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REVIEW

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Safety and efficacy of galcanezumab in chronic and episodic migraine patients: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background The humanized monoclonal antibody galcanezumab is an anti-calcitonin-gene-related-peptide (CGRP) and frequently used for migraine prevention. However, the literature revealed limited data with conflicting results. This study aims to assess the safety and efficacy of galcanezumab in treating patients with episodic or chronic migraine.

Methods We searched for randomized controlled trials till September 2022 from six databases (Cochrane library, Embase, PubMed, Web of Science, Scopus, and Clinicaltrials.gov registry). Our primary outcomes were the change in the number of monthly migraine headache days (MHDs) and adverse events. We extracted the data and analyzed it by RevMan (5.4) software.

Results Eight studies with 4964 patients were included. Galcanezumab (≥ 120 mg) significantly reduced the MHDs for six months in migraine patients compared to placebo. The monthly risk ratio (RR) ranged from − 2.33 to − 1.62 for episodic migraine and − 2.86 to − 2.44 for chronic migraine. The response rate of ≥ 50%, ≥ 75% and 100% were higher with galcanezumab groups. The rate ranged from 1.72 to 4.19 for episodic migraine and 1.84 to 2.47 for chronic migraine. It is generally safe except for injection site safety outcomes (erythema, reaction, pruritis, and swelling), the results were significantly higher with galcanezumab groups. It appears dose independent except for injection site reaction, which showed higher with galcanezumab 120 mg only. Furthermore, any adverse events, serious adverse events (SAE) and that led to discontinuation were higher with galcanezumab 240 mg.

Conclusion Galcanezumab is effective in patients with episodic or chronic migraine after one to six months use. It reduced MHDs and had an effective response rate. Moreover, it is generally safe except for injection site adverse events, and SAE, especially with galcanezumab 240mg.

Keywords Galcanezumab, LY2951742, Migraine, Headache, Meta-analysis

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Introduction

Migraine is one of the worldwide debilitating neurological disorders which affects many aspects of a patient's lifestyle [1, 2]. According to the US government health survey, in 2018, 40% of US adults had migraine with more than 4.3 million office visits recorded[3]. Patients with chronic and episodic migraine have a poor quality of life and significant psychological disturbance not to mention the increased economic burden [1, 4, 5]; In the US, it costs Over $20 billion every year [6]. Migraine is classified into two types; episodic and chronic migraine. Episodic migraine is diagnosed with up to 14 episodes per month while chronic migraine is diagnosed with 15 or more attacks per month and at least eight of those attacks have migraine-like symptoms [7]. Those headache episodes are characterized by nausea, vomiting, photophobia, or phonophobia [7].

Multiple drugs are used for migraine treatment. This includes calcium channel blockers, beta-blockers, anticonvulsants, angiotensin receptor blockers, or angiotensin-converting enzyme inhibitors, antidepressants, and antihypertensives [8–11]. However, the efficacy of those medications is still low. In addition, their tolerability is considerably leading to the need for new strategies [12]. The calcitonin gene-related peptide (CGRP) is a neuropeptide generated across the nervous system, especially sensory neurons. This peptide causes transmit pain via trigeminal neuron activation [13, 14]. CGRP is responsible for neurogenic inflammation, vasodilation, and nociceptive modulation, which are involved in migraine pathogenesis [15]. During migraines, the external jugular vein's CGRP increases [16]. Moreover, infusion of CGRP into migraine patients can cause migraine-like episodes [17]. Due to CGRP's crucial role in migraine, monoclonal antibodies targeting it were developed. CGRP receptor antagonists significantly affect the treatment and prevention of migraine and represent a new approach to migraine management [18, 19].

Galcanezumab is a selective humanized monoclonal antibody that targets CGRP functions [20]. Studies reported that galcanezumab is useful and tolerable in migraine patients, and prior failure of prophylactic medication [21, 22]. However, some adverse events were reported in the literature, and the results are still conflicting [23–26]. Hence, we conduct this systematic review and meta-analysis aiming to evaluate the safety and efficacy of galcanezumab for episodic or chronic migraine patients.

Methods

We conducted this study following the guidelines of the Cochrane handbook of systematic reviews of interventions [27] and the PRISMA statement [28].

Database search and data collection

We systematically searched and reviewed the literature on the following databases; Embase, SCOPUS, PubMed, Cochrane Library, Web of Science (WoS), and Clinicaltrials.gov till September 2022. The search terms were galcanezumab, LY2951742, migraine and headache.

Eligibility criteria

We included randomized controlled trials (RCTs) that compared safety and efficacy of galcanezumab versus placebo in patients with episodic or chronic migraine. We excluded non-randomized trials, non-English studies, non-human studies, conference abstracts, and those with no available full text.

Screening and study selection

We used Endnote software to collect the retrieved studies from the database search into a Microsoft Excel sheet. We performed a three-steps screening. This included title and abstract then full-text screening. In addition to, manual screening of the references of the included studies. Each step was done by four independent authors, and the fifth author resolved any conflicts.

Data extraction

Six authors extracted the data based on three main categories; summary of included studies, baseline characteristics of the recruited participants, and outcomes. The summary of the included studies comprised registration number, migraine definition, administration interval, duration of the trial, and primary outcome of each study. The baseline characteristics included study arms, sample size, age, gender, race, BMI (kg/m^2), migraine illness duration, MHDs/month, MHDs/month with acute medication use, and prior preventive treatment in the past five years.

Outcomes

The efficacy outcomes included the change of monthly migraine headache days (MHDs) at one to six months. Additionally, we assessed chronic and episodic migraine change on monthly MHDs (Months 1–3), ≥ 50%, ≥ 75%, and 100% response rates, and change in monthly MHDs with acute medication use. The safety outcomes included ≥ 1 adverse, serious adverse event (SAE), adverse event leading to discontinuation, injection site (pain, erythema, reaction, pruritis, swelling) nasopharyngitis, sinusitis, upper respiratory tract infection, neck pain, back pain, and diarrhea.

Quality assessment

The Cochrane risk of bias tool was utilized to assess the included RCTs [29]. It evaluates selection bias, blinding (participants, personnel and outcome assessment), insufficient outcome data, selective reporting, and other sources of bias. The final judgment is low, high, or unclear risk of bias. This step was done by four different authors with a fifth author solving any conflict.

Statistical analysis

The review manager software 5.4 was used for meta-analysis. Dichotomous data were described as risk ratio (RR) with 95% confidence intervals (CI). While mean difference (MD) and 95% CI descried continuous data. A random-effects model was used to pool the heterogeneous outcomes. Cochrane's *P* values and I^2 were used to assess each study's heterogeneity. Data were considered heterogeneous when $p < 0.1$ and $I2 > 50\%$. We did a sensitivity analysis to solve heterogeneity by leaving one out method. We were unable to assess publication bias because all outcomes were reported in less than ten publications. We conducted a subgroup analysis based on the treatment regimen.

Results

Summary of studies selection and general characteristics of included studies

A total of 2,535 studies were retrieved from six different databases; PubMed (n = 280), SCOPUS (n = 514), Cochrane Library (n = 282), WoS (n = 483), Embase (n = 949) and Clinicaltrials.gov (n = 27). After removing duplicates, 1211 studies were eligible for the title and abstract screening. We performed full-text screening for 32 studies, and eight studies [20, 23–26, 30–32] were included in our meta-analysis. Figure 1 shows the PRISMA flow diagram of study search and selection.

Our meta-analysis pooled data from 4964 patients from eight clinical trials. The mean age was 41.5 years, and most of them were females (84%). The mean migraine illness duration was 20 years. The general and baseline characteristics of the included studies and population are shown in Tables 1 and 2.

Results of the quality assessment

Most of the included trials were judged as low risk regarding first six domains. Only the study by Oakes et al. [26] did not report adequate data regarding the randomization and allocation processes; So, it was put at unclear risk of bias. However, all studies may have other bias as they funded by pharmaceutical companies. Figure 2 shows the summary of the quality assessment results.

Analysis of the outcomes

Change of migraine headache days after one month

Episodic migraine Galcanezumab 120/150 mg was evaluated by seven studies [20, 24–26, 30–32]. Galcanezumab 120/150 mg significantly reduced MHDs than placebo after one month; MD = -2.13, 95% CI [− 2.75, − 1.52], $p < 0.00001$. The pooled analysis was heterogeneous ($p = 0.0007$, $I^2 = 74\%$) and could not be solved by sensitivity analysis. As for galcanezumab 240/300 mg, it was reported by four studies [20, 26, 31, 32]. Galcanezumab 240/300 mg significantly reduced MHDs after one month; MD = − 1.88, 95% CI [− 2.37, − 1.40], $p < 0.00001$. The analysis was homogeneous; $p = 0.25$, $I^2 = 27\%$. Figure 3

Chronic migraine This outcome was reported by two studies [23, 25]. Galcanezumab 120 mg significantly reduced MHDs after one month; MD = − 2.62, 95% CI [− 3.82, − 1.42], $p < 0.0001$. The pooled analysis was homogeneous, $p = 0.24$, $I^2 = 28\%$. Figure 3

Change of migraine headache days after two to five months

Galcanezumab 120/150 and 240/300 mg significantly lowered MHDs in episodic migraine patients after two, three, four, and five months compared with the placebo; $p < 0.05$. Additionally, 120 and 240 mg galcanezumab significantly lowered MHDs in chronic migraine patients after two and three months than placebo; $p < 0.05$, Figs. 4, 5, 6, 7.

Change of migraine headache days after six months

This outcome was reported by three studies [20, 31, 32]. Galcanezumab 120 mg significantly decreased MHDs after six months in episodic migraine patients; MD = − 1.99, 95% CI [− 2.53, − 1.44], $P < 0.00001$. The pooled data was homogeneous; $p = 0.3$, $I^2 = 17\%$. Also, 240 mg galcanezumab significantly decreased MHDs after six months in episodic migraine patients; MD = − 2.28, 95% CI [-3.17, − 1.39], $p < 0.00001$. The pooled analysis was heterogeneous $p = 0.05$, $I^2 = 67\%$. Figure 8a Heterogeneity was solved after the exclusion of Sakai et al. [31]; $p = 0.77$, $I^2 = 0\%$. The pooled analysis remained significant; MD = -1.83, 95% CI [− 2.42, − 1.24], $p < 0.00001$, Figure 8b.

Change in monthly migraine headache days (Months 1–3)

Episodic migraine This outcome was reported by three studies [24, 25, 30]. Galcanezumab 120/150 mg significantly reduced the monthly MHDs after one to three months; MD = − 1.87, 95% CI [− 2.60, − 1.14], $p < 0.00001$. The pooled analysis was heterogeneous $p = 0.06$, $I^2 = 64\%$. Fig S1a This was solved after excluding Dodick et al. [30];

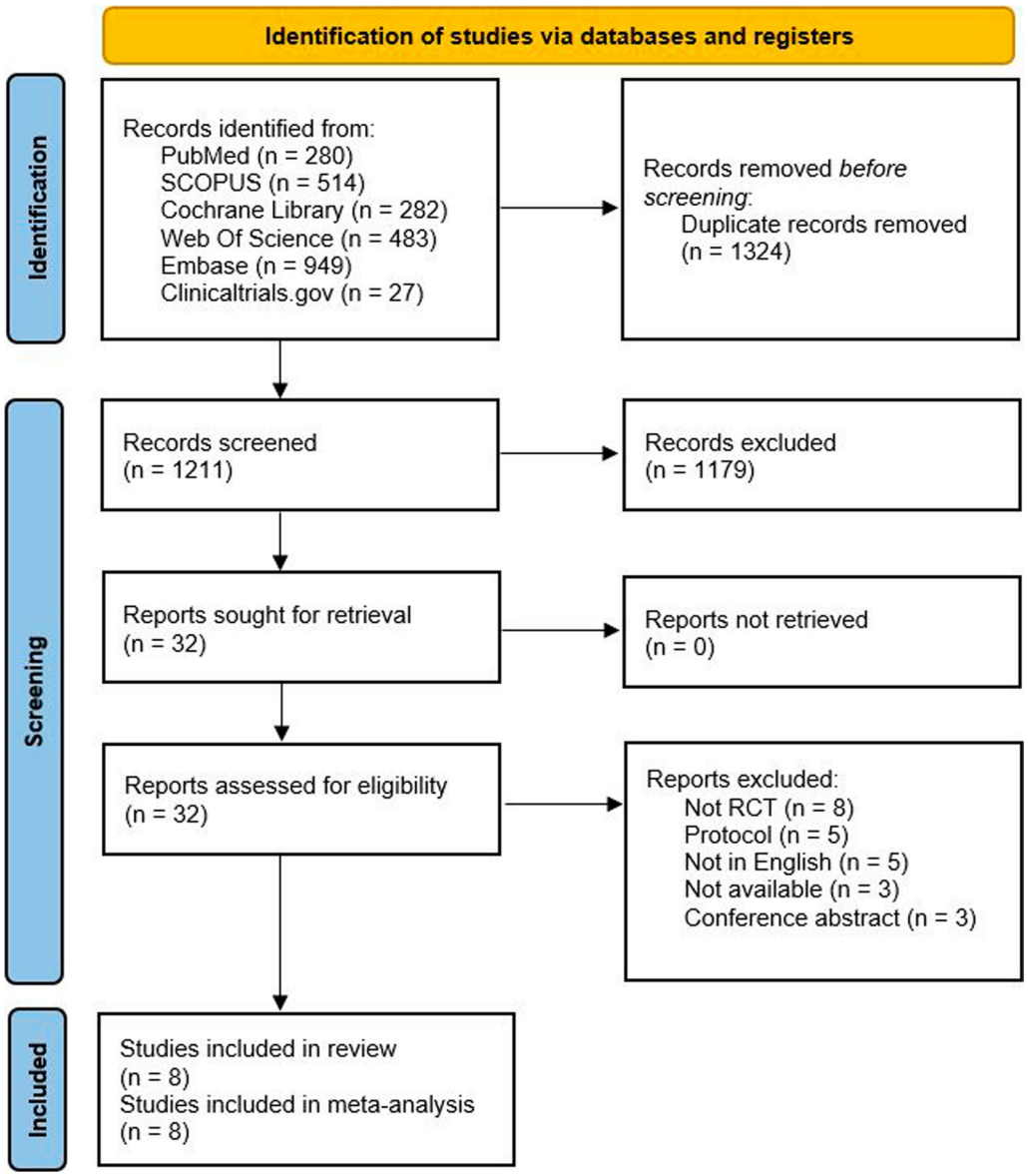

Fig. 1 PRISMA flow diagram

Table 1 Summary of the included studies

ID	Registration	Migraine definition	Administration interval	Duration of trial	Main outcome
Detke et al. 2018	NCT2614261	ICHD-3β	Monthly	Three months	MHDs
Dodick et al. 2014	NCT1625988	ICHD-II	Every two weeks	Three months	MHDs
Hu et al. 2022	NCT3963232	ICHD-3; 1.1 or 1.2	Monthly	Three months	MHDs
Mulleners et al. 2021	NCT3559257	ICHD3	Monthly	Three months	MHDs
Oakes et al. 2018	NCT2163993	ICHD-3β	Monthly	Three months	TEAEs
Sakai et al. 2020	NCT2959177	ICHD-3; 1.1 or 1.2	Monthly	Six months	MHDs
Skljarevski et al. 2018	NCT2614196	ICHD-3β	Monthly	Six months	MHDs
Stauffer et al. 2018	NCT2614183	ICHD-3β	Monthly	Six months	MHDs

ICHD international classification of headache disorders, *MHDs* migraine headache days, *TEAEs* Treatment-emergent adverse events

Table 2 Baseline characteristics of the included studies

ID	Study arms	Sample	Age, M ± SD	Female, n (%)	White race, n (%)	BMI (kg/m^2), M ± SD	Migraine illness duration years, M ± SD	MHDs/month, n (%)	MHDs/month with acute medication use, n (%)	Prior preventive treatment in the past 5 y, n (%)
Detke et al. 2018	Galcanezumab 120 mg	278	39.7 (11.9)	237 (85)	223 (80)	26.4 (5.5)	20.4 (12.7)	19.4 (4.3)	15.1 (6.3)	211 (76)
	Galcanezumab 240 mg	277	41.1 (12.4)	226 (82)	224 (81)	26.7 (5.2)	20.1 (12.7)	19.2 (4.6)	14.5 (6.3)	220 (79)
	Placebo	558	41.6 (12.1)	483 (87)	432 (77)	26.9 (5.6)	21.9 (12.9)	19.6 (4.6)	15.5 (6.6)	435 (78)
Dodick et al. 2014	Galcanezumab 150 mg	107	40.9 (11.4)	88 (82)	76 (71)	29.44 (6.3)	NR	6.7 (2.4)	NR	NR
	Placebo	110	41.9 (11.7)	96 (87)	74 (67)	29.03 (7.5)	NR	7.0 (2.5)	NR	NR
Hu et al. 2022	Galcanezumab 120 mg	261	37.2 (9.3)	188 (72.0)	22 (8.4)	23.4 (3.8)	12.8 (9.2)	8.2 (2.8	5.4 (4.9)	112 (42.9)
	Placebo	259	36.8 (9.8)	196 (75.7)	20 (7.7)	22.5 (3.2)	12.4 (8.2)	8.3 (2.7)	4.9 (4.5)	120 (46.3)
Mulleners et al. 2021	Galcanezumab 120 mg	232	45.9 (11.3)	195 (84)	183 (79)	26.0 (5.5)	22.7 (13.2)	13.4 (6.1)	12.3 (6.0)	All patients
	Placebo	230	45.7 (12.3)	202 (88)	182 (79)	25.6 (5.5)	23.8 (13.9)	13.0 (5.7)	12.4 (6.0)	
Oakes et al. 2018	Galcanezumab (all)	273	40.6 (11.9)	231 (84.6)	NR	NR	NR	6.7 (2.6)	NR	NR
	Placebo	137	39.5 (12.1)	109 (79.6)	NR	NR	NR	6.6 (2.7)	NR	NR
Sakai et al. 2020	Galcanezumab 120 mg	115	43.2 (10.0)	97 (84.2)	NR	NR	21.1 (11.8)	8.6 (2.8)	7.3 (2.9)	68 (59.1)
	Galcanezumab 240 mg	114	44.8 (10.2)	94 (82.6)	NR	NR	22.1 (11.6)	9.0 (3.0)	7.8 (3.0)	70 (61.4)
	Placebo	230	44.2 (10.0)	196 (85.2)	NR	NR	21.2 (11.6)	8.6 (3.0)	7.4 (3.0)	140 (60.9)
Skljarevski et al. 2018	Galcanezumab 120 mg	231	40.9 (11.2)	197 (85.3)	166 (71.9)	NR	19.93 (11.7)	9.07 (2.9)	7.47 (3.3)	157 (68)
	Galcanezumab 240 mg	233	41.9 (10.8)	200 (85.7)	159 (68.2)	NR	20.01 (12.1)	9.06 (2.9)	7.47 (3.3)	151 (64.6)
	Placebo	461	42.3 (11.3)	393)85.3	325 (70.5)	NR	20.01 (12.1)	9.2 (3.0)	7.6 (3.4)	298 (64.6)
Stauffer et al. 2018	Galcanezumab 120 mg	213	40.9 (11.9)	181 (85.0)	169 (79.3)	27.8 (5.3)	21.1 (13.0)	9.2 (3.1)	7.4 (3.7)	133 (62.4)
	Galcanezumab 240 mg	212	39.1 (11.5)	175 (82.6)	165 (77.8)	28.6 (5.7)	19.3 (11.9)	9.1 (2.9)	7.3 (3.3)	125 (59.0)
	Placebo	433	41.3 (11.4)	362 (83.6)	356 (82.2)	28.6 (5.5)	19.9 (12.3)	9.1 (3.0)	7.4 (3.5)	257 (59.4)

MHDs migraine headache days, *BMI* body mass index, *NR* not reported, *M ± SD* mean ± standard deviation, *n* number, *y* year

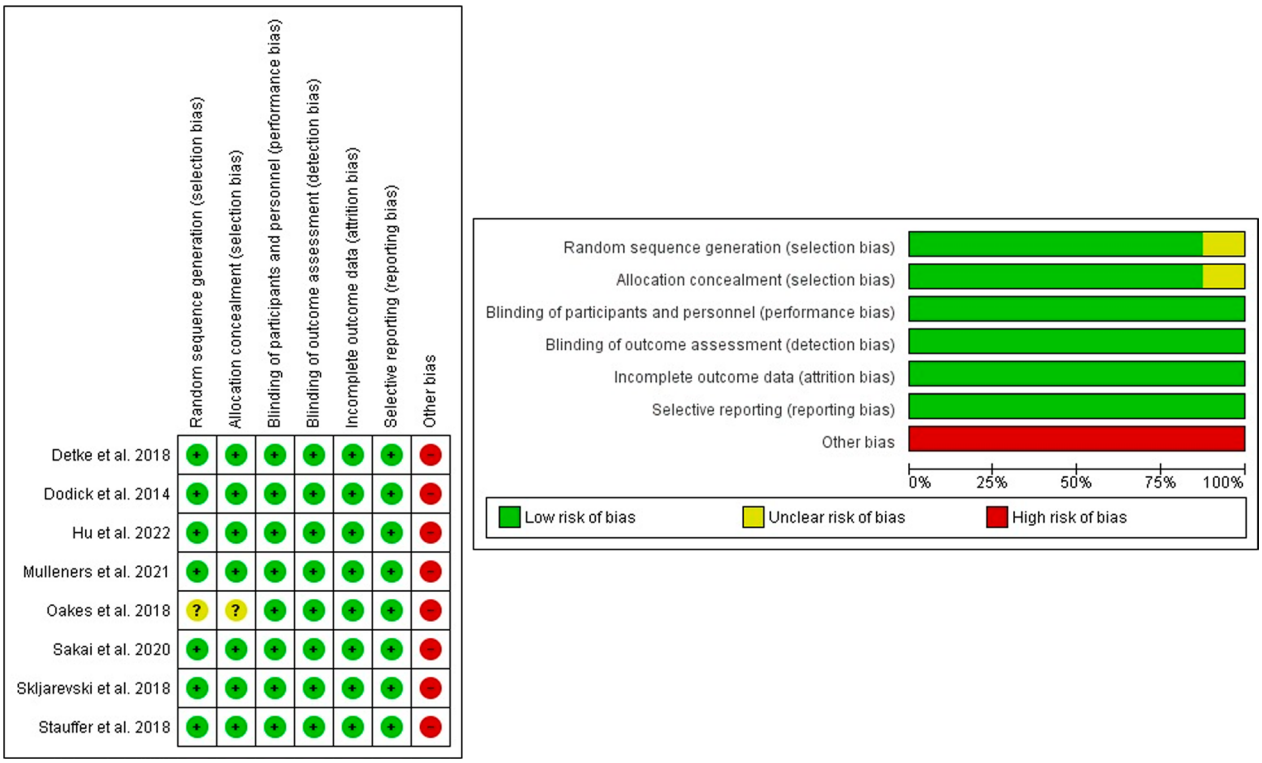

Fig. 2 Risk of bias summary and graph

p = 0.24, I^2 = 28%. The pooled data remained in favor of galcanezumab; MD = − 1.56, 95% CI [− 2.16, − 0.96], p < 0.00001, Fig. S1b.

Chronic migraine This outcome was reported by two studies [23, 25]. Galcanezumab 120 mg significantly lowered the monthly MHDs after one to three months of usage; MD = − 2.86, 95%CI [− 4.16, − 1.57], p < 0.0001. The analysis was homogeneous p = 0.22, I^2 = 34%, Fig. S1.

Change in monthly migraine headache days with acute medication use

Episodic migraine Two studies [24, 25] evaluated the 120 mg galcanezumab for 1–3 months. Galcanezumab 120 mg significantly decreased the monthly MHDs with acute medication use after one to three months; MD = -2.25, 95% CI [-3.25, -1.25], p < 0.00001. The pooled analysis was heterogeneous; p = 0.05, I^2 = 74%. Another two studies [20, 31] evaluated the 120 mg galcanezumab after one to six months of usage. It showed a significant reduction; MD = − 2.32, 95% CI [− 3.40, − 1.25], p < 0.00001. The pooled analysis was heterogeneous; p = 0.02, I^2 = 82%. As for galcanezumab 240 mg, two studies [20, 31] reported a significant reduction after one to six months of usage; MD = − 2.51, 95% CI [− 3.10, − 1.20], p < 0.00001. The pooled analysis was heterogeneous; p = 0.02, I^2 = 82%. The heterogeneity of this outcome could not be solved by sensitivity analysis, Fig. S2.

Chronic migraine This outcome was reported by two studies [23, 25]. Galcanezumab 120 mg significantly lowered the number of monthly MHDs with acute medication use after one to three months; MD = -3.09, 95% CI [-4.53, -1.65], p < 0.0001. The data were homogeneous; p = 0.13, I2 = 57%, Fig. S2.

Response rates

Episodic migraine Compared with placebo, galcanezumab 120 mg significantly increased the 50%, 75%, and 100% response rates of episodic migraine after one to three months (RR = 1.9, 2.65, 4.19) and one to six months (RR = 1.78, 2.02, 2.42), respectively. Additionally, the gal-

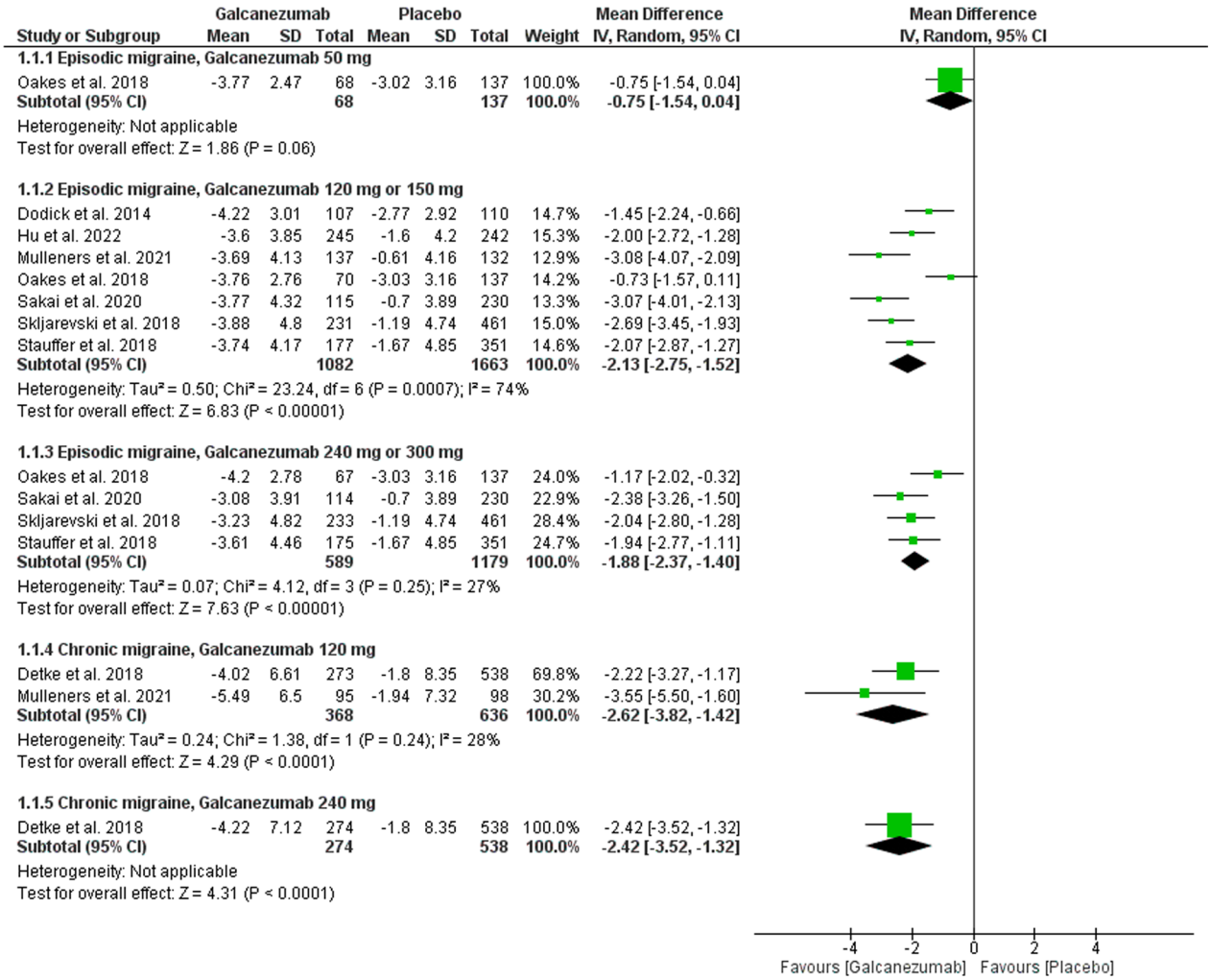

Fig. 3 A forest plot of the change in the migraine headache days after one month

canezumab 240 mg significantly increased the 50%, 75% and 100% response rates of episodic migraine after one to six months (RR = 1.72, 2.04, 2.51), respectively, Fig. S3–S5.

Chronic migraine Galcanezumab 120 and 240 mg significantly enhanced the 50% and 75% response rates of chronic migraine patients after one to three months than placebo; $p < 0.05$. In contrast, there were insignificant results with galcanezumab 120 or 240 mg regarding the 100% response rate of chronic migraine patients after one to three months; $p > 0.05$, Fig. S3–S5.

Safety outcomes

Most of the included trials reported the incidence of adverse events. Regarding injection site outcomes, the results were significantly higher with galcanezumab 120 mg group. This includes erythema; RR = 3.76, 95% CI [1.91, 7.40], reaction; RR = 6.44, 95% CI [2.10, 19.77], pruritis; RR = 26.7, 95% CI [7.27, 97.93], and swelling; RR = 7.17, 95% CI [2.22, 23.17]. Also, these adverse events were higher with the galcanezumab 240 mg group except for injection site reaction, which showed higher with galcanezumab 120 mg only. Any adverse events were noticed higher with galcanezumab 120 and 240 mg groups. Furthermore, serious adverse events and adverse events that led to discontinuation were higher with galcanezumab 240 mg only; RR = 3.12, 95% CI [1.08, 9.04] and RR = 2.59, 95% CI [1.06, 6.35], respectively. The rest of adverse events showed no variation between galcanezumab and placebo groups. Table 3 and Fig. S6–S19.

Discussion

This meta-analysis aimed to assess the efficacy and safety of galcanezumab subcutaneous injection in migraine patients. The pooled analysis was built on data from 4964 patients from eight RCTs. Five doses of galcanezumab were evaluated in patients with chronic and episodic migraine. This included 50 mg, 120 mg, 150 mg, 240 mg, and 300 mg. Our pooled analysis showed that different doses of galcanezumab (≥120 mg) lowered MHDs after one to six months. Additionally, galcanezumab significantly lowered the monthly episodic and chronic MHDs with acute medication use after one to six months. Galcanezumab also significantly increased the 50%, 75%, and 100% response rates. Regarding safety, galcanezumab showed higher adverse events incidence compared to the placebo. This includes the injection site safety outcomes (erythema, reaction, pruritis, and swelling), any adverse events, SAE, and adverse events that led to discontinuation.

Galcanezumab selectively targets CGRP without binding the CGRP receptor. Targeting CGRP prevents migraine episodes [20, 32]. Moreover, galcanezumab was approved by the FDA for episodic cluster headache prevention. It has been linked to a lower incidence of cluster headache attacks per week [33, 34]. A study by Förderreuther et al. revealed that galcanezumab-treated

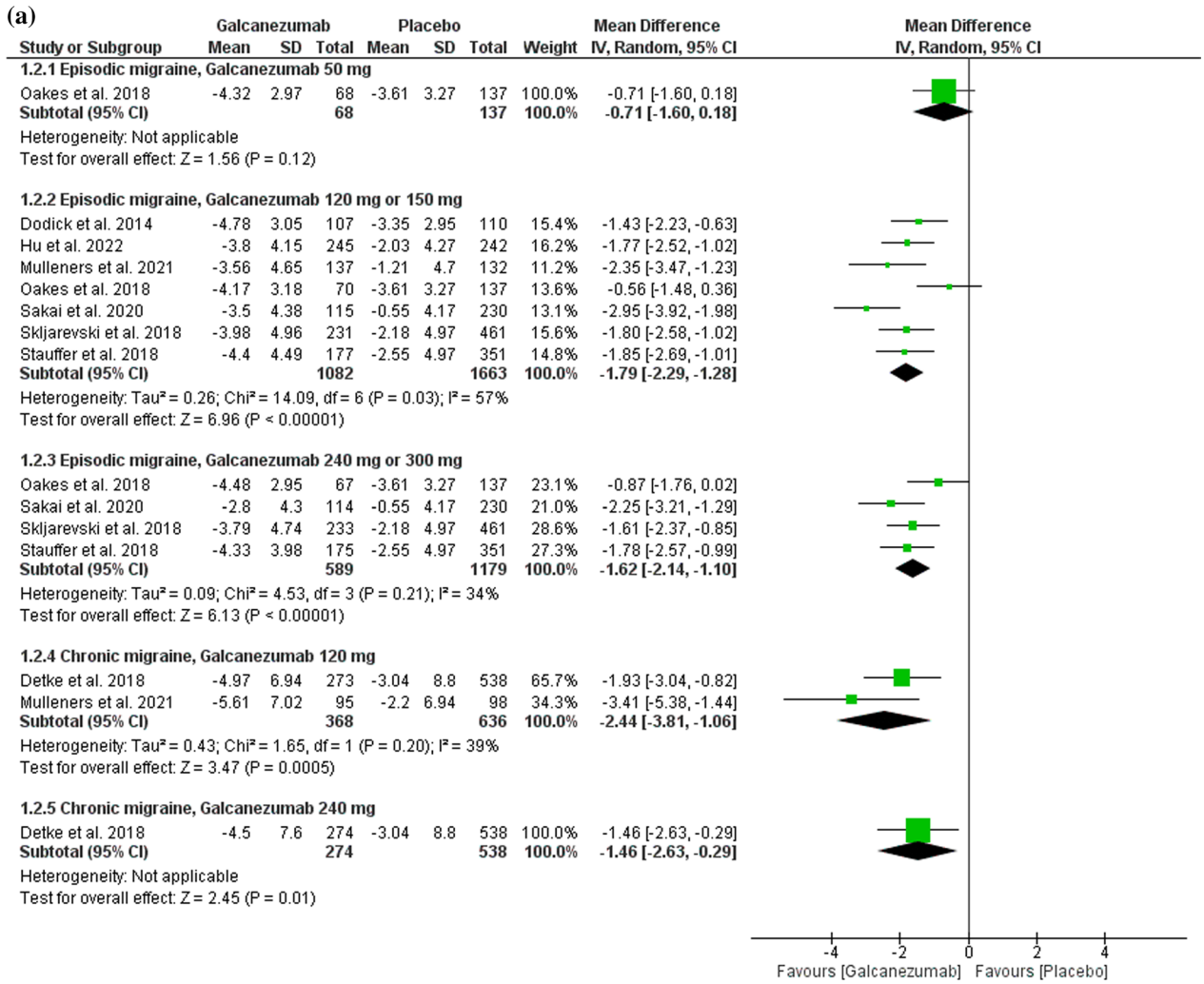

Fig. 4 **a** A forest plot of the change in the migraine headache days after two months before sensitivity analysis. **b** A forest plot of the change in the migraine headache days after two months after sensitivity analysis

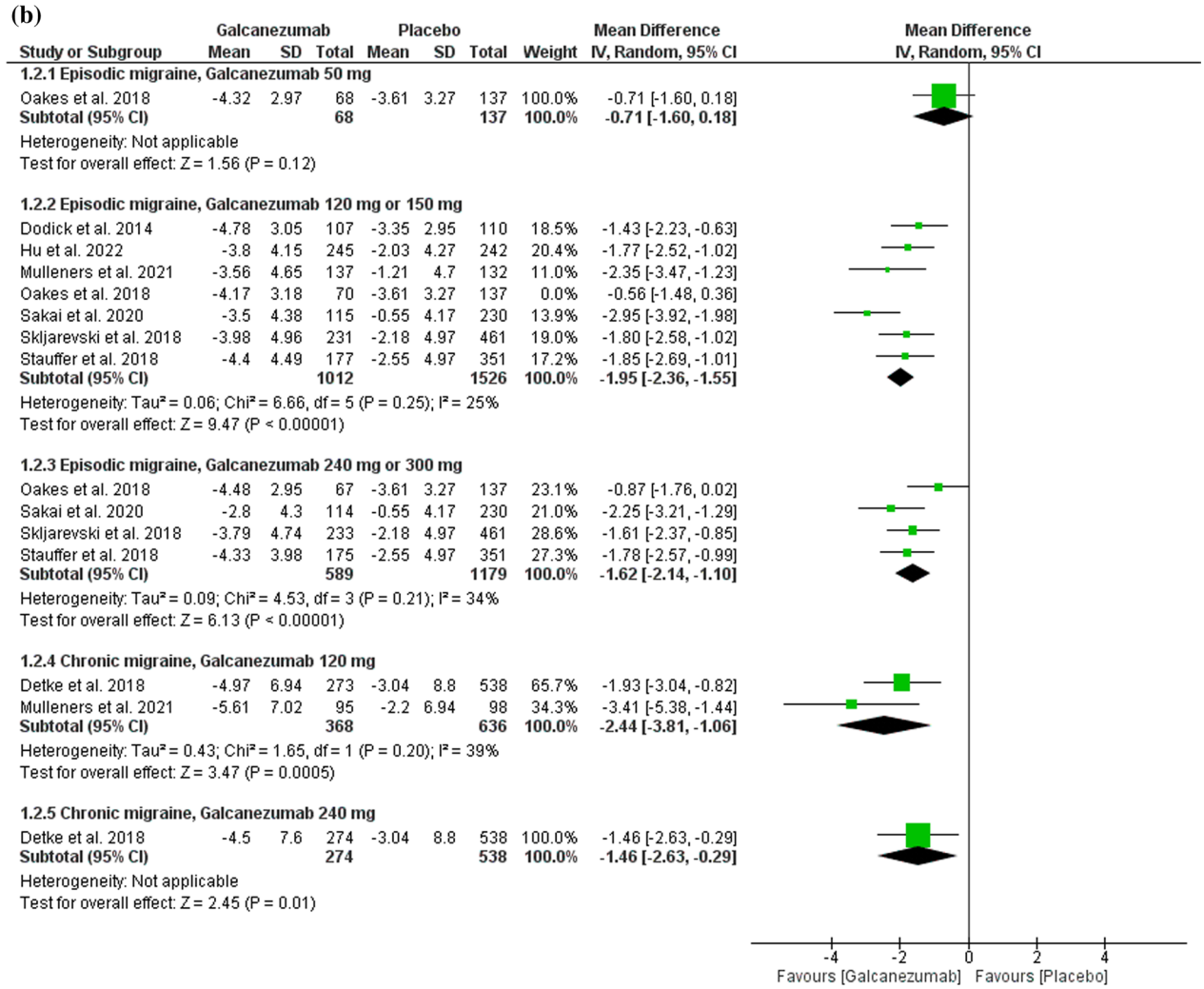

Fig. 4 continued

patients showed a persistent response of up to six months in episodic migraine patients and up to three months in chronic migraine patients [35]. Even after the end of the treatment, its performance remains. Phase III trials revealed that the overall therapeutic benefit of galcanezumab was diminished. However, it did not return to the baseline values [36, 37]. Besides its prolonged action, galcanezumab showed a rapid onset of action. The significant reduction of the MHDs started in the first week, and half of the patients experienced this reduction after one month [38].

Several regimens have been evaluated in the literature, including 50, 120, 150, 240, and 300 mg. Oakes et al. [26] found insignificant difference between galcanezumab 50 mg and placebo regarding MHDs after one, two, and three months. Additionally, they found non-significant results regarding the 120 mg and 240 mg galcanezumab regimens. Concerning the response rate, Detke et al. [23] and Mulleners et al. [25] found insignificant results between galcanezumab 120 mg and placebo regarding the 75% and 100% response rates against chronic migraine at one to three months. Additionally, Detke et al. [23]

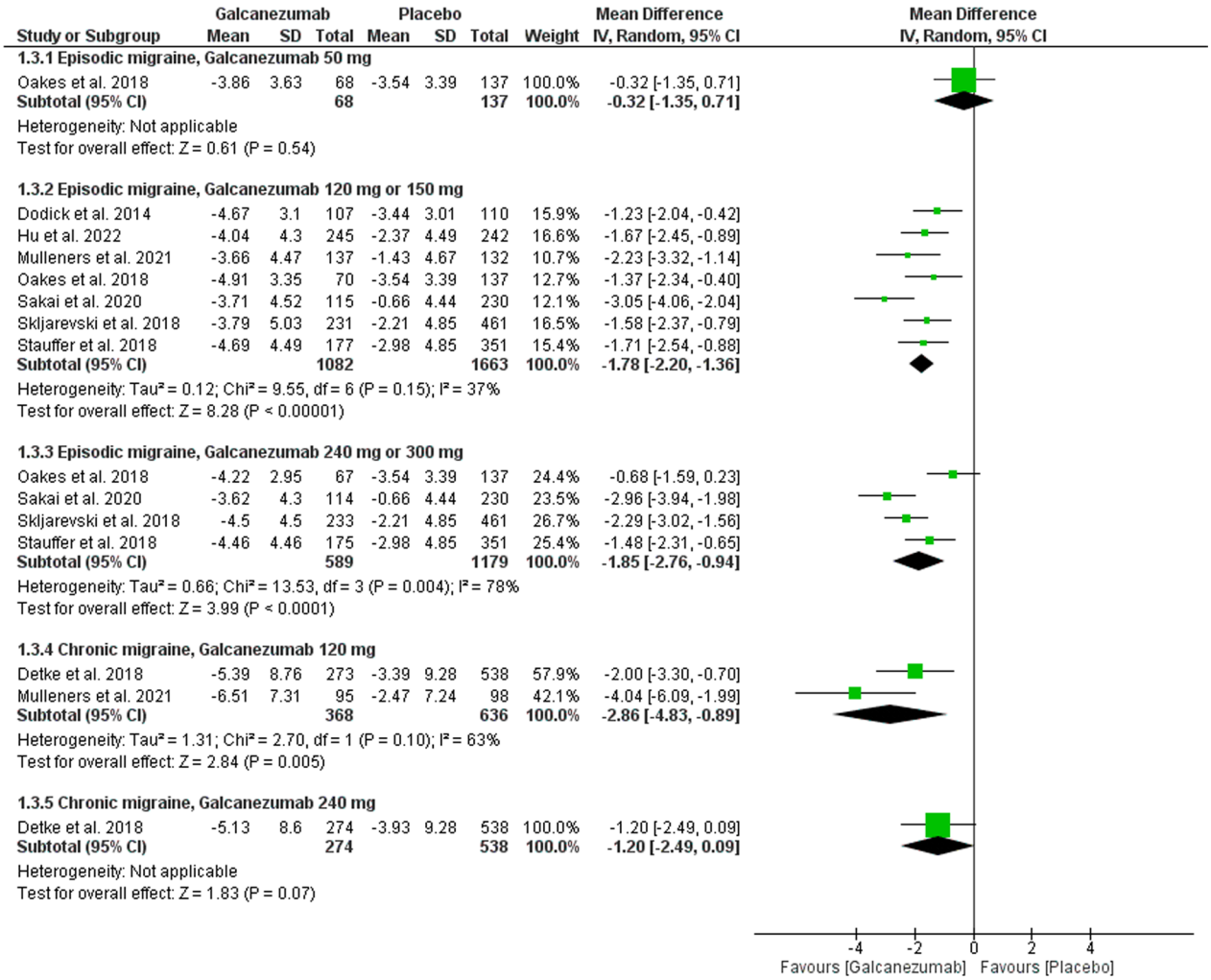

Fig. 5 A forest plot of the change in the migraine headache days after three months

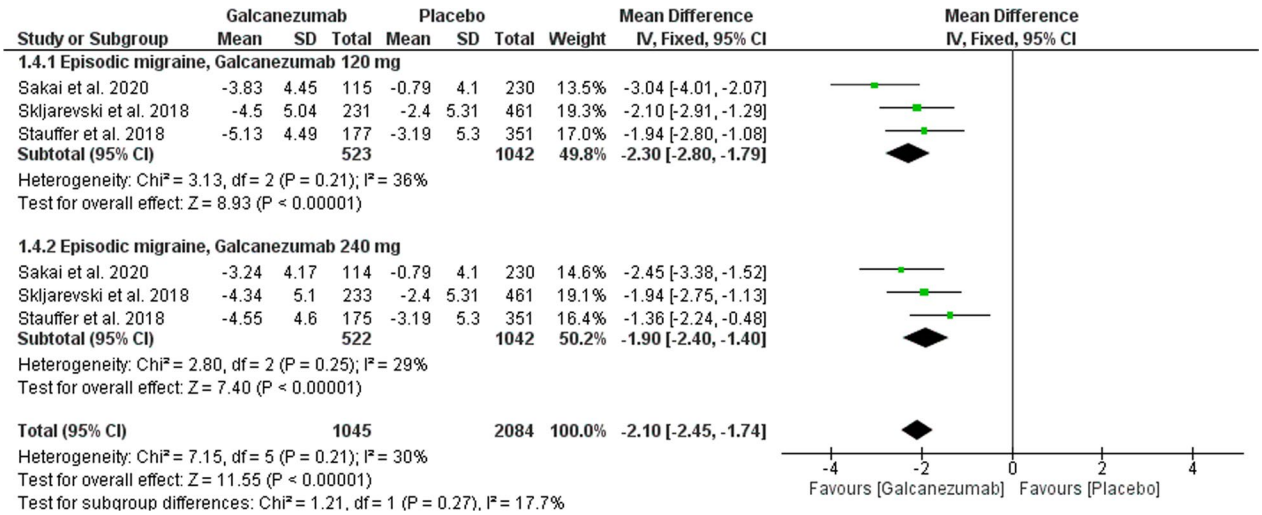

Fig. 6 A forest plot of the change in the migraine headache days after four months

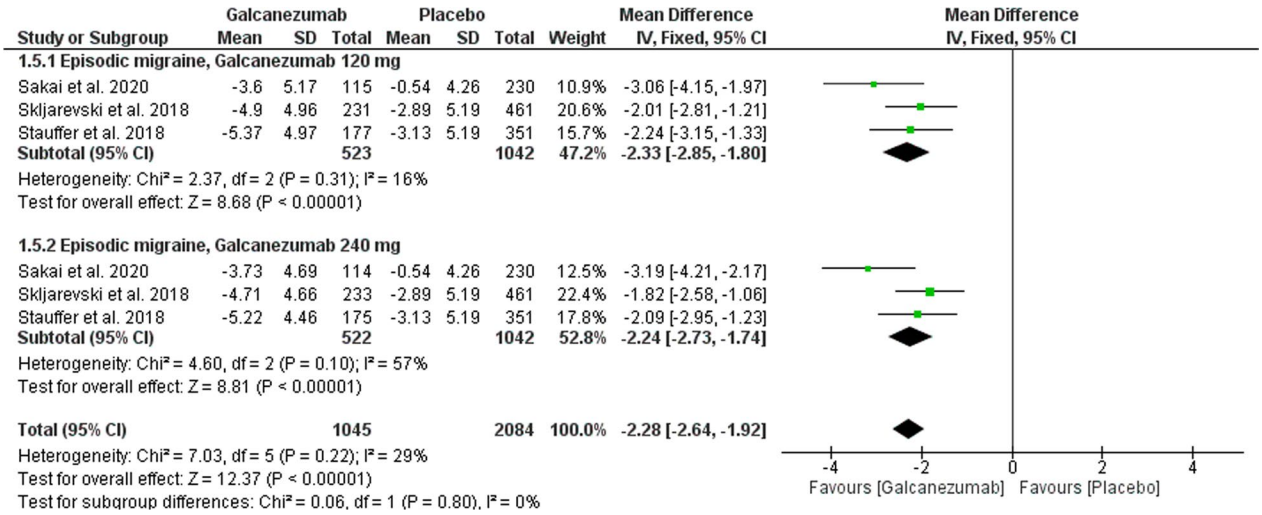

Fig. 7 A forest plot of the change in the migraine headache days after five months

reported no significant difference between both study arms regarding the 100% response rate of galcanezumab 240 mg at one to three months. Our meta-analysis found that galcanezumab (≥120 mg) lowered the episodic and chronic MHDs, and the MHDs with acute medication use after one to six months. Moreover, it significantly increased the 50%, 75%, and 100% response rates.

Our efficacy results concord with the 2020 meta-analysis by Yang et al. [39]. They revealed that galcanezumab (≥120 mg) significantly increased the response rates and reduced MHDs compared with placebo. Additionally, galcanezumab 300 mg reduced up to 50% of cluster headache attacks in the third week. However, they differed from ours regarding safety. They reported that upper respiratory infection and injection site pain were the most common adverse events. Also, SAE were increased with galcanezumab 120 and 240 mg. Interestingly, they found that galcanezumab 300 mg did not increase the incidence of adverse and SAE. They differed from ours as they did not discriminate between episodic and chronic migraine and included cluster headache patients.

In their meta-analysis, Abu-Zaid et al. [40] found that 120 and 240 mg galcanezumab decreased the MHDs, MHDs with acute medication use, and severity score. Quality-of-life and disability scores were significantly better with the 240 mg galcanezumab only. The nasopharyngitis and injection-site pain incidence did not significantly differ between both doses of galcanezumab and the placebo group. Unlike the 240 mg dose, the galcanezumab 120 mg showed a higher incidence of upper respiratory tract infection (URTI). This meta-analysis did not differentiate between the results of episodic and chronic migraine patients and did not report the results at different time intervals as we did. Galcanezumab is of great benefit for migraine prevention. Gklinos et al. [41] reported that 120 and 240 mg galcanezumab were effective for migraine. Additionally, it was safe with mild to moderate adverse events. Similar findings were reported by Zhao et al. [42].

Masoud et al. [43], in their network meta-analysis of data published before January 2019, compared the efficacy of multiple CGRP receptor blockers in reducing the MHDs. The pooled analysis of MHDs revealed that fremanezumab 900 mg, and erenumab 140 mg exhibited the most significant effects at six, eight, and twelve weeks. Galcanezumab revealed the best benefit across all comparators after six weeks for episodic migraine patients. The most effective doses were 300 mg, 150 mg, 120 mg, 50 mg, and 240 mg ordered from the most effective. In contrast, erenumab 140 mg was the most effective agent for episodic migraine after eight and twelve weeks. Many trials were published after this study, so another network meta-analysis is required to prove the safety and efficacy of CGRP receptor blockers and show the best treatment for migraine patients.

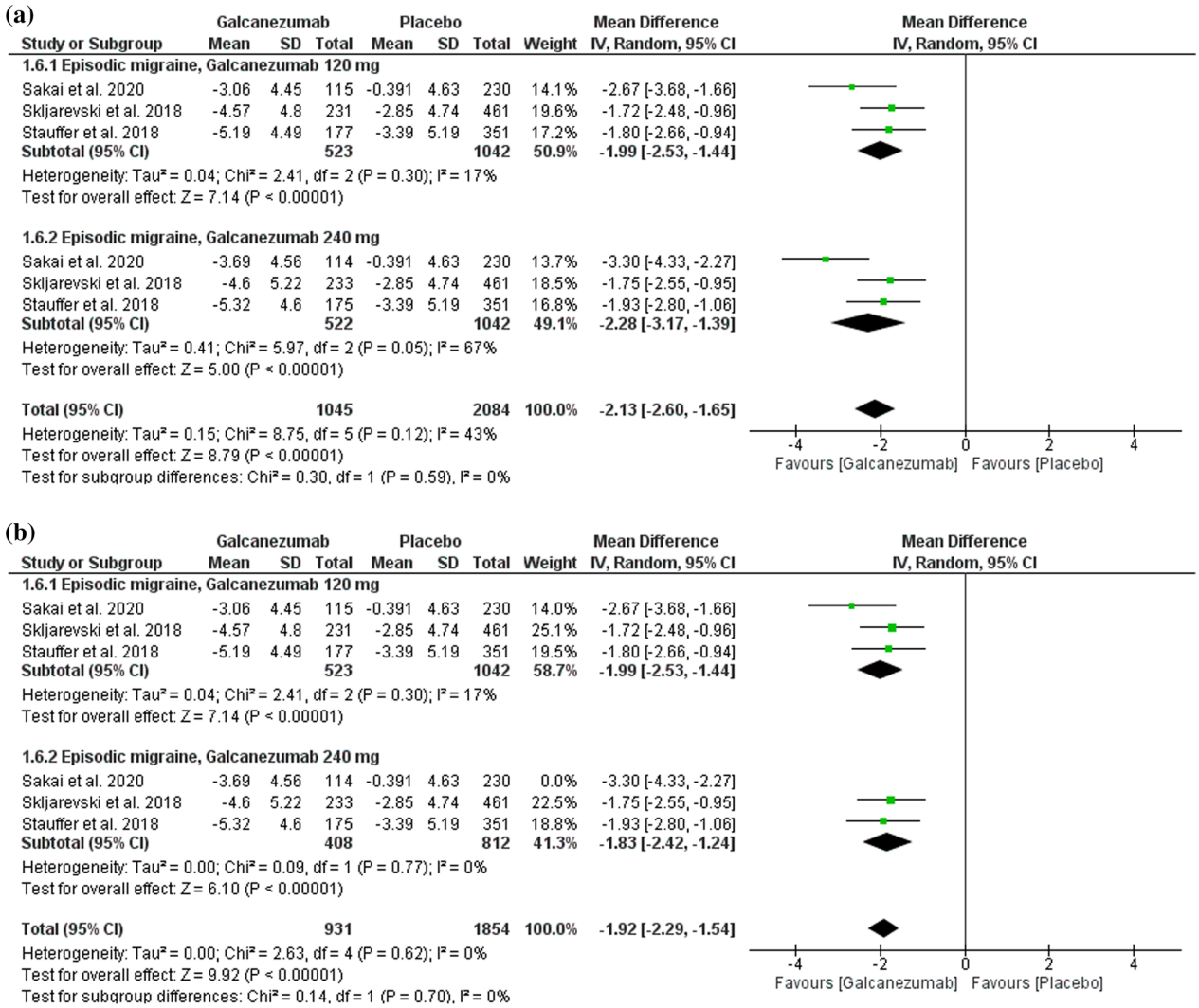

Fig. 8 **a** A forest plot of the change in the migraine headache days after six months before sensitivity analysis. **b** A forest plot of the change in the migraine headache days after six months after sensitivity analysis

Our study has certain points of strength. We included only RCTs, which represent the highest evidence. Almost all included trials were of low risk of bias regarding most domains. We analyzed data from 4964 patients, a large sample size supporting our pooled effect estimate. We assessed the different doses of galcanezumab at different treatment periods in episodic and chronic migraines. All safety and efficacy outcomes reported in the included studies were evaluated in our study, and nearly all of the included outcomes were homogeneous. Our study had few limitations. The heterogeneity of some outcomes could not be solved by sensitivity analysis. Additionally, the evidence generated regarding some outcomes was based on reports from two or three trials. So, more high-quality trials are needed to support the generalizability of the evidence generated.

Conclusion

Compared with placebo, subcutaneous injection of monoclonal antibody galcanezumab 120 mg, 240 mg, and 150 mg is effective in treating patients with episodic and chronic migraine after one to six months use. It significantly reduced the MHDs and improved the 50%, 75%, and 100% response rates. It is generally safe, however, it showed higher injection site adverse events, and the higher dose (240mg) showed higher adverse events, SAE and that led to discontinuation.

Table 3 Adverse events summary of patients with episodic migraine

Outcomes	Subgroup	Studies	Participants	Significance			Heterogeneity	
				RR	95% CI	p-value	I^2 (%)	p-value
Patients with ≥ 1 adverse events	Galcanezumab 120mg	5	2397	1.13	[1.02, 1.25]	0.02	56	0.06
	Galcanezumab 120mg after sensitivity analysis	4	1178	1.07	[1, 1.16]	0.07	0	0.8
	Galcanezumab 240/300mg	4	1889	1.15	[1.06, 1.25]	0.0005	26	0.26
Patients with ≥ 1 serious events	Galcanezumab 120mg	2	1093	2.59	[0.91, 7.39]	0.07	45	0.18
	Galcanezumab 240mg	2	1033	3.12	[1.08, 9.04]	0.04	0	0.66
Patients with adverse event leading to discontinuation	Galcanezumab 120mg	2	1032	3.94	[0.22, 69.50]	0.35	72	0.06
	Galcanezumab 240mg	2	1033	2.59	[1.06, 6.35]	0.04	0	0.35
Injection site pain	Galcanezumab 120/150mg	6	2614	1.66	[1.01, 2.72]	0.05	68	0.009
	Galcanezumab 240/300mg	4	1889	1.8	[0.95, 3.39]	0.07	71	0.02
Injection site erythema	Galcanezumab 120/150mg	5	2407	3.76	[1.91, 7.40]	0.0001	23	0.27
	Galcanezumab 240mg	3	1685	4.14	[1.12, 15.32]	0.03	81	0.005
	Galcanezumab 240mg after sensitivity analysis	2	1341	2.11	[1.01, 4.41]	0.05	7	0.3
Injection site Reaction	Galcanezumab 120mg	3	1845	6.44	[2.10, 19.77]	0.001	14	0.31
	Galcanezumab 240mg	2	1341	9.08	[0.11, 761.88]	0.33	88	0.003
Injection site pruritis	Galcanezumab 120mg	4	2190	26.7	[7.27, 97.93]	< 0.00001	0	0.98
	Galcanezumab 240mg	3	1897	30.9	[8.20, 116.44]	< 0.00001	0	0.41
Injection site swelling	Galcanezumab 120mg	2	1032	7.17	[2.22, 23.17]	0.001	0	0.32
	Galcanezumab 240mg	2	1033	5.48	[1.63, 18.37]	0.006	0	0.95
Nasopharyngitis	Galcanezumab 120/150mg	3	1375	0.95	[0.60, 1.51]	0.83	1	0.37
Sinusitis	Galcanezumab 120/150mg	2	855	1.24	[0.63, 2.47]	0.53	26	0.24
Upper respiratory tract infection	Galcanezumab 120/150mg	4	1631	1.43	[0.98, 2.07]	0.06	0	0.7
	Galcanezumab 240/300mg	2	891	1.13	[0.62, 2.04]	0.69	44	0.18
Neck pain	Galcanezumab 120/150mg	2	855	1.78	[0.59, 5.42]	0.31	0	0.81
Back pain	Galcanezumab 120/150mg	3	1062	1.2	[0.60, 2.37]	0.61	0	0.69
Diarrhea	Galcanezumab 120mg	2	1207	1.01	[0.48, 2.11]	0.98	0	0.4

RR risk ratio

Abbreviations

CGRP Calcitonin gene-related peptide
MHDs Migraine headache days
PRISMA The Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs Randomized controlled trials
WoS Web of Science
SAE Serious adverse event
RR Risk ratio
CI Confidence interval
MD Mean difference
URTI Upper respiratory tract infection

Supplementary Information

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Supplementary Material 1.

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Conceptualization and methodology: MSZ and AAE; data collection and screening: RYE, GA, IZ, AS, MHA and ME(Elshennawy); data extraction: OKFF, HFA, ZA, RIA, ABE, and ME (Eleyan); risk of bias: RYE, GA, IZ, HA and RAE; formal analysis: MSZ, ABE, AAE and YHA; writing—original draft: AMF, EAN, AS, MHA, ME(Elshennawy), JS and YHA; writing—review & editing: All authors; project administration: MSZ; supervision: AAE. All authors reviewed the manuscript and approved it for publication.

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Declarations

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