (−12.07 to −9.74)	72.5	0.020
HIT-6 1 months	5	−7.96 (−8.93 to −6.99)	77.3	<0.001
HIT-6 3 months	14	−10.03 (−11.32 to −8.73)	93.3	<0.001
HIT-6 6 months	11	−10.33 (−12.52 to −8.13)	95.8	<0.001
HIT-6 9 months	4	−11.49 (−13.25 to −9.73)	66.6	0.026
HIT-6 12 months	5	−11.97 (−14.29 to −9.64)	86.3	<0.001

Abbreviations: CI, confidence interval; HIT-6, Headache Impact Test; I^2, heterogeneity; MHD, monthly headache days; MMD, monthly migraine days; *n*, number of studies; *p*-value, *p*-value of heterogeneity.

Secondary analyses

Sensitivity analyses

Removing studies individually from the analyses did not significantly affect the results. When studies with a high risk of bias were excluded, no significant differences were found, except for NDM at 9 months (five studies, two at risk) and 12 months (three studies, one at risk), and RR >50% MMD at 12 months (four studies, one at risk).

When studies using any conversion tool were excluded, no significant differences were observed for most outcomes at any time point. However, some outcomes showed significant differences when medians were converted to means using the Hozo et al. method[24]: AMI at 6 months (eight studies, one using the Hozo tool [lower MD]), MHD at 3 months (17 studies, five using the Hozo tool [higher MD]), MHD at 6 months (12 studies, one using the Hozo tool [higher MD]), and PI at 9 months (two studies, one using the Hozo tool [lower MD]).

When the WebPlotDigitizer tool was used, significant differences were found only for AMI at 9 months (three studies, two using WebPlotDigitizer [lower MD]) and HIT-6 at 9 months (four studies, one using WebPlotDigitizer [higher MD]). The HIT-6 score at 3 months was the only outcome that differed significantly between studies that did not use tools and those that used any tool but did not differ significantly for any specific tool (14 studies, nine with some tool use [higher MD]).

Meta-regressions

The meta-regression models revealed statistically significant differences for some outcomes. Age was found to be a factor in the HIT-6, with 0.34 (95% CI: 0.06, 0.62, $p=0.017$; 13 studies); 0.59 (95% CI: 0.24, 0.94, $p=0.001$; five studies) progressive coefficient at 3 and 12 months; in AMI, −1.70 (95% CI:−3.06, −0.35, $p=0.010$; eight studies); −2.95 (95% CI: −5.16, −0.75, $p=0.010$; three studies); and −2.01 (95% CI: −3.48, −0.55, $p=0.007$; five studies) at 6, 9, and 12 months, respectively.

The baseline values of the outcomes had negative coefficients at several or all the study time points for MMD, MIDAS, NDM, and AMI. Medication overuse was also analyzed; for MIDAS, the

TABLE 2 Pooled estimates of the proportion of response rates at 3, 6, and 12 months for monthly headache days and monthly migraine days.

Response rate	Length of study (months)	Prevalence (95% CI)	I^2 (%)	*p*-value	Number of studies
RR >50% MHD	3	0.60 (0.53 to 0.66)	77.9	<0.001	7
	6	0.57 (0.47 to 0.67)	70.3	0.010	5
	12	0.45 (0.22 to 0.69)	91.4	<0.001	2
RR >50% MMD	1	0.50 (0.42 to 0.59)	81.8	<0.001	7
	3	0.63 (0.57 to 0.69)	65.5	0.060	8
	6	0.63 (0.58 to 0.68)	42.7	0.397	6
	12	0.57 (0.43 to 0.70)	87.7	<0.001	4
RR >75% MHD	3	0.30 (0.21 to 0.39)	87.9	<0.001	5
	6	0.33 (0.19 to 0.48)	84.9	<0.001	4
	12	0.32 (0.29 to 0.35)	0.0	0.883	2
RR >75% MMD	1	0.24 (0.17 to 0.32)	70.3	0.062	5
	3	0.31 (0.27 to 0.35)	14.3	0.670	5
	6	0.35 (0.30 to 0.44)	3.7	0.590	2
RR 100% MHD	1	0.01 (0.01 to 0.03)	0.0	0.970	2
	3	0.02 (0.01 to 0.05)	40.0	0.224	2
RR 100% MMD	1	0.03 (0.00 to 0.11)	87.1	0.044	3
	3	0.05 (0.02 to 0.09)	57.2	0.183	3
	6	0.07 (0.04 to 0.10)	14.6	0.415	2

Abbreviations: CI, confidence interval; I^2, heterogeneity; MHD, monthly headache days; MMD, monthly migraine days; *p*-value, *p*-value of heterogeneity; RR, response rate.

coefficients were −0.30 (95% CI: −0.52, −0.08, $p=0.007$; five studies) and −0.34 (95% CI: −0.54, −0.15, $p=0.001$; seven studies) at 9 and 12 months, respectively.

With respect to the percentage of females, MMD had a positive coefficient at all time points (1 to 12 months, $p<0.050$), increasing from 0.16 at 1 month to 0.57 at 9 months. Similarly, MHD presented a positive coefficient, although only MHD at 3 months, with more studies available, showed a statistically significant difference of 0.44 (95% CI: 0.18, 0.71; $p=0.001$).

The EM variables did not differ significantly. Meta-regression analyses between covariates revealed no interactions between age and sex or between baseline levels and medication overuse. In addition, no statistically significant differences were found in the MHD/MMD RR or in the prevalence of safety outcomes (Tables S8 and S9).

Subgroup analyses

The study design was associated with differences in some outcomes across time points. MHD at 3 months (nine prospective and seven retrospective studies), MMD at 1 month (three prospective and six retrospective studies) and 3 months (six prospective and nine retrospective studies), and NDM at 3 months (five prospective and three retrospective studies) and 12 months (two prospective and one retrospective study) showed greater reductions in days in prospective studies. Conversely, injection site reactions and related reactions at 3 months (four prospective and two retrospective studies) were less frequent in prospective studies (Table S10).

With respect to geographical distribution, subgroup analyses comparing European and non-European studies indicated greater reductions in MHD at 1 month (two European and six non-European studies), MMD at 1 month (four European and five non-European studies) and 3 months (11 European and five non-European studies), and HIT-6 at 6 months (10 European and one non-European study) in European studies than in non-European studies.

Studies that included only patients with CM showed significant reductions in days at 3, 6, 9, and 12 months (three studies at 3 months, 10 studies at 6 months, five studies at 9 months, and six studies at 12 months).

DISCUSSION

Main findings

To our knowledge, this is the first real-world meta-analysis providing clinical evidence of the effects of CGRP ligand inhibition on MMD, MHD, HIT-6, MIDAS, AMI, NDM, and PI scores, as well as treatment safety, in patients with migraine. Our results revealed that galcanezumab reduced the number of migraine and headache days at 1, 3, 6, 9, and 12 months (MMD: −6.93 to −10.90; MHD: −8.55 to −10.97), with progressive improvements in the HIT-6 score (−7.96

TABLE 3 Pooled estimates of the proportion of adverse events at 3 and 6 months and any adverse events at 3, 6, and 12 months.

Adverse event	Length of study (months)	Prevalence (95% CI)	I^2 (%)	*p*-value	Number of studies
Any adverse event	3	0.23 (0.07 to 0.44)	95.3	<0.001	6
	6	0.25 (0.14 to 0.38)	54.6	0.092	3
	12	0.35 (0.27 to 0.45)	4.7	0.563	2
Constipation	3	0.06 (0.02 to 0.11)	71.6	<0.001	7
	6	0.16 (0.06 to 0.29)	83.5	<0.001	5
Injection-site reactions and related	3	0.10 (0.03 to 0.22)	91.5	<0.001	6
	6	0.05 (0.01 to 0.11)	64.8	0.035	4
Fatigue–asthenia	3	0.03 (0.00 to 0.09)	48.9	0.184	2
	6	0.03 (0.00 to 0.07)	50.1	0.184	3
Dizziness–vertigo	3	0.05 (0.01 to 0.09)	32.4	0.293	3
	6	0.02 (0.00 to 0.07)	35.8	0.227	3

Abbreviations: CI, confidence interval; I^2, heterogeneity; *p*-value, *p*-value of heterogeneity.

to −11.97) and MIDAS score (−42.61 at 3 months; −50.52 to −55.17 from 6 to 12 months). Reductions were also observed in NDM (−6.79 to −13.01), AMI (−11.85 to −19.35), and PI (−2.04 at 1 month; −1.67 to −2.29 from 3 to 12 months). Approximately two-thirds of patients achieved a RR >50% in MMD/MHD at 3 to 6 months; one-third achieved a RR >75%; and between 2% and 7% achieved a complete response. Adverse events were infrequent, with constipation being the most common, followed by injection site reactions. Demographic data had a minimal impact on effectiveness or safety; although age influenced HIT-6 improvement; higher baseline values led to greater reductions in MMD, MIDAS, NDM, and AMI; and medication overuse and female sex were associated with smaller improvements in some outcomes. European studies showed slightly greater reductions, whereas episodic migraine had no significant effect.

Interpretation

Previous meta-analyses have evaluated the effects of galcanezumab in clinical and randomized trials and concluded that it is an effective preventive treatment for adult patients with CM and EM. This conclusion is based on its ability to reduce the primary outcome, MHD, as well as secondary outcomes, including MIDAS and NDM, while demonstrating an acceptable safety profile.[11–14,63] Our real-world results corroborate previous findings with respect to MHD, MIDAS, NDM, and safety. Although there is a meta-analysis of observational studies involving a variety of anti-CGRP agents,[64] 87% of these studies focus on erenumab. Therefore, we provide the first real-world evidence to support trial outcomes, with additional effectiveness measures including MMD, HIT-6, AMI, and PI.

To add further value, we provide evidence for all these outcomes in a study population that appears to be highly representative of patients who have initiated treatment with galcanezumab. Our analysis included a wide range of adult patients, that is, young and older, male and female, with and without medication overuse, with and without multiple previous treatment failures (including some who had received OnabotulinumtoxinA), responders and nonresponders, patients with EM and CM, and patients previously treated with CGRP mAbs—although these were very few, representing genuine and naïve results from four different continents.

All these characteristics could explain the greater reductions observed compared with those reported in RCTs, particularly in patients with higher baseline levels. This finding may be especially important because severely affected patients experience substantial benefits. Our study also demonstrated considerable heterogeneity in many outcomes. We explored the sources of this heterogeneity, which were mainly related to prospective and European studies, as well as differences in baseline outcome levels contributing to variability in quantitative reductions. Population characteristics, standards of care, and access to new medications differ between continents. These factors, together with prospective patient follow-up, may explain some of the observed heterogeneity.

However, real-world studies with high heterogeneity may reflect the inclusion of a broad spectrum of patients, which is consistent with the aim of this study and allows for greater generalization of the findings. Although there is some risk of bias, it does not appear to have a significant impact on the results. The trim-and-fill method produced imputed values close to the observed results, and the asymmetry detected by Egger's test can be attributed to considerable heterogeneity. Finally, the use of the Hozo tool appears to introduce only slight bias.[24]

Over the past three decades, CGRP has been widely recognized as a key factor in migraine pathogenesis. However, receptor subunits, neuropeptides, and other factors also play important roles in migraine pathophysiology. Blocking this pathway has been shown to reduce symptoms and improve study outcomes.[7,9] Anti-CGRP mAbs have a different mechanism of action than CGRP ligand- or receptor-targeted agents, which may explain the differences in efficacy and treatment response between naïve patients and some treatment-resistant patients.[65–68]

Sex bias in migraine remains a current issue. A review summarized several studies showing that migraine affects only female

rodents or that the effects are more pronounced in females.[9] CGRP has multiple sites of action, both peripheral and central, and has a significant genetic contribution to migraine. This genetic influence, together with clinical factors, affects the response to several anti-CGRP treatments. In a study of 289 patients at the first follow-up, 36.7% of patients receiving erenumab, 28.4% receiving fremanezumab, and 34.9% receiving galcanezumab achieved reductions in MMD. In this study, galcanezumab had a greater effect on females than on males.[69]

In our meta-analysis examining the effect of sex on MMD, although there were potential biases and limitations (lower baseline values may have influenced the results, and sex could be a confounding factor), the opposite trend was observed: Females may have a smaller treatment effect. Chase et al. conducted a mixed anti-CGRP study (which included an anti-receptor agent, erenumab) with nonspecific timing that may help explain these findings. The only drug-specific real-world meta-analysis of anti-CGRP mAbs published to date suggests that erenumab may have a lower RR in MMD/MHD in females.[70] Direct comparative studies are needed to confirm any potential differences between agents.

In an exploratory descriptive comparison between similar populations in terms of MMD reduction and RR, the present real-world meta-analysis of galcanezumab showed slightly superior results compared with those of erenumab. However, it is important to note that meta-regression indicates an effect of heterogeneity on the mean reduction in MMD and other outcomes. Although the effectiveness outcomes reported in both real-world meta-analyses revealed a superior effect for galcanezumab at 3 and 6 months and a similar effect at 12 months, with very similar safety profiles, no firm conclusions can be drawn. Direct comparative studies are needed to confirm the potential differences suggested by exploratory descriptive comparisons.

Our results suggest that a single injection and 1 month may be sufficient to achieve meaningful results. However, effectiveness appears to improve over time, with a trend toward stabilization or slower progression at approximately 12 months. Previously, the European Headache Federation guidelines recommended assessing potential treatment discontinuation at 6 or 12 months. This recommendation was maintained in the 2022 update, which is consistent with our findings.[10,71] Robust real-world data beyond 12 months are still needed to inform treatment decisions. Finally, our finding that baseline values affect outcomes seems logical: The higher the baseline values, the greater the potential reduction. Nevertheless, the MMD/MHD RRs were not affected by the baseline value itself. This observation is noteworthy, and further studies are needed to investigate the benefits of galcanezumab for complex and chronic patients.

Constipation may result from disruption of the normal physiological function of CGRP, which plays a role in stimulating efferent neurotransmission in the digestive tract. Galcanezumab inhibits this function by blocking CGRP receptors, which may explain why constipation is observed as an adverse effect. In fact, constipation is the most common adverse event associated with erenumab. Although a clinical trial suggested possible mechanistic differences, galcanezumab also inhibits amylin 1 (AMY1) receptors, which have motility-slowing effects that could explain its slightly superior efficacy compared with erenumab. However, few studies met the inclusion criteria for our meta-analysis, and constipation may not have been reported unless it was specifically assessed.[72–74] Injection site reactions and related reactions were less common than those reported in RCTs, where the prevalence exceeded 10%. Safety reports with a prevalence greater than 10% are available in agency-approved monographs. However, these observations cannot be considered definitive because the analysis is subject to bias and direct comparisons are not possible.

Updates demonstrating the long-term safety and efficacy of anti-CGRP mAbs support institutional statements, such as the 2024 American Headache Society (AHS) consensus, which recommends anti-CGRP mAbs as first-line preventive treatment for EM and/or CM.[75,76] Similarly, according to AHS guidelines, a reduction of >50% is often used to define the success of preventive treatment after 3 months. In our study, the pooled proportion of patients who achieved at least a 50% reduction in MMD/MHD exceeded 60% after 3 months, with mean reductions in MMD and MHD of −8.63 and −10.58, respectively, in a population with baseline MMD levels ranging from 8 to 27.4 days and baseline MHD levels ranging from 11.0 to 30.0 days. These results indicate that galcanezumab is an effective preventive treatment for migraine in the general population.

However, no real-world meta-analyses have yet been published for fremanezumab or eptinezumab, highlighting the need for additional studies and meta-analyses to establish the efficacy of each anti-CGRP mAb. These findings, together with ongoing studies, are essential for determining the best treatment option for each patient. Finally, to improve the generalizability of the results, future studies should include patients and regions that are currently underrepresented.

Limitations

Our study has several limitations that should be considered. First, because this is a real-world meta-analysis, most studies did not have a control group or undergo blinding. This increases the risk of bias due to patient expectations, which could lead to an overestimation of perceived benefits, especially with regard to subjective outcomes. Second, the inclusion criteria differed between the included studies, which may have biased the results. Some studies reported marked differences in baseline outcome values, as is evident from our meta-analysis: Generally, the higher the baseline value, the greater the MD. Furthermore, most of the included patients were females, which can be explained by the fact that migraine is more prevalent in females than in males. Third, some outcomes were mainly based on migraine diaries completed by patients according to their subjective perceptions of their migraine episodes or for safety reasons, depending on how these data were

compiled or considered. Fourth, some studies were excluded because of their language. Fifth, some of the better results at 6, 9, and 12 months may be due to nonresponders discontinuing treatment because of a lack of effectiveness. However, the RR results are based on the total population included in the studies, so dropouts and withdrawals could represent a lower RR. Sixth, some continents have few or no studies. In addition, Spain and Italy account for all studies in Europe, and subgroup analysis revealed a greater effect in the European population, so this is a bias. Seventh, some studies showed publication bias and a lack of robustness. We performed a sensitivity analysis to identify and control for this. Using tools to convert medians to means or extract data from images may result in a slight modification of the observed effect. Eighth, with regard to safety, real-world studies are limited in their ability to capture low-frequency adverse events, and they could also underestimate such events owing to incomplete reporting. Ninth, the majority of studies did not report the possible concomitant use of OnabotulinumtoxinA. In Table S2, we present the NA data. If there is concomitant use, this could bias the results and is a potential confounder. However, these studies only wanted to investigate the use of anti-CGRP mAbs, so the use of OnabotulinumtoxinA is unlikely. Tenth and last, some meta-regressions included few studies due to a lack of information on some covariates, which limited the statistical power of the estimates and the external validity of the study.

CONCLUSIONS

This study suggests that galcanezumab effectively reduces MMD and MHD (RR 50%, 75%, and 100%), as well as NDM, AMI, PI, HIT-6, and MIDAS scores, in a real-world population while maintaining a favorable safety profile. Therefore, galcanezumab may play a key role in the management of migraine in clinical practice, providing effective and well-tolerated treatment. Importantly, it offers a therapeutic option for patients with multiple comorbidities or a high baseline disease burden, improving quality of life by alleviating migraine and reducing the need for acute medication, as supported by our meta-regression analysis. Further research, including comparative, change, demographic, and genetic studies, is needed to identify the most effective and safest strategies in general and specific patient populations. The high heterogeneity observed in our results limits the certainty of the evidence, highlighting the need for additional high-quality, controlled, comparative studies to confirm the effectiveness and safety of galcanezumab and determine which subgroups may benefit most.

AUTHOR CONTRIBUTIONS

Jaime Fernández-Bravo-Rodrigo: Conceptualization; methodology; data curation; investigation; formal analysis; writing – review and editing; writing – original draft. **Carlos Pascual-Morena:** Methodology; data curation; investigation; writing – original draft; writing – review and editing; supervision. **Alicia Saz-Lara:** Formal analysis; validation; visualization; writing – review and editing. **Irene Martínez-García:** Formal analysis; validation; visualization; writing – review and editing. **Carla Geovanna Lever-Megina:** Validation; visualization; formal analysis; writing – review and editing. **Silvana Patiño-Cardona:** Validation; visualization; writing – review and editing. **Amparo Flor-García:** Validation; visualization; writing – review and editing; formal analysis. **Iván Cavero-Redondo:** Methodology; data curation; investigation; writing – original draft; writing – review and editing; project administration; supervision; funding acquisition.

INTERNATIONAL PROSPECTIVE REGISTER OF SYSTEMATIC REVIEWS (PROSPERO) REGISTRATION NUMBER

CRD42021266322.

FUNDING INFORMATION

This study is supported by the University of Castilla–La Mancha. IM-G is supported by a grant from the Spain Ministry of Science, Innovation, and University (FPU21/06866). CGL-M is supported by a grant from Junta de Comunidades de Castilla-La Mancha (2025-PRED-22671), funded through Fondo Social Europeo Plus (FSE+).

CONFLICT OF INTEREST STATEMENT

Jaime Fernández-Bravo-Rodrigo, Carlos Pascual-Morena, Alicia Saz-Lara, Irene Martínez-García, Carla Geovanna Lever-Megina, Silvana Patiño-Cardona, Amparo Flor-García, and **Iván Cavero-Redondo** have no conflicts of interest to declare.

ORCID

Jaime Fernández-Bravo-Rodrigo https://orcid.org/0000-0003-1026-7561
Carlos Pascual-Morena https://orcid.org/0000-0003-1154-8752
Alicia Saz-Lara https://orcid.org/0000-0003-0669-8625
Irene Martínez-García https://orcid.org/0000-0001-7835-6953
Carla Geovanna Lever-Megina https://orcid.org/0009-0009-8801-2148
Silvana Patiño-Cardona https://orcid.org/0009-0001-3470-1724
Iván Cavero-Redondo https://orcid.org/0000-0003-2617-0430

REFERENCES

1. Puledda F, Silva EM, Suwanlaong K, Goadsby PJ. Migraine: from pathophysiology to treatment. *J Neurol*. 2023;270:3654-3666.
2. Steiner TJ, Stovner LJ, Jensen R, Uluduz D, Katsarava Z. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. *J Headache Pain*. 2020;21:137.
3. Simmonds L, Mehta D, Cheema S, Matharu M. Epidemiology of migraine. *Handb Clin Neurol*. 2023;198:31-38.
4. Stovner LJ, Hagen K, Linde M, Steiner TJ. The global prevalence of headache: an update, with analysis of the influences of methodological factors on prevalence estimates. *J Headache Pain*. 2022;23:34.

5. Lipton RB, Silberstein SD. Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention. *Headache*. 2015;55(suppl 2):103-106.
6. Silberstein SD. Preventive migraine treatment. *Continuum (Minneap Minn)*. 2015;21:973-989.
7. Silvestro M, Iannone LF, Orologio I, et al. Migraine treatment: towards new pharmacological targets. *Int J Mol Sci*. 2023;24:12268.
8. Barral E, Buonanotte F. Pain catastrophizing and medication overuse in patients with chronic migraine. *Rev Neurol*. 2020;70:282-286.
9. Russo AF, Hay DL. CGRP physiology, pharmacology, and therapeutic targets: migraine and beyond. *Physiol Rev*. 2023;103:1565-1644.
10. Sacco S, Amin FM, Ashina M, et al. European headache federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention - 2022 update. *J Headache Pain*. 2022;23:67.
11. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: the randomized, double-blind, placebo-controlled REGAIN study. *Neurology*. 2018;91:e2211-e2221.
12. Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of galcanezumab for the prevention of episodic migraine: the EVOLVE-1 randomized clinical trial. *JAMA Neurol*. 2018;75:1080-1088.
13. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. 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.
14. Skljarevski V, Oakes TM, Zhang Q, et al. Effect of different doses of galcanezumab vs placebo for episodic migraine prevention: a randomized clinical trial. *JAMA Neurol*. 2018;75:187-193.
15. Orlando B, Egeo G, Aurilia C, Fiorentini G, Barbanti P. Calcitonin gene-related peptide monoclonal antibodies: key lessons from real-world evidence. *Brain Sci*. 2024;14:948.
16. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *J Am Med Assoc*. 2000;283:2008-2012.
17. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
18. Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd ed. John Wiley & Sons; 2019. doi:10.1002/9781119536604
19. Fernández-Bravo-Rodrigo J, Pascual-Morena C, Flor-García A, et al. The safety and efficacy of calcitonin gene-related peptide (CGRP) monoclonal antibodies for the preventive treatment of migraine: a protocol for multiple-treatment systematic review and meta-analysis. *Int J Environ Res Public Health*. 2022;19:1753.
20. Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Meas*. 1960;20:37-46.
21. Ma LL, Wang YY, Yang ZH, Huang D, Weng H, Zeng XT. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? *Mil Med Res*. 2020;7:7.
22. Sidik K, Jonkman JN. A simple confidence interval for meta-analysis. *Stat Med*. 2002;21:3153-3159.
23. Freeman MF, Tukey JW. Transformations related to the angular and the square root. *Ann Math Stat*. 1950;21:607-611.
24. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5:13.
25. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-634.
26. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56:455-463.
27. Krymchantowski AV, Jevoux C, Krymchantowski AG, Silva-Néto RP. Monoclonal antibodies for chronic migraine and medication overuse headache: a real-world study. *Front Neurol*. 2023;14:1129439.
28. Krymchantowski AV, Jevoux C, Krymchantowski AG, Silva-Néto RP. Medication overuse headache, chronic migraine and monoclonal antibodies anti-CGRP: a real-world study. *Clin Neuropharmacol*. 2023;46:181-185.
29. Viudez-Martínez A, Pascual-Carrasco A, Beltrán-Blasco I, et al. Effectiveness and safety of erenumab and galcanezumab in the prevention of chronic and episodic migraine: a retrospective cohort study. *J Clin Pharm Ther*. 2022;47:814-823.
30. López-Bravo A, Oliveros-Cid A, Sevillano-Orte L. Treatment satisfaction with calcitonin gene-related peptide monoclonal antibodies as a new patient-reported outcome measure: a real-life experience in migraine. *Acta Neurol Scand*. 2022;145:669-675.
31. Munoz-Vendrell A, Campoy S, Caronna E, et al. Effectiveness and safety of anti-CGRP monoclonal antibodies in patients over 65 years: a real-life multicentre analysis of 162 patients. *J Headache Pain*. 2023;24:63.
32. Alpuente A, Torre-Sune A, Caronna E, Gine-Cipres E, Torres-Ferrús M, Pozo-Rosich P. Impact of anti-CGRP monoclonal antibodies on migraine attack accompanying symptoms: a real-world evidence study. *Cephalalgia*. 2023;43:3331024231177636.
33. Alex A, Vaughn C, Rayhill M. Safety and tolerability of 3 CGRP monoclonal antibodies in practice: a retrospective cohort study. *Headache*. 2020;60:2454-2462.
34. Altamura C, Brunelli N, Marcosano M, et al. Conversion from chronic to episodic migraine in patients treated with galcanezumab in real life in Italy: the 12-month observational, longitudinal, cohort multicenter GARLIT experience. *J Neurol*. 2022;269:5848-5857.
35. Pons-Fuster E, Lozano-Caballero O, Martín-Balbuena S, et al. AntiCGRP monoclonal antibodies in resistant migraine: preliminary real-world effectiveness and clinical predictors of response at two years. *Int J Clin Pharmacol*. 2024;46:1317-1326.
36. Ilgaz Aydinlar E, Erdogan Soyukibar T, Yalinay Dikmen P. Effectiveness of galcanezumab on sleep quality, migraine outcome, and multidimensional patient-reported outcome measures: a real-world experience in Turkish patients with episodic and chronic migraine. *Front Neurol*. 2024;15:1411238.
37. Vernieri F, Altamura C, Aurilia C, et al. Effectiveness, safety, and tolerability of galcanezumab in a real-life setting in patients with migraine in Italy (the GARLIT study). *Neurol Sci*. 2020;41:487-488.
38. Vernieri F, Altamura C, Brunelli N, et al. Galcanezumab for the prevention of high frequency episodic and chronic migraine in real life in Italy: a multicenter prospective cohort study (the GARLIT study). *J Headache Pain*. 2021;22:35.
39. Vernieri F, Brunelli N, Messina R, et al. Discontinuing monoclonal antibodies targeting CGRP pathway after one-year treatment: an observational longitudinal cohort study. *J Headache Pain*. 2021;22:154.
40. Vernieri F, Brunelli N, Marcosano M, et al. Maintenance of response and predictive factors of 1-year galcanezumAb treatment in real-life migraine patients in Italy: the multicenter prospective cohort GARLIT study. *Eur J Neurol*. 2023;30:224-234.
41. Vernieri F, Iannone LF, Guerzoni S, et al. Long-term effectiveness of galcanezumab in the prevention of migraine: an Italian retrospective analysis (REALITY). *Neurol Ther*. 2024;13:415-435.
42. Sacca F, Braca S, Sansone M, et al. A head-to-head observational cohort study on the efficacy and safety of monoclonal antibodies

against calcitonin gene-related peptide for chronic and episodic migraine. *Headache*. 2023;63:788-794.
43. di Cola F, Bolchini M, Ceccardi G, et al. An observational study on monoclonal antibodies against calcitonin-gene-related peptide and its receptor. *Eur J Neurol*. 2023;30:1764-1773.
44. Lee HC, Cho S, Kim BK. Predictors of response to galcanezumab in patients with chronic migraine: a real-world prospective observational study. *Neurol Sci*. 2023;44:2455-2463.
45. Ray JC, Dalic L, Baker J, Cheng S, Hutton EJ, Matharu M. Twelve-month efficacy of CGRP monoclonal antibodies and predictive value of short-term response: results of an Australian multicentre study. *BMJ Neurol Open*. 2024;6:e000547.
46. Suzuki K, Suzuki S, Shiina T, et al. Could efficacy at 1 week after galcanezumab administration for patients with migraine predict responders at 3 months? A real world study. *J Neurol*. 2023;270:4377-4384.
47. Suzuki K, Suzuki S, Shiina T, et al. Effectiveness of three calcitonin gene-related peptide monoclonal antibodies for migraine: a 12-month, single-center, observational real-world study in Japan. *Cephalalgia*. 2023;43:3331024231177649.
48. Grazzi L, Giossi R, Montisano DA, et al. Real-world effectiveness of anti-CGRP monoclonal antibodies compared to Onabotulinumtoxin A (RAMO) in chronic migraine: a retrospective, observational, multicenter, cohort study. *J Headache Pain*. 2024;25:14.
49. Cantarelli L, Pestana Grafiña D, Gonzalez Perez A, et al. Efficacy and safety of erenumab, galcanezumab, and fremanezumab in the treatment of drug-resistant chronic migraine: experience in real clinical practice. *Ann Pharmacother*. 2023;57:416-424.
50. Iannone LF, Fattori D, Benemei S, Chiarugi A, Geppetti P, De Cesaris F. Long-term effectiveness of three anti-CGRP monoclonal antibodies in resistant chronic migraine patients based on the MIDAS score. *CNS Drugs*. 2022;36:191-202.
51. Shibata M, Fujita K, Hoshino E, et al. Real-world experience with calcitonin gene-related peptide-targeted antibodies for migraine prevention: a retrospective observational cohort study at two Japanese headache centers. *BMC Neurol*. 2024;24:32.
52. Silvestro M, Tessitore A, Orologio I, et al. Galcanezumab effect on "whole pain burden" and multidimensional outcomes in migraine patients with previous unsuccessful treatments: a real-world experience. *J Headache Pain*. 2022;23:69.
53. Braca S, De Simone R, Stornaiuolo A, Cretella G, Miele A, Russo CV. Adding corticosteroids to galcanezumab in medication overuse headache: a three-arm head-to-head prospective observational cohort study. *Rev Neurol (Paris)*. 2025;181:106-113.
54. Díaz Insa S, Guerrero Á, Viguera J, et al. Observational retrospective study in patients treated with galcanezumab as preventive treatment for migraine: the ORYGAM study. *Pain Ther*. 2024;13:557-576.
55. Guerzoni S, Baraldi C, Brovia D, Cainazzo MM, Castro FL, Pani L. Monoclonal anti-CGRP antibodies in post-menopausal women: a real-life study. *Acta Neurol Belg*. 2023;123:1039-1047.
56. Guerzoni S, Baraldi C, Castro FL, Cainazzo MM, Pani L. Galcanezumab for the treatment of chronic migraine and medication overuse headache: real-world clinical evidence in a severely impaired patient population. *Brain Behav*. 2023;13:e2799.
57. Kwon S, Gil YE, Lee MJ. Real-world efficacy of galcanezumab for the treatment of migraine in Korean patients. *Cephalalgia*. 2022;42:705-714.
58. Takizawa T, Ohtani S, Watanabe N, et al. Real-world evidence of galcanezumab for migraine treatment in Japan: a retrospective analysis. *BMC Neurol*. 2022;22:512.
59. Obach V, Velasco F, Alvarez Escudero R, et al. Long-term effectiveness and tolerability of galcanezumab in patients with migraine excluded from clinical trials: real-world evidence of 1055 patients with 1 year follow-up from the Galca-only registry. *J Headache Pain*. 2023;24:157.
60. Rattanawong W, Anukoolwittaya P, Hiransuthikul A, et al. Medication underuse in real-life practice: the impact of galcanezumab towards achieving very low frequency episodic migraine in a southeast Asian middle-income nation. *J Headache Pain*. 2025;26:13.
61. Tereshko Y, Dal Bello S, Pez S, et al. Comparative study of the efficacy of anti-CGRP mAbs on migraineurs: analysis of the first year of therapy, 1-month suspension period, and reprisal. *J Clin Med*. 2023;12:7329.
62. Ito Y, Mitsufuji T, Okada M, et al. Early effect of calcitonin gene-related peptide monoclonal antibodies in migraine with medication overuse: a single-center retrospective study. *Intern Med*. 2023;62:3455-3460.
63. Ren Z, Zhang H, Wang R, Yuan Q, Pan L, Chen C. The treatment efficacy of galcanezumab for migraine: a meta-analysis of randomized controlled trials. *Clin Neurol Neurosurg*. 2019;186:105428.
64. Ferreira VL, Mainka FF, Wiens A, Pontarolo R. Effectiveness of calcitonin gene-related peptide monoclonal antibodies in the prevention of migraine: a systematic review and meta-analysis of observational cohort studies. *Clin Drug Investig*. 2023;43:669-680. doi:10.1007/s40261-023-01301-7
65. Bhakta M, Vuong T, Taura T, Wilson DS, Stratton JR, Mackenzie KD. Migraine therapeutics differentially modulate the CGRP pathway. *Cephalalgia*. 2021;41:499-514.
66. Basedau H, Sturm LM, Mehnert J, Peng KP, Schellong M, May A. Migraine monoclonal antibodies against CGRP change brain activity depending on ligand or receptor target - an fMRI study. *Elife*. 2022;11:e77146.
67. Basedau H, Oppermann T, Gundelwein Silva E, Peng KP, May A. Galcanezumab modulates capsaicin-induced C-fiber reactivity. *Cephalalgia*. 2022;42:1331-1338.
68. Vikelis M, Rikos D, Argyriou AA, Dermitzakis EV, Andreou AP, Russo A. Switching between anti-CGRP monoclonal antibodies in migraine prophylaxis. *Expert Rev Neurother*. 2025;25(3):359-374. Online ahead of print.
69. Chase BA, Semenov I, Rubin S, et al. Characteristics associated with response to subcutaneously administered anti-CGRP monoclonal antibody medications in a real-world community cohort of persons living with migraine: a retrospective clinical and genetic study. *Headache*. 2024;64:68-92.
70. Fernández-Bravo-Rodrigo J, Cavero-Redondo I, Lucerón-Lucas-Torres M, et al. Real-world effectiveness and safety of erenumab for the treatment of migraine: a systematic review and meta-analysis. *Eur J Pharmacol*. 2024;976:176702.
71. Sacco S, Bendtsen L, Ashina M, et al. European Headache Federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention. *J Headache Pain*. 2019;20:6.
72. Ailani J, Kaiser EA, Mathew PG, et al. Role of calcitonin gene-related peptide on the gastrointestinal symptoms of migraine-clinical considerations: a narrative review. *Neurology*. 2022;99:841-853.
73. Janković SM, Janković SV. Anti-calcitonin gene-related peptide monoclonal antibodies in migraine: focus on drug interactions. *Eur J Drug Metab Pharmacokinet*. 2024;49:263-275.
74. Kudrow D, Nguyen L, Semler J, et al. A phase IV clinical trial of gastrointestinal motility in adult patients with migraine before and after initiation of a calcitonin gene-related peptide ligand (galcanezumab) or receptor (erenumab) antagonist. *Headache*. 2022;62:1164-1176.
75. Nicol KS, Burkett JG. Review: an update on CGRP monoclonal antibodies for the preventive treatment of episodic migraine. *Curr Pain Headache Rep*. 2025;29:55.

76. Jančuljak D, Petravić D, Mahović Lakušić D, et al. Croatian guidelines for specific preventive treatment of migraine with monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) (eptinezumab, fremanezumab, and galcanezumab) or the CGRP receptor (erenumab). *Acta Clin Croat*. 2024;63:436-450.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Fernández-Bravo-Rodrigo J, Pascual-Morena C, Saz-Lara A, et al. Real-world effectiveness and safety of galcanezumab for the treatment of migraine: A systematic review and meta-analysis. *Headache*. 2026;66:262-277. doi:10.1111/head.70003