Galcanezumab for the Management of Migraine: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials

Ahmed Abu-Zaid 1 , Saud K. Al
Batati 1 , Abdullah M. AlHossan 2 , Rayan A. Al
Matrody 1 , Ayman AlGzi 1 , Rayan A. Al-Shari
ef 3 , Faris M. Alsobyani 4 , Amena F. Almubara
k 5 , Nadeen S. Alatiyah 1

1. Internal Medicine, College of Medicine, Alfaisal University, Riyadh, SAU 2. Surgery, College of Medicine, Alfaisal University, Riyadh, SAU 3. Neurology, College of Medicine, King Abdulaziz University, Rabigh, SAU 4. Internal Medicine, College of Medicine, Arabian Gulf University, Manama, BHR 5. Internal Medicine, College of Medicine, Dar Al Uloom University, Riyadh, SAU

Corresponding author: Ahmed Abu-Zaid, aabuzaid@live.com

Abstract

Introduction

Migraine is a frequent neurological condition manifested by several episodes of headache. Calcitonin generelated peptide (CGRP) has been shown to play a key role in the pathophysiology of migraine. Galcanezumab is a monoclonal antibody that binds CGRP and inhibits its action, without affecting the CGRP receptor. The aim of this study is to carry out a systematic review and meta-analysis of all randomized placebo-controlled trials that evaluated the efficacy of galcanezumab (120 mg or 240 mg) for the management of migraine.

Methods

We screened four databases (PubMed, SCOPUS, Embase, and Cochrane Central) from inception to October 10, 2020. Studies meeting the following criteria were included: (i) Patients: individuals with migraine, (ii) Intervention: galcanezumab at a dose of 120 mg or 240 mg, (iii) Comparator: placebo, (iv) Outcomes: prespecified efficacy and safety outcomes, and (v) Study design: randomized placebo-controlled trials. Efficacy outcomes included change in migraine headache days (MHDs), change in MHDs with acute medication use, patient global impression of severity (PGI-S) score, migraine-specific quality of life role function-restrictive domain (MSQ RF-R) score, and migraine disability assessment (MIDAS) score. Safety outcomes included frequency of injection-site pain, nasopharyngitis, and upper respiratory tract infection (URTI). Moreover, we used the Cochrane Collaboration's risk of bias tool to assess the risk of bias of the included studies. Review Manager Software, version 5.4.1, was used for statistical analysis. Mean difference and risk ratio with 95% confidence interval were used to analyze continuous and dichotomous outcomes, respectively. We used the fixed-effects and random-effects models to analyze homogeneous and heterogeneous data, respectively.

Results

A total of six studies comprising 4,023 patients were included in this systematic review and meta-analysis. When compared to placebo, both doses of galcanezumab were highly effective in decreasing MHDs (p<0.001), reducing MHDs with acute medication use (p<0.001), and improving the PGI-S score (p<0.001). On the other hand, MSQ RF-R and MIDAS scores were significantly enhanced only in the 240-mg dose group (p<0.001). With regard to side effects, the rates of injection-site pain and nasopharyngitis did not substantially differ between galcanezumab (inclusive of 120 mg and 240 mg) and placebo groups. Nonetheless, when compared to placebo, galcanezumab 120 mg, but not galcanezumab 240 mg, substantially correlated with a higher rate of URTI.

Conclusions

Galcanezumab is clinically safe and efficient for the management of migraine, and the use of a higher dose increases its efficacy. Future research directions should be geared toward determining the optimal dose of galcanezumab in the management of patients with migraine. Moreover, head-to-head comparative studies between galcanezumab and other related anti-CGRP receptor monoclonal antibodies are warranted.

Categories: Neurology

Keywords: calcitonin gene-related peptide, galcanezumab, migraine, headache

Introduction

Migraine is a frequent neurological condition manifested by several episodes of headache. These episodes are often accompanied by nausea, vomiting, and light hypersensitivity [1]. Migraine is categorized into two main types in accordance with the frequency of headaches: episodic migraine (<15 headache days per

Review began 10/17/2020 Review ended 11/11/2020 Published 11/22/2020

© Copyright 2020

Abu-Zaid et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

How to cite this article

Abu-Zaid A, Albatati S K, Alhossan A M, et al. (November 22, 2020) Galcanezumab for the Management of Migraine: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials. Cureus 12(11): e11621. DOI 10.7759/cureus.11621

month) and chronic migraine (≥15 headache days per month) [2]. Migraine pathophysiology is not exactly known [1]. However, the accumulating body of research highlights a key role of calcitonin gene-related peptide (CGRP) in migraine pathophysiology [3,4]. This notion is supported by the observation that intravenous injection of CGRP results in spontaneous episodes of headache and migraine in migraineurs [3]. Moreover, blood levels of CGRPs are dramatically increased during migraine attacks [4].

Galcanezumab is a monoclonal antibody that binds CGRP and inhibits its action, without affecting the CGRP receptor [5,6]. Many clinical trials were performed investigating the efficacy of galcanezumab for the management of migraine. However, these clinical trials varied substantially with regard to the range of doses used. Moreover, till now, the proposed evidence from these clinical trials is contradictory. Therefore, the need for a comprehensive research that pools this evidence has become more required, which constituted the basic core of why we aimed to conduct this study to fill the literature gap. The objective of this study is to carry out a systematic review and meta-analysis of all randomized placebo-controlled trials that specifically evaluated the efficacy and safety of galcanezumab (120 mg or 240 mg) in patients with migraine.

Materials And Methods

Research protocol

This research was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7] and the Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 [8].

Search strategy

Four databases (PubMed, SCOPUS, Embase, and Cochrane Central) were screened from inception to October 5, 2020. The following search strategy was used in screening for relevant studies: (galcanezumab OR emgality OR LY2951742 OR LY-2951742 OR ajovy OR galcanezumab-gnlm OR aimovig) AND (migraine). There was no language restriction.

Eligibility criteria

Studies meeting the following criteria were included: (i) Patients: individuals with migraine, (ii) Intervention: galcanezumab at a dose of 120 mg or 240 mg, (iii) Comparator: placebo, (iv) Outcomes: prespecified efficacy (primary) and safety (secondary) outcomes, and (v) Study design: randomized placebocontrolled trials. Exclusion criteria included (i) patients with conditions other than migraine, (ii) interventional monoclonal antibodies other than galcanezumab, (iii) doses of galcanezumab other than 120 mg or 240 mg, (iv) animal trials, (v) nonrandomized human clinical trials, and (vi) studies not reporting the prespecified efficacy or safety outcomes.

Study selection

After screening of studies, duplicates were removed, and the remaining studies underwent a two-stage screening process. The first stage involved title and abstract screening. The second stage involved conducting full-text screening to exclude irrelevant trials. Moreover, we manually searched the reference lists of included studies to consider additional relevant studies. Two authors independently screened the studies and conflicts were resolved by a third author.

Risk of bias assessment

Cochrane Collaboration's risk of bias tool was used to assess the risk of bias of the included randomized placebo-controlled trials [9]. This risk tool consists of six domains: (i) sequence generation, (ii) allocation concealment, (iii) outcomes blinding, (iv) incomplete data, (v) selective reporting, and (vi) other bias. We scored each domain as unclear, low, or high risk. Two authors independently assessed the risk of bias, and conflicts were resolved by a third author.

Data extraction

The following three categories of data were collected: (i) baseline characteristics of the included studies, (ii) efficacy outcomes, and (iii) safety outcomes. Baseline characteristics of the included studies included first author, year of publication, national clinical trial (NCT) identifier, phase of clinical trial, type of migraine, study group, and sample size. Efficacy outcomes included change in monthly migraine headache days (MHDs), change in monthly MHDs with acute medication use, patient global impression of severity (PGI-S) score, migraine-specific quality of life role function-restrictive (MSQ RF-R) domain score, and migraine disability assessment (MIDAS) score. Safety outcomes included frequency of injection-site pain, nasopharyngitis, and upper respiratory tract infection (URTI). Several authors extracted the necessary data.

Data analysis

Review Manager Software Version 5.4.1 was used for statistical analysis. Mean difference (MD) and risk ratio

(RR) with 95% confidence interval (95% CI) were used to analyze continuous and dichotomous outcomes, respectively. Fixed-effects and random-effects models were used to analyze homogenous and heterogeneous data, respectively. Statistical heterogeneity between studies was assessed by I-squared (I^2) test and the p-value of heterogeneity. Statistical heterogeneity was determined when I^2 measured >50% and p-value of heterogeneity measured <0.1. Sensitivity analysis using Cochrane's leave-one-out method was used to resolve heterogonous outcomes. For all outcomes, subgroup analysis according to the galcanezumab dose was conducted (120 mg/240 mg versus placebo).

Results

Literature search

Literature search yielded 510 studies. After screening, 490 studies were excluded because they did not match our inclusion criteria. Full-text screening of the remaining 20 studies resulted in an elimination of 14 studies that did not match our inclusion criteria. Finally, six studies comprising 4,023 patients were included in this systematic review and meta-analysis [5,10-14]. Figure *1* shows the PRISMA flowchart.

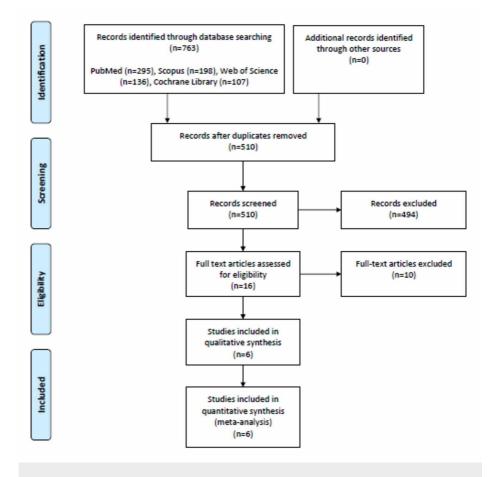


FIGURE 1: PRISMA flowchart.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Galcanezumab and placebo were administered to 1,974 and 2,049 patients, respectively. The baseline characteristics of the included studies are depicted in Table *1*.

Cureus

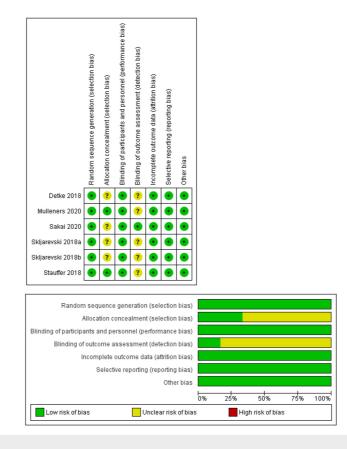
Study identifier	NCT identifier	Phase	Condition	Study group	n	Female (%)	Migraine attacks per month, mean (SD)	MHDs per month with acute medication use, mean (SD)	MIDAS baseline score, mean (SD)
				Galcanezumab (120 mg)	213	85	5.6 (1.7)	7.4 (3.7)	32.9 (28.2)
Stauffer et al., 2018 [5]	NCT02614183	3	Episodic migraine	Galcanezumab (240 mg)	212	82.6	5.7 (1.8)	7.3 (3.3)	36.1 (27.8)
				Placebo	433	83.6	5.8 (1.7)	7.4 (3.5)	31.8 (27.3)
				Galcanezumab (120 mg)	278	85	NR	15.1 (6.3)	62.5 (49.5)
Detke et al., 2018 [14]	NCT02614261	3	Chronic migraine	Galcanezumab (240 mg)	277	82	NR	14.5 (6.3)	69.2 (64.1)
				Placebo	558	87	NR	15.5 (6.6)	68.7 (57.4)
Skljarevski et al., 2018 [10]	NCT02163993	2	Episodic migraine	Galcanezumab (120 mg)	70	84.6	4.6 (1.6)	NR	NR
uii, 2010 [10]				Placebo	137	79.6	4.7 (1.5)	NR	NR
				Galcanezumab (120 mg)	231	85.3	5.54 (1.8)	7.47 (3.3)	30.9 (27.9)
Skljarevski et al., 2018 [11]	NCT02614196	3	Episodic migraine	Galcanezumab (240 mg)	231	85.7	5.66 (1.8)	7.47 (3.3)	32.8 (28.8)
				Placebo	461	85.3	5.7 (1.8)	7.6 (3.4)	34.3 (31.0)
				Galcanezumab (120 mg)	115	82.6	5.6 (1.7)	7.3 (2.9)	14.8 (18.1)
Sakai et al., 2020 [12]	NCT02959177	2	Episodic migraine	Galcanezumab (240 mg)	114	84.2	5.5 (1.8)	7.8 (3.0)	13.7 (13.9)
				Placebo	230	85.2	5.5 (1.7)	7.4 (3.0)	15.8 (19.3)
Mulleners et al., 2020 [13]	NCT03559257	3	Episodic migraine and chronic	Galcanezumab (120 mg)	232	84	NR	12.3 (6)	50.9 (46)
a., 2020 [13]			migraine	Placebo	230	88	NR	12.4 (6)	51 (45.5)

TABLE 1: Baseline characteristics of the included studies.

MHD, monthly headache days; MIDAS, migraine disability assessment; NCT, national clinical trial; NR, not reported; SD, standard deviation

Results of risk of bias assessment

All studies showed low risk of bias for the domains of random sequence generation, blinding of participants and personnel, incomplete outcome data, and selective reporting. Inadequate details were provided for allocation concealment and blinding of outcome assessments in some studies, and hence these domains were scored as unclear risk. Overall, all included studies revealed low-to-moderate risk of bias. Figure 2 shows the risk of bias summary and graph.





Efficacy outcome: overall mean change from baseline in the number of monthly MHDs

The overall effect size significantly favored galcanezumab over placebo (MD=2.28; 95% CI [2.02, 2.55]; p<0.001). Pooled results were homogeneous (I^2 =34%; p=0.15), and the fixed-effects model was used (Figure 3). Subgroup analysis was performed according to the galcanezumab dose. For galcanezumab 120 mg versus placebo, the overall effect size significantly favored the galcanezumab group (MD=2.39; 95% CI: [2.04, 2.74]; p<0.001). Pooled results were homogeneous (I^2 =46%; p=0.11). For galcanezumab 240 mg versus placebo, the overall effect size significantly favored the galcanezumab group (MD=2.14; 95% CI [1.73, 2.55]; p<0.001). Pooled results were homogeneous (I^2 =22%; p=0.28).

	Galca	nezum	ab	Pl	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
1.4.1 Galcanezumat	120 mg	vs Plac	ebo						
Skljarevski 2018a	4.3	3.35	70	3.4	2.98	137		Not estimable	
Stauffer 2018	4.7	5.22	210	2.8	5.15	425	9.8%	1.90 [1.04, 2.76]	
Skljarevski 2018b	4.3	4.56	231	2.3	4.29	461	14.5%	2.00 [1.29, 2.71]	
Detke 2018	4.8	1.65	273	2.7	9.28	538	11.1%	2.10 [1.29, 2.91]	
Sakai 2020	3.5	3.2	115	0.59	3.48	230	13.3%	2.91 [2.17, 3.65]	
Mulleners 2020	4.14	4.85	230	1.02	4.83	228	9.2%	3.12 [2.23, 4.01]	
Subtotal (95% CI)			1059			1882	57.8%	2.39 [2.04, 2.74]	◆
Heterogeneity: Chi ² =	= 7.43, df =	= 4 (P =	0.11);	I ² = 469	%				
Test for overall effect	Z = 13.2	4 (P < (0.0000	1)					
1.4.2 Galcanezumat	240 mg	vs Plac	ebo						
Stauffer 2018	4.6	5.48	208	2.8	5.15	425	9.1%	1.80 [0.91, 2.69]	
Detke 2018	4.6	6.62	274	2.7	9.28	538	5.9%	1.90 [0.79, 3.01]	
Skljarevski 2018b	4.2	4.47	223	2.3	4.29	461	14.5%	1.90 [1.19, 2.61]	
Sakai 2020	3.36	3.3	114	0.59	3.48	230	12.7%	2.77 [2.02, 3.52]	
Sakai 2020			819			1654	42.2%	2.14 [1.73, 2.55]	•
Sakai 2020 Subtotal (95% Cl)									
	= 3.86, df:	= 3 (P =	0.28);	I ² = 229	%				
Subtotal (95% CI)					%				
Subtotal (95% CI) Heterogeneity: Chi [#] = Test for overall effect			0.0000		%	2520	100.00	0.0010.00.0.551	
Subtotal (95% CI) Heterogeneity: Chi ² = Test for overall effect Total (95% CI)	t: Z = 10.1	4 (P < (1878	1)		3536	100.0%	2.28 [2.02, 2.55]	
Subtotal (95% CI) Heterogeneity: Chi [#] = Test for overall effect Total (95% CI) Heterogeneity: Chi [#] =	t: Z = 10.1 = 12.09, d	4 (P < (f= 8 (P	1878 = 0.15	1)); I² = 34		3536	100.0%	2.28 [2.02, 2.55]	- <u>+</u> + + + + + + + + + + + + + + + + + +
Subtotal (95% CI) Heterogeneity: Chi ² = Test for overall effect Total (95% CI)	t: Z = 10.1 = 12.09, d t: Z = 16.6	4 (P < (f = 8 (P 5 (P < (0.0000 1878 = 0.15 0.0000	1)); I² = 34 1)	1%			2.28 [2.02, 2.55]	-4 -2 0 2 4 Favours [Placebo] Favours [Galcanezumab

FIGURE 3: Forest plot showing the change in monthly migraine headache days between galcanezumab and placebo groups.

Efficacy outcome: overall mean change from baseline in the number of monthly MHDs with acute medication use

The overall effect size significantly favored galcanezumab over placebo (MD=2.22; 95% CI [1.82, 2.63];

p<0.001). Pooled results were heterogeneous (I^2 =60%; p=0.010), and the random-effects model was used (Figure 4). Subgroup analysis was performed according to the galcanezumab dose. For galcanezumab 120 mg versus placebo, the overall effect size significantly favored the galcanezumab group (MD=2.44; 95% CI [1.81,

3.06]; p<0.001). Pooled results were heterogeneous (I^2 =69%; p=0.01). Heterogeneity was best resolved (I^2 =50%; p=0.11) by omitting Mulleners et al.' study [13], and the overall effect size still significantly favored the galcanezumab group (MD=2.19; 95% CI [1.65, 2.73]; p<0.001). For galcanezumab 240 mg versus placebo, the overall effect size significantly favored the galcanezumab group (MD=1.97; 95% CI [1.49, 2.44]; p<0.001). Pooled results were homogeneous (I^2 =39%; p=0.18).

^										
Α		nezum			acebo			Mean Difference	Mean Difference	
Study or Subgroup	Mean			Mean	SD	fotal	weight	IV, Random, 95% Cl	IV, Random, 95% Cl	
3.4.1 Galcanezumat										
Stauffer 2018	4	4.35	210		5.36	425	11.1%	1.80 [1.02, 2.58]		
Skljarevski 2018b	3.7	3.04	231		4.29	461	14.0%	1.80 [1.25, 2.35]		
Detke 2018	4.7	6.61	273		6.96	538	8.9%	2.50 [1.52, 3.48]		_
Sakai 2020	3.02	3.64	115		3.63	230	10.7%	2.90 [2.09, 3.71]		
Mulleners 2020	4.19	4.85	230	0.8	4.68	228	10.0%	3.39 [2.52, 4.26]		•
Subtotal (95% CI)			1059			1882	54.8%	2.44 [1.81, 3.06]	-	
Heterogeneity: Tau ² :					: 0.01)	² = 69	1%			
Test for overall effect	: Z = 7.59	I (P < 0	.00001)						
3.4.2 Galcanezumat	240 mg		oobo							
	-				c 00	100	44.000	4 00 10 07 0 001		
Stauffer 2018	3.8	3.89	208		5.36	425	11.6%	1.60 [0.87, 2.33]		
Skljarevski 2018b	3.6	2.99	223		4.29	461	14.0%	1.70 [1.15, 2.25]		
Detke 2018	4.3	6.62	274		6.96	538	8.9%	2.10 [1.12, 3.08]		_
Sakai 2020 Subtotal (95% CI)	2.81	3.63	114 819	0.12	3.63	230 1654	10.7% 45.2%	2.69 [1.88, 3.50]		_
Subtotal (95% CI)	0.00.0	. 19		a (D				1.97 [1.49, 2.44]		
Heterogeneity: Tau ²					U.18); I	*= 399	6			
Test for overall effect	: Z = 8.07	(P < 0	.00001)						
Total (95% CI)			1878			3536	100.0%	2.22 [1.82, 2.63]	•	
Heterogeneity: Tau ² :	- 0.22. CI	hi≅ – 20		- 9 (P -	0.010			LILL [110L, L100]		
Test for overall effect					0.010	0.1 - 0	0.0		-4 -2 0 2	4
Test for subgroup di					- 0.2	1) 12 - 1	26.30		Favours (Placebo) Favours (Galcanez	umab]
B			1.00,1	ai — i (i	- 0.2		20.070			
-		nezum			acebo			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total				Weight	Mean Difference IV, Random, 95% Cl	Mean Difference IV, Random, 95% Cl	
Study or Subgroup 3.4.1 Galcanezumab	Mean 120 mg	SD vs Plac	Total cebo	Mean	SD	Total		IV, Random, 95% CI		
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018	Mean 120 mg 4	SD vs Plac 4.35	Total cebo 210	Mean 2.2	SD 5.36	Total 425	12.0%	IV, Random, 95% CI		
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018 Skljarevski 2018b	Mean 120 mg 4 3.7	SD vs Plac 4.35 3.04	Total cebo 210 231	Mean 2.2 1.9	SD 5.36 4.29	Total 425 461	12.0% 17.5%	IV, Random, 95% Cl 1.80 [1.02, 2.58] 1.80 [1.25, 2.35]		
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018 Skljarevski 2018b Detke 2018	Mean 120 mg 4 3.7 4.7	SD vs Plac 4.35 3.04 6.61	Total cebo 210 231 273	Mean 2.2 1.9 2.2	SD 5.36 4.29 6.96	Total 425 461 538	12.0% 17.5% 8.8%	V, Random, 95% Cl 1.80 [1.02, 2.58] 1.80 [1.25, 2.35] 2.50 [1.52, 3.48]		_
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018 Skljarevski 2018b Detke 2018 Sakai 2020	Mean 120 mg 4 3.7 4.7 3.02	SD vs Plac 4.35 3.04 6.61 3.64	Total cebo 210 231 273 115	Mean 2.2 1.9 2.2 0.12	SD 5.36 4.29 6.96 3.63	Total 425 461 538 230	12.0% 17.5% 8.8% 11.3%	V, Random, 95% Cl 1.80 [1.02, 2.58] 1.80 [1.25, 2.35] 2.50 [1.52, 3.48] 2.90 [2.09, 3.71]		
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018 Skijarevski 2018b Detke 2018 Sakai 2020 Mulleners 2020	Mean 120 mg 4 3.7 4.7	SD vs Plac 4.35 3.04 6.61	Total 210 231 273 115 230	Mean 2.2 1.9 2.2 0.12	SD 5.36 4.29 6.96	Total 425 461 538 230 228	12.0% 17.5% 8.8% 11.3% 0.0%	V, Random, 95% Cl 1.80 [1.02, 2.58] 1.80 [1.25, 2.35] 2.50 [1.52, 3.48] 2.90 [2.09, 3.71] 3.39 [2.52, 4.26]		
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018 Skljarevski 2018b Detke 2018 Sakai 2020 Mulleners 2020 Subtotal (95% CI)	Mean 120 mg 4 3.7 4.7 3.02 4.19	SD 4.35 3.04 6.61 3.64 4.85	Total 210 231 273 115 230 829	Mean 2.2 1.9 2.2 0.12 0.8	5.36 4.29 6.96 3.63 4.68	Total 425 461 538 230 228 1654	12.0% 17.5% 8.8% 11.3% 0.0% 49.6 %	V, Random, 95% Cl 1.80 [1.02, 2.58] 1.80 [1.25, 2.35] 2.50 [1.52, 3.48] 2.90 [2.09, 3.71]		
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018 Skijarevski 2018b Detke 2018 Sakai 2020 Mulleners 2020 Subtotal (95% CI) Heterogeneity: Tau ² :	Mean 120 mg 4 3.7 4.7 3.02 4.19 = 0.15; Cl	SD 4.35 3.04 6.61 3.64 4.85 hi ² = 6.0	Total 210 231 273 115 230 829 03, df =	Mean 2.2 1.9 2.2 0.12 0.8 3 (P = 1	5.36 4.29 6.96 3.63 4.68	Total 425 461 538 230 228 1654	12.0% 17.5% 8.8% 11.3% 0.0% 49.6 %	V, Random, 95% Cl 1.80 [1.02, 2.58] 1.80 [1.25, 2.35] 2.50 [1.52, 3.48] 2.90 [2.09, 3.71] 3.39 [2.52, 4.26]		
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018 Skljarevski 2018b Detke 2018 Sakai 2020 Mulleners 2020 Subtotal (95% CI)	Mean 120 mg 4 3.7 4.7 3.02 4.19 = 0.15; Cl	SD 4.35 3.04 6.61 3.64 4.85 hi ² = 6.0	Total 210 231 273 115 230 829 03, df =	Mean 2.2 1.9 2.2 0.12 0.8 3 (P = 1	5.36 4.29 6.96 3.63 4.68	Total 425 461 538 230 228 1654	12.0% 17.5% 8.8% 11.3% 0.0% 49.6 %	V, Random, 95% Cl 1.80 [1.02, 2.58] 1.80 [1.25, 2.35] 2.50 [1.52, 3.48] 2.90 [2.09, 3.71] 3.39 [2.52, 4.26]		
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018 Skljarevski 2018b Detke 2018 Sakai 2020 Mulleners 2020 Subtotal (95% CI) Heterogeneiky: Tau ² : Test for overall effect	Mean 120 mg 4 3.7 4.7 3.02 4.19 = 0.15; Cl : Z = 7.94	SD vs Plac 4.35 3.04 6.61 3.64 4.85 hi ² = 6.0 (P < 0.0	Total cebo 210 231 273 115 230 829 03, df = .00001	Mean 2.2 1.9 2.2 0.12 0.8 3 (P = 1	5.36 4.29 6.96 3.63 4.68	Total 425 461 538 230 228 1654	12.0% 17.5% 8.8% 11.3% 0.0% 49.6 %	V, Random, 95% Cl 1.80 [1.02, 2.58] 1.80 [1.25, 2.35] 2.50 [1.52, 3.48] 2.90 [2.09, 3.71] 3.39 [2.52, 4.26]		
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018 Skijarevski 2018b Detke 2018 Sakai 2020 Multeners 2020 Subtotal (95% CI) Heterogeneity: Tau ² : Test for overall effect 3.4.2 Galcanezumab	Mean 120 mg 4 3.7 4.7 3.02 4.19 = 0.15; Cl : Z = 7.94 240 mg	SD vs Plac 4.35 3.04 6.61 3.64 4.85 hi ² = 6.0 (P < 0.0 vs Place	Total cebo 210 231 273 115 230 829 D3, df = .00001 cebo	Mean 2.2 1.9 2.2 0.12 0.8 3 (P = 1	5.36 4.29 6.96 3.63 4.68 0.11); I	Total 425 461 538 230 228 1654 *= 50%	12.0% 17.5% 8.8% 11.3% 0.0% 49.6 %	M, Random, 95% Cl 1.80 [1.02, 2.58] 1.80 [1.25, 2.35] 2.50 [1.52, 3.48] 2.90 [2.09, 3.71] 3.39 [2.52, 4.26] 2.19 [1.65, 2.73]		
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018 Skjarevski 2018b Detke 2018 Sakai 2020 Mulleners 2020 Subtotal (95% Cl) Heterogeneity: Tau ² : Test for overall effot 3.4.2 Galcanezumab Stauffer 2018	Mean 120 mg 4 3.7 4.7 3.02 4.19 = 0.15; Cl : Z = 7.94 240 mg 3.8	SD vs Plac 4.35 3.04 6.61 3.64 4.85 hi² = 6.0 (P < 0.0)	Total cebo 210 231 273 115 230 829 03, df = 00001 cebo 208	Mean 2.2 1.9 2.2 0.12 0.8 3 (P = 1 2.2	5.36 4.29 6.96 3.63 4.68 0.11);1	Total 425 461 538 230 228 1654 *= 50% 425	12.0% 17.5% 8.8% 11.3% 0.0% 49.6%	M, Random, 95% CI 1.80 [1.02, 2.58] 1.80 [1.25, 2.35] 2.50 [1.52, 3.48] 2.90 [2.09, 3.71] 3.39 [2.52, 4.26] 2.19 [1.65, 2.73] 1.60 [0.87, 2.33]		
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018 Skijarevski 2018b Detke 2018 Sakai 2020 Multeners 2020 Subtotal (95% C1) Heterogeneity: Tau ² : Test for overall effect 3.4.2 Galcanezumab Stauffer 2018	Mean 120 mg 4 3.7 4.7 3.02 4.19 = 0.15; Cl : Z = 7.94 240 mg 3.8 3.6	SD vs Plac 4.35 3.04 6.61 3.64 4.85 hi² = 6.0 (P < 0.)	Total 210 231 273 115 230 829 03, df= .00001 208 223	Mean 2.2 1.9 2.2 0.12 0.8 3 (P = 1 2.2 1.9	SD 5.36 4.29 6.96 3.63 4.68 0.11);1 5.36 4.29	Total 425 461 538 230 228 1654 ² = 50% 425 461	12.0% 17.5% 8.8% 11.3% 0.0% 49.6% 5	M, Random, 95% CI 1.80 [1.02, 2.58] 1.80 [1.25, 2.35] 2.50 [1.52, 3.48] 2.90 [2.09, 3.71] 3.39 [2.52, 4.26] 2.19 [1.65, 2.73] 1.60 [0.87, 2.33] 1.70 [1.15, 2.25]		
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018 Skijarevski 2018b Detke 2018 Sakai 2020 Multeners 2020 Subtotal (95% CI) Heterogeneity: Tau ² : Test for overall effect 3.4.2 Galcanezumab Stauffer 2018 Skijarevski 2018b	Mean 120 mg 4 3.7 4.7 3.02 4.19 = 0.15; Cl : Z = 7.94 240 mg 3.8 3.6 4.3	SD vs Plac 4.35 3.04 6.61 3.64 4.85 hi ² = 6.0 (P < 0. vs Plac 3.89 2.99 6.62	Total cebo 210 231 273 115 230 829 03, df= .00001 cebo 208 223 274	Mean 2.2 1.9 2.2 0.12 0.8 3 (P = 1 2.2 1.9 2.2	SD 5.36 4.29 6.96 3.63 4.68 0.11);1 5.36 4.29 6.96	Total 425 461 538 230 228 1654 ² = 50% 425 461 538	12.0% 17.5% 8.8% 11.3% 0.0% 49.6% 5 12.9% 17.5% 8.8%	M, Random, 95% Cl 1.80 [1.02, 2.58] 1.80 [1.25, 2.35] 2.50 [1.52, 3.48] 2.90 [2.09, 3.71] 3.39 [2.52, 4.26] 2.19 [1.65, 2.73] 1.60 [0.87, 2.33] 1.70 [1.15, 2.25] 2.10 [1.12, 3.08]		
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018 Skjarevski 2018b Detke 2018 Sakai 2020 Mulleners 2020 Subtotal (95% CI) Heterogeneity: Tau ² - Test for overall effect 3.4.2 Galcanezumab Stauffer 2018 Skijarevski 2018b Detke 2018 Sakai 2020	Mean 120 mg 4 3.7 4.7 3.02 4.19 = 0.15; Cl : Z = 7.94 240 mg 3.8 3.6	SD vs Plac 4.35 3.04 6.61 3.64 4.85 hi² = 6.0 (P < 0.)	Total 210 231 273 115 230 829 03, df = .00001 208 223 274 114	Mean 2.2 1.9 2.2 0.12 0.8 3 (P = 1 2.2 1.9 2.2	SD 5.36 4.29 6.96 3.63 4.68 0.11);1 5.36 4.29	Total 425 461 538 230 228 1654 ² = 50% 425 461 538 230	12.0% 17.5% 8.8% 11.3% 0.0% 49.6% 5 12.9% 17.5% 8.8% 11.3%	M, Random, 95% CI 1.80 [1.02, 2.58] 1.80 [1.22, 2.58] 2.50 [1.52, 3.48] 2.90 [2.09, 3.71] 3.39 [2.52, 4.26] 2.19 [1.65, 2.73] 1.60 [0.87, 2.33] 1.70 [1.15, 2.25] 2.10 [1.12, 3.08] 2.69 [1.88, 3.50]		
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018 Skijarevski 2018b Detke 2018 Sakai 2020 Mulleners 2020 Subtotal (95% CI) Heterogeneity: Tau ² - Test for overall effect 3.4.2 Galcanezumab Stauffer 2018 Detke 2018 Sakai 2020 Subtotal (95% CI)	Mean 120 mg 4 3.7 4.7 3.02 4.19 = 0.15; Cl : Z = 7.94 240 mg 3.8 3.6 4.3 2.81	SD vs Plac 4.35 3.04 6.61 3.64 4.85 hi ² = 6.0 (P < 0. vs Plac 3.89 2.99 6.62 3.63	Total 210 231 273 115 230 829 03, df = 00001 208 223 274 114 819	Mean 2.2 1.9 2.2 0.12 0.8 3 (P = 1) 2.2 1.9 2.2 1.9 2.2 0.12	SD 5.36 4.29 6.96 3.63 4.68 0.11);1 5.36 4.29 6.96 3.63	Total 425 461 538 230 228 1654 ² = 50% 425 461 538 230 1654	12.0% 17.5% 8.8% 11.3% 0.0% 49.6% 49.6% 12.9% 17.5% 8.8% 11.3% 50.4%	M, Random, 95% Cl 1.80 [1.02, 2.58] 1.80 [1.25, 2.35] 2.50 [1.52, 3.48] 2.90 [2.09, 3.71] 3.39 [2.52, 4.26] 2.19 [1.65, 2.73] 1.60 [0.87, 2.33] 1.70 [1.15, 2.25] 2.10 [1.12, 3.08]		
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018 Skijarevski 2018b Detke 2018 Sakai 2020 Mulleners 2020 Subtotal (95% CI) Heterogeneity: Tauffer 3.4.2 Galcanezumab Stauffer 2018 Skajarevski 2018b Detke 2018 Sakai 2020 Subtotal (95% CI) Heterogeneity: Tauffer	Mean 120 mg 4 3.7 4.7 3.02 4.19 = 0.15; CI: Z= 7.94 240 mg 3.8 3.6 4.3 2.81 = 0.09; CI	SD vs Plac 4.35 3.04 6.61 3.64 4.85 hi ² = 6.0 (P < 0. vs Plac 3.89 6.62 3.63 hi ² = 4.8	Total 210 231 273 115 230 829 03, df= 00001 208 223 274 114 819 89, df=	Mean 2.2 1.9 2.2 0.12 0.8 3 (P = 1) 2.2 1.9 2.2 1.9 2.2 1.9 2.2 0.12 0.8 3 (P = 1) 2.2 1.9 2.2 0.12 0.8 3 (P = 1) 2.2 0.12 0.8 3 (P = 1) 2.2 0.12 0.8 1.9 0.12 0.8 1.9 0.12 0.8 1.9 0.12 0.8 0.12 0.8 0.12 0.12 0.8 0.12 0.8 0.12 0.12 0.8 0.12 0.12 0.8 0.12	SD 5.36 4.29 6.96 3.63 4.68 0.11);1 5.36 4.29 6.96 3.63	Total 425 461 538 230 228 1654 ² = 50% 425 461 538 230 1654	12.0% 17.5% 8.8% 11.3% 0.0% 49.6% 49.6% 12.9% 17.5% 8.8% 11.3% 50.4%	M, Random, 95% CI 1.80 [1.02, 2.58] 1.80 [1.22, 2.58] 2.50 [1.52, 3.48] 2.90 [2.09, 3.71] 3.39 [2.52, 4.26] 2.19 [1.65, 2.73] 1.60 [0.87, 2.33] 1.70 [1.15, 2.25] 2.10 [1.12, 3.08] 2.69 [1.88, 3.50]		
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018 Skijarevski 2018b Detke 2018 Sakai 2020 Mulleners 2020 Subtotal (95% CI) Heterogeneity: Tau ² - Test for overall effect 3.4.2 Galcanezumab Stauffer 2018 Detke 2018 Sakai 2020 Subtotal (95% CI)	Mean 120 mg 4 3.7 4.7 3.02 4.19 = 0.15; CI: Z= 7.94 240 mg 3.8 3.6 4.3 2.81 = 0.09; CI	SD vs Plac 4.35 3.04 6.61 3.64 4.85 hi ² = 6.0 (P < 0. vs Plac 3.89 6.62 3.63 hi ² = 4.8	Total 210 231 273 115 230 829 03, df= 00001 208 223 274 114 819 89, df=	Mean 2.2 1.9 2.2 0.12 0.8 3 (P = 1) 2.2 1.9 2.2 1.9 2.2 1.9 2.2 0.12 0.8 3 (P = 1) 2.2 1.9 2.2 0.12 0.8 3 (P = 1) 2.2 0.12 0.8 3 (P = 1) 2.2 0.12 0.8 1.9 0.12 0.8 1.9 0.12 0.8 1.9 0.12 0.8 0.12 0.8 0.12 0.12 0.8 0.12 0.8 0.12 0.12 0.8 0.12 0.12 0.8 0.12	SD 5.36 4.29 6.96 3.63 4.68 0.11);1 5.36 4.29 6.96 3.63	Total 425 461 538 230 228 1654 ² = 50% 425 461 538 230 1654	12.0% 17.5% 8.8% 11.3% 0.0% 49.6% 49.6% 12.9% 17.5% 8.8% 11.3% 50.4%	M, Random, 95% CI 1.80 [1.02, 2.58] 1.80 [1.22, 2.58] 2.50 [1.52, 3.48] 2.90 [2.09, 3.71] 3.39 [2.52, 4.26] 2.19 [1.65, 2.73] 1.60 [0.87, 2.33] 1.70 [1.15, 2.25] 2.10 [1.12, 3.08] 2.69 [1.88, 3.50]		
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018 Skajarevski 2018b Detke 2018 Sakai 2020 Mulleners 2020 Subtotal (95% CI) Heterogeneity: Tauffect 3.4.2 Galcanezumab Stauffer 2018 Skajarevski 2018b Detke 2018 Sakai 2020 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect	Mean 120 mg 4 3.7 4.7 3.02 4.19 = 0.15; CI: Z= 7.94 240 mg 3.8 3.6 4.3 2.81 = 0.09; CI	SD vs Plac 4.35 3.04 6.61 3.64 4.85 hi ² = 6.0 (P < 0. vs Plac 3.89 6.62 3.63 hi ² = 4.8	Total cebo 210 231 273 115 230 829 03, df = 00001 cebo 208 223 274 114 819 89, df = 00001	Mean 2.2 1.9 2.2 0.12 0.8 3 (P = 1) 2.2 1.9 2.2 1.9 2.2 1.9 2.2 0.12 0.8 3 (P = 1) 2.2 1.9 2.2 0.12 0.8 3 (P = 1) 2.2 0.12 0.8 3 (P = 1) 2.2 0.12 0.8 1.9 0.12 0.8 1.9 0.12 0.8 1.9 0.12 0.8 0.12 0.8 0.12 0.12 0.8 0.12 0.8 0.12 0.12 0.8 0.12 0.12 0.8 0.12	SD 5.36 4.29 6.96 3.63 4.68 0.11);1 5.36 4.29 6.96 3.63	Total 425 461 538 230 228 1654 *= 50% 425 461 538 230 1654 *= 39%	12.0% 17.5% 8.8% 11.3% 0.0% 49.6% 12.9% 12.9% 17.5% 8.8% 11.3% 50.4%	M, Random, 95% CI 1.80 [1.02, 2.58] 1.80 [1.25, 2.35] 2.50 [1.52, 3.48] 2.90 [2.09, 3.71] 3.39 [2.52, 4.26] 2.19 [1.65, 2.73] 1.60 [0.87, 2.33] 1.70 [1.15, 2.25] 2.10 [1.12, 3.08] 2.69 [1.88, 3.50] 1.97 [1.49, 2.44]		
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018 Skjarevski 2018b Detke 2018 Sakai 2020 Mulleners 2020 Subtotal (95% CI) Heterogeneity, Tau ² - Test for overall effect 3.4.2 Galcanezumab Stauffer 2018 Skjarevski 2018b Detke 2018 Sakai 2020 Subtotal (95% CI) Heterogeneity, Tau ² - Test for overall effect Total (95% CI)	Mean 4 3.7 4.7 3.02 4.19 = 0.15; Cl : Z = 7.94 240 mg 3.8 3.6 4.3 2.81 = 0.09; Cl : Z = 8.07	SD vs Plac 4.35 3.04 6.61 3.64 4.85 if (P < 0.	Total cebo 210 231 273 115 230 829 003, df= 208 223 274 114 89, df= 000011 114 89, df= 0000011 1648	Mean 2.2 1.9 2.2 0.12 0.8 3 (P = 0 2.2 1.9 2.2 0.12 0.8 3 (P = 0 2.2 1.9 2.2 0.12 0.8 3 (P = 0 2.2 0.12 0	SD 5.36 4.29 6.96 3.63 4.68 0.11); 1 5.36 4.29 6.96 3.63 0.18); 1	Total 425 461 538 230 228 1654 230 425 461 538 230 1654 230 1654 239% 3308	12.0% 17.5% 8.8% 11.3% 0.0% 49.6% 17.5% 8.8% 11.3% 50.4%	M, Random, 95% CI 1.80 [1.02, 2.58] 1.80 [1.22, 2.58] 2.50 [1.52, 3.48] 2.90 [2.09, 3.71] 3.39 [2.52, 4.26] 2.19 [1.65, 2.73] 1.60 [0.87, 2.33] 1.70 [1.15, 2.25] 2.10 [1.12, 3.08] 2.69 [1.88, 3.50]		
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018 Stauffer 2018 Stauffer 2018 Detke 2018 Sakai 2020 Multeners 2020 Subtotal (95% CI) Heterogeneity: Tau ² : Test for overall effect 3.4.2 Galcanezumab Stauffer 2018 Detke 2018 Sakai 2020 Subtotal (95% CI) Heterogeneity: Tau ² : Test for overall effect Total (95% CI) Heterogeneity: Tau ² :	Mean 120 mg 4 3.7 4.7 3.02 4.19 = 0.15; Cl; Z = 7.94 240 mg 3.8 3.6 4.3 2.81 = 0.09; Cl; Z = 8.07	$\frac{\text{SD}}{\text{vs Plac}}$ $\frac{4.35}{3.04}$ $\frac{4.35}{3.04}$ $\frac{6.61}{3.64}$ $\frac{4.85}{4.85}$ $\frac{1}{4.85}$ $\frac{1}{4.$	Total Cebo 210 231 273 115 230 829 03, df = 000011 cebo 208 223 274 114 819 89, df = 0000011 1648 .48, df	Mean 2.2 1.9 2.2 0.12 0.8 3 (P = (1.9 2.2 0.8 3 (P = (1.9 2.2 0.12 0	SD 5.36 4.29 6.96 3.63 4.68 0.11); 1 5.36 4.29 6.96 3.63 0.18); 1	Total 425 461 538 230 228 1654 230 425 461 538 230 1654 230 1654 239% 3308	12.0% 17.5% 8.8% 11.3% 0.0% 49.6% 17.5% 8.8% 11.3% 50.4%	M, Random, 95% CI 1.80 [1.02, 2.58] 1.80 [1.25, 2.35] 2.50 [1.52, 3.48] 2.90 [2.09, 3.71] 3.39 [2.52, 4.26] 2.19 [1.65, 2.73] 1.60 [0.87, 2.33] 1.70 [1.15, 2.25] 2.10 [1.12, 3.08] 2.69 [1.88, 3.50] 1.97 [1.49, 2.44]	N, Random, 95% Cl	
Study or Subgroup 3.4.1 Galcanezumab Stauffer 2018 Skjarevski 2018b Detke 2018 Sakai 2020 Mulleners 2020 Subtotal (95% CI) Heterogeneity, Tau ² - Test for overall effect 3.4.2 Galcanezumab Stauffer 2018 Skjarevski 2018b Detke 2018 Sakai 2020 Subtotal (95% CI) Heterogeneity, Tau ² - Test for overall effect Total (95% CI)	Mean 4 3.7 4.7 3.02 4.19 = 0.15; Cl : Z = 7.94 240 mg 3.8 3.6 4.3 2.81 = 0.09; Cl : Z = 8.07 = 0.09; Cl : Z = 11.9	SD vs Plac 4.35 3.04 6.61 3.64 4.85 hi² = 6.0 (P < 0.	Total cebo 210 231 273 115 230 829 03, df= 208 223 274 114 208 224 274 114 89, df= 0.000011 1648 448, df 0.000001	Mean 2.2 1.9 2.2 0.12 0.12 0.8 3 (P = 1) 2.2 1.9 2.2 1.9 2.2 1.9 2.2 1.9 2.2 1.9 3 (P = 1) 7 2.2 1.9 2.7 1.9 2.7 1.9 2.7 1.9 2.7 1.9 2.7 1.9 1.9 1.9 1.9 1.9 1.9 1.9 1.9	5.36 4.29 6.96 3.63 4.68 0.11); I 5.36 4.29 6.96 3.63 3.63 3.63 3.63 3.63 3.63 3.6	Total 425 461 538 220 1654 425 461 538 230 1654 230 1654 3308 P= 39	12.0% 17.5% 8.8% 11.3% 0.0% 49.6% 5 12.9% 17.5% 8.8% 11.3% 50.4% 5 400.0%	M, Random, 95% CI 1.80 [1.02, 2.58] 1.80 [1.25, 2.35] 2.50 [1.52, 3.48] 2.90 [2.09, 3.71] 3.39 [2.52, 4.26] 2.19 [1.65, 2.73] 1.60 [0.87, 2.33] 1.70 [1.15, 2.25] 2.10 [1.12, 3.08] 2.69 [1.88, 3.50] 1.97 [1.49, 2.44]	N, Random, 95% Cl	

FIGURE 4: Forest plot showing the change in monthly migraine headache days with acute medication use between galcanezumab and placebo groups before (A) and after (B) sensitivity analysis using the leave-one-out method.

Efficacy outcome: PGI-S score

The overall effect size significantly favored galcanezumab over placebo (MD=0.26; 95% CI [0.18, 0.34]; p<0.001). Pooled results were homogenous (I^2 =0%; p=0.84), and the fixed-effects model was used (Figure 5). Subgroup analysis was performed according to the galcanezumab dose. For galcanezumab 120 mg versus placebo, the overall effect size significantly favored the galcanezumab group (MD=0.24; 95% CI [0.13, 0.35]; p<0.001). Pooled results were homogeneous (I^2 =0%; p=0.44). For galcanezumab 240 mg versus placebo, the overall effect size significantly favored the galcanezumab group (0.28 [0.16, 0.41]; p<0.001). Pooled results were homogeneous (I^2 =0%; p=0.99).

	Galca	nezum	ah	PI	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD		Mean	SD		Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
4.4.1 Galcanezumab				moun	00	rotai	roigit	in, intellige of the	
Sakai 2020	0.25	0.85	115	0.15	0.9	230	17.6%	0.10 [-0.09, 0.29]	
Detke 2018	0.8	1.65	273		2.32	538	8.6%	0.20 [-0.08, 0.48]	
Skljarevski 2018b	1.2	1.52	231	0.9	2.15	461	8.6%	0.30 [0.02, 0.58]	
Stauffer 2018	1.6	1.51	189	1.3	1.55	377	9.4%	0.30 [0.03, 0.57]	
Mulleners 2020	0.664	1.31	228	0.283	1.29	225	11.6%	0.38 [0.14, 0.62]	
Subtotal (95% CI)			1036			1831	55.8%	0.24 [0.13, 0.35]	•
Heterogeneity: Chi ² =	: 3.79, df	= 4 (P =	= 0.44)	l ² = 0%					
Test for overall effect	: Z = 4.28	(P < 0	0001)						
4.4.2 Galcanezumab	240 mg	vs plac	ebo						
Sakai 2020	0.41		114	0.15	0.9	230	17.5%	0.26 [0.07, 0.45]	
Skljarevski 2018b	1.2	1.49	223	0.9	2.15	461	8.6%	0.30 [0.02, 0.58]	
Detke 2018	0.9	1.66	274	0.6	2.32	538	8.6%	0.30 [0.02, 0.58]	
Stauffer 2018	1.6	1.49	184	1.3	1.55	377	9.4%	0.30 [0.03, 0.57]	
Subtotal (95% CI)			795			1606	44.2%	0.28 [0.16, 0.41]	-
Heterogeneity: Chi ² =									
Test for overall effect	: Z = 4.54	(P < 0	.00001)					
Total (95% CI)			1831			3437	100.0%	0.26 [0.18, 0.34]	
Heterogeneity: Chi ² =									-0.5 -0.25 0 0.25 0.5
Test for overall effect									Favours [Placebo] Favours [Galcanezumab]
Test for subgroup dif	ferences	: Chi ² =	0.30,	df = 1 (P	= 0.5	B), I² = ()%		

FIGURE 5: Forest plot showing PGI-S between galcanezumab and placebo groups.

PGI-S, global impression score of severity

Efficacy outcome: MSQ RF-R score

The overall effect size significantly favored galcanezumab over placebo (MD=4.39; 95% CI [2.10, 6.68]; p<0.001). Pooled results were heterogeneous (I^2 =72%; p<0.001), and the random-effects model was used (Figure 6). Subgroup analysis was performed according to the galcanezumab dose. For galcanezumab 120 mg versus placebo, the overall effect size did not significantly differ between both groups (MD=2.06; 95% CI [-1.79, 5.90]; p=0.32). Pooled results were heterogeneous (I^2 =80%; p=0.002). Heterogeneity was best resolved (I^2 =0%; p=0.53) by omitting Sakai et al.'s study [12], and the overall effect size still did not favor any group

(MD=0.37; 95% CI [-1.75, 2.50]; p=0.73). For galcanezumab 240 mg versus placebo, the overall effect size significantly favored the galcanezumab group (MD=6.59; 95% CI [4.92, 8.26]; p<0.001). Pooled results were homogeneous ($I^2=0\%$; p=0.88).

Α		anezum			lacebo			Mean Difference	Mean Difference
Study or Subgroup	Mean			Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
5.4.1 Galcanezumat	-								
Detke 2018		23.13	273		26.48	274	11.2%	-1.30 [-5.47, 2.87]	
Stauffer 2018		20.62	189	32.1	15.6	184	12.1%	0.30 [-3.40, 4.00]	
Skljarevski 2018b		18.24	231		17.92	223	12.9%	1.50 [-1.83, 4.83]	
Sakai 2020	17.1	12.65	115	10.1	11.5	230	14.1%	7.00 [4.25, 9.75]	
Subtotal (95% CI)			808			911	50.2%	2.06 [-1.79, 5.90]	
Heterogeneity: Tau ² Test for overall effect				f= 3 (P	= 0.002)	; I* = 81	3%		
5.4.2 Galcanezumat	o 240 mg	vs Plac	ebo						
Sakai 2020	15.9	12.8	114	10.1	11.5	230	14.0%	5.80 [3.02, 8.58]	
Detke 2018	23.1	26.48	274	16.8	27.83	538	11.6%	6.30 [2.38, 10.22]	
Skljarevski 2018b	27	17.92	223		19.32	461	13.7%	7.30 [4.36, 10.24]	
Stauffer 2018	32.1	15.6	184	24.7	39.02	377	10.4%	7.40 [2.86, 11.94]	
Subtotal (95% CI)			795			1606	49.8%	6.59 [4.92, 8.26]	•
Heterogeneity: Tau ²					1.88); I² =	= 0%			
Test for overall effect	t: Z = 7.7	4 (P < 0.)	00001)						
Total (95% CI)			1603	_			100.0%	4.39 [2.10, 6.68]	
Heterogeneity: Tau ²				= 7 (P =	U.0007)	; I ² = 7:	2%		-10 -5 0 5 10
Test for overall effect									Favours (Placebo) Favours (Galcanezumab)
Test for subgroup di	fferences	s: Chi*=	4.50, c	if = 1 (P	= 0.03),	* = 77	.8%		
-									
В	Galc	anezum	ab	Р	lacebo			Mean Difference	Mean Difference
B Study or Subgroup	Galc Mean			P Mean		Total	Weight	Mean Difference IV, Random, 95% Cl	Mean Difference IV, Random, 95% Cl
	Mean	SD	Total			Total	Weight		
Study or Subgroup	Mean 120 mg	SD	Total	Mean		Total	Weight 13.1%		
Study or Subgroup 5.4.1 Galcanezumat	Mean 120 mg 21.8	SD vs Plac	Total ebo	Mean	SD			IV, Random, 95% Cl	
Study or Subgroup 5.4.1 Galcanezumat Detke 2018	Mean 120 mg 21.8 32.4	SD vs Plac 23.13	Total ebo 273	Mean 23.1 32.1	SD 26.48	274	13.1%	IV, Random, 95% Cl -1.30 [-5.47, 2.87]	
Study or Subgroup 5.4.1 Galcanezumat Detke 2018 Stauffer 2018 Skijarevski 2018b Sakai 2020	Mean 120 mg 21.8 32.4 28.5	SD vs Plac 23.13 20.62	Total ebo 273 189 231 115	Mean 23.1 32.1	SD 26.48 15.6	274 184 223 230	13.1% 14.1% 14.9% 0.0%	N, Random, 95% Cl -1.30 [-5.47, 2.87] 0.30 [-3.40, 4.00] 1.50 [-1.83, 4.83] 7.00 [4.25, 9.75]	
Study or Subgroup 5.4.1 Galcanezumat Detke 2018 Stauffer 2018 Sklijarevski 2018b Sakai 2020 Subtotal (95% CI)	Mean 21.8 32.4 28.5 17.1	SD vs Plac 23.13 20.62 18.24 12.65	Total ebo 273 189 231 115 693	Mean 23.1 32.1 27 10.1	SD 26.48 15.6 17.92 11.5	274 184 223 230 681		V, Random, 95% Cl -1.30 [-5.47, 2.87] 0.30 [-3.40, 4.00] 1.50 [-1.83, 4.83]	
Study or Subgroup 5.4.1 Galcanezumat Detke 2018 Stauffer 2018 Skijarevski 2018b Sakai 2020	Mean 120 mg 21.8 32.4 28.5 17.1 = 0.00; C	SD vs Plac 23.13 20.62 18.24 12.65 hi ² = 1.0	Total ebo 273 189 231 115 693 6, df =	Mean 23.1 32.1 27 10.1	SD 26.48 15.6 17.92 11.5	274 184 223 230 681	13.1% 14.1% 14.9% 0.0%	N, Random, 95% Cl -1.30 [-5.47, 2.87] 0.30 [-3.40, 4.00] 1.50 [-1.83, 4.83] 7.00 [4.25, 9.75]	
Study or Subgroup 5.4.1 Galcanezumati Detke 2018 Stauffer 2018 Skijarevski 2018b Sakai 2020 Subtotal (95% Cl) Heterogeneity: Tau ² : Test for overall effect 5.4.2 Galcanezumati	Mean 120 mg 21.8 32.4 28.5 17.1 = 0.00; C : Z = 0.34 240 mg	SD vs Plac 23.13 20.62 18.24 12.65 hi² = 1.0 4 (P = 0.7) vs Plac	Total ebo 273 189 231 115 693 6, df = 73) ebo	Mean 23.1 32.1 27 10.1 2 (P = 0	SD 26.48 15.6 17.92 11.5 .59); I ² =	274 184 223 230 681 :0%	13.1% 14.1% 14.9% 0.0% 42.1%	IV, Random, 95% Cl -1.30 [-5.47, 2.87] 0.30 [-3.40, 4.00] 1.50 [-1.83, 4.83] 7.00 [4.25, 9.75] 0.37 [-1.75, 2.50]	
Study or Subgroup 5.4.1 Galcanezumat Detke 2018 Stauffer 2018 Skala 2020 Subtotal (95% CI) Heterogeneily: Tau ² : Test for overall effect 5.4.2 Galcanezumat Sakai 2020	Mean 120 mg 21.8 32.4 28.5 17.1 = 0.00; C : Z = 0.34 240 mg 15.9	SD vs Plac 23.13 20.62 18.24 12.65 hi² = 1.0 4 (P = 0.3) vs Plac 12.8	Total ebo 273 189 231 115 693 6, df = 73) ebo 114	Mean 23.1 32.1 27 10.1 2 (P = 0 10.1	SD 26.48 15.6 17.92 11.5 .59); I ² = 11.5	274 184 223 230 681 :0% 230	13.1% 14.1% 14.9% 0.0% 42.1%	N, Random, 95% Cl -1.30 [-5.47, 2.87] 0.30 [-3.40, 4.00] 1.50 [-1.83, 4.83] 7.00 [4.25, 9.75] 0.37 [-1.75, 2.50] 5.80 [3.02, 8.58]	
Study or Subgroup 5.4.1 Galcanezumat Detke 2018 Stauffer 2018 Skijarevski 2018b Sakai 2020 Subtotal (95% CI) Heterogeneity: Tau ² : Test for overall effect 5.4.2 Galcanezumat Sakai 2020 Detke 2018	Mean 120 mg 21.8 32.4 28.5 17.1 = 0.00; C : Z = 0.34 240 mg 15.9 23.1	SD vs Plac 23.13 20.62 18.24 12.65 hi² = 1.0 4 (P = 0.3) vs Plac 12.8 26.48	Total ebo 273 189 231 115 693 6, df = 73) ebo 114 274	Mean 23.1 32.1 27 10.1 2 (P = 0 10.1 16.8	SD 26.48 15.6 17.92 11.5 .59); I ² = 11.5 27.83	274 184 223 230 681 :0% 230 538	13.1% 14.1% 14.9% 0.0% 42.1% 16.2% 13.6%	M, Random, 95% Cl -1.30 [-5.47, 2.87] 0.30 [-3.40, 4.00] 1.50 [-1.83, 4.83] 7.00 [4.25, 9.75] 0.37 [-1.75, 2.50] 5.80 [3.02, 8.58] 6.30 [2.38, 10.22]	
Study or Subgroup 5.4.1 Galcanezumat Detke 2018 Stauffer 2018 Sakai 2020 Subtotal (95% CI) Heterogeneity, Tau ² . Test for overall effect 5.4.2 Galcanezumat Sakai 2020 Detke 2018 Skijarevski 2018b	Mean 120 mg 21.8 32.4 28.5 17.1 = 0.00; C : Z = 0.3 240 mg 15.9 23.1 27	SD vs Plac 23.13 20.62 18.24 12.65 hi ² = 1.0 4 (P = 0.1) vs Plac 12.8 26.48 17.92	Total ebo 273 189 231 115 693 6, df = 73) ebo 114 274 223	Mean 23.1 32.1 27 10.1 2 (P = 0 10.1 16.8 19.7	SD 26.48 15.6 17.92 11.5 .59); I ² = 11.5 27.83 19.32	274 184 223 681 :0% 230 538 461	13.1% 14.1% 14.9% 0.0% 42.1% 16.2% 13.6% 15.8%	M, Random, 95% Cl -1.30 [-5.47, 2.87] 0.30 [-3.40, 4.00] 1.50 [-1.83, 4.83] 7.00 [4.25, 9.75] 0.37 [-1.75, 2.50] 5.80 [3.02, 8.58] 6.30 [2.38, 10.22] 7.30 [4.36, 10.24]	
Study or Subgroup 5.4.1 Galcanezumat Detke 2018 Stauffer 2018 Skijarevski 2018b Sakai 2020 Subtotal (95% CI) Heterogeneily: Tau ² : Test for overall effect 5.4.2 Galcanezumat Sakai 2020 Detke 2018 Skijarevski 2018b Stauffer 2018	Mean 120 mg 21.8 32.4 28.5 17.1 = 0.00; C : Z = 0.34 240 mg 15.9 23.1	SD vs Plac 23.13 20.62 18.24 12.65 hi² = 1.0 4 (P = 0.3) vs Plac 12.8 26.48	Total ebo 273 189 231 115 693 6, df = 73) ebo 114 274 223 184	Mean 23.1 32.1 27 10.1 2 (P = 0 10.1 16.8 19.7	SD 26.48 15.6 17.92 11.5 .59); I ² = 11.5 27.83	274 184 223 230 681 :0% 230 538 461 377	13.1% 14.1% 14.9% 0.0% 42.1% 16.2% 13.6% 15.8% 12.3%	M, Random, 95% C1 -1.30 [-5.47, 2.87] 0.30 [-3.40, 4.00] 1.50 [-1.33, 4.83] 7.00 [4.25, 9.75] 0.37 [-1.75, 2.50] 5.80 [3.02, 8.58] 6.30 [2.38, 10.22] 7.30 [4.36, 10.24] 7.40 [2.46, 11.94]	
Study or Subgroup 5.4.1 Galcanezumat Detke 2018 Stauffer 2018 Stauffer 2018 Skala 2020 Subtotal (95% CI) Heterogeneity: Tau ² : Test for overall effect 5.4.2 Galcanezumat Sakai 2020 Detke 2018 Skijarevski 2018 Stauffer 2018 Subtotal (95% CI)	Mean 21.8 32.4 28.5 17.1 = 0.00; C : Z = 0.34 240 mg 23.1 27 32.1	SD vs Plac 23.13 20.62 18.24 12.65 hi ² = 1.0 4 (P = 0.1 vs Plac 12.8 26.48 17.92 15.6	Total ebo 273 189 231 115 693 6, df = 73) ebo 114 274 223 184 795	Mean 23.1 32.1 27 10.1 2 (P = 0 10.1 16.8 19.7 24.7	SD 26.48 15.6 17.92 11.5 1.59); I ² = 11.5 27.83 19.32 39.02	274 184 223 230 681 :0% 230 538 461 377 1606	13.1% 14.1% 14.9% 0.0% 42.1% 16.2% 13.6% 15.8%	M, Random, 95% Cl -1.30 [-5.47, 2.87] 0.30 [-3.40, 4.00] 1.50 [-1.83, 4.83] 7.00 [4.25, 9.75] 0.37 [-1.75, 2.50] 5.80 [3.02, 8.58] 6.30 [2.38, 10.22] 7.30 [4.36, 10.24]	
Study or Subgroup 5.4.1 Galcanezumat Detke 2018 Stauffer 2018 Skijarevski 2018b Sakai 2020 Subtotal (95% CI) Heterogeneily: Tau ² : Test for overall effect 5.4.2 Galcanezumat Sakai 2020 Detke 2018 Skijarevski 2018b Stauffer 2018	Mean 21.8 32.4 28.5 17.1 = 0.00; C : Z = 0.3 ³ 240 mg 23.1 27 32.1 = 0.00; C	SD vs Plac 23.13 20.62 18.24 12.65 hi² = 1.0 4 (P = 0.3) vs Plac 12.8 26.48 17.92 15.6 hi² = 0.6	Total ebo 273 189 231 115 693 6, df = 73) ebo 114 274 223 184 795 8, df =	Mean 23.1 32.1 27 10.1 2 (P = 0 10.1 16.8 19.7 24.7	SD 26.48 15.6 17.92 11.5 1.59); I ² = 11.5 27.83 19.32 39.02	274 184 223 230 681 :0% 230 538 461 377 1606	13.1% 14.1% 14.9% 0.0% 42.1% 16.2% 13.6% 15.8% 12.3%	M, Random, 95% C1 -1.30 [-5.47, 2.87] 0.30 [-3.40, 4.00] 1.50 [-1.33, 4.83] 7.00 [4.25, 9.75] 0.37 [-1.75, 2.50] 5.80 [3.02, 8.58] 6.30 [2.38, 10.22] 7.30 [4.36, 10.24] 7.40 [2.46, 11.94]	
Study or Subgroup 5.4.1 Galcanezumat Detke 2018 Stauffer 2018 Skijarevski 2018b Sakai 2020 Subtotal (95% cf) Heterogeneity: Tau ² : Test for overall effect 5.4.2 Galcanezumat Sakai 2020 Detke 2018 Skijarevski 2018b Stauffer 2018 Stauffer 2018 Stauffer 2018	Mean 21.8 32.4 28.5 17.1 = 0.00; C : Z = 0.3 ³ 240 mg 23.1 27 32.1 = 0.00; C	SD vs Plac 23.13 20.62 18.24 12.65 hi² = 1.0 4 (P = 0.3) vs Plac 12.8 26.48 17.92 15.6 hi² = 0.6	Total ebo 273 189 231 115 693 6, df = 73) ebo 114 274 223 184 795 8, df =	Mean 23.1 32.1 27 10.1 2 (P = 0 10.1 16.8 19.7 24.7	SD 26.48 15.6 17.92 11.5 1.59); I ² = 11.5 27.83 19.32 39.02	274 184 223 681 :0% 230 538 461 377 1606 :0%	13.1% 14.1% 14.9% 0.0% 42.1% 16.2% 13.6% 15.8% 12.3%	M, Random, 95% C1 -1.30 [-5.47, 2.87] 0.30 [-3.40, 4.00] 1.50 [-1.33, 4.83] 7.00 [4.25, 9.75] 0.37 [-1.75, 2.50] 5.80 [3.02, 8.58] 6.30 [2.38, 10.22] 7.30 [4.36, 10.24] 7.40 [2.46, 11.94]	
Study or Subgroup 5.4.1 Galcanezumat Detke 2018 Stauffer 2018 Stauffer 2018 Sakai 2020 Subtotal (95% CI) Heterogeneity: Tau ² : Test for overall effect 5.4.2 Galcanezumat Sakai 2020 Detke 2018 Stauffer 2018 Stauffer 2018 Subtotal (95% CI) Heterogeneity: Tau ² : Total (95% CI)	Mean 120 mg 21.8 32.4 28.5 17.1 = 0.00; C : Z = 0.34 240 mg 15.9 23.1 27 32.1 = 0.00; C : Z = 7.74 = 8.57; C	SD vs Plac 23.13 20.62 18.24 12.65 hi² = 1.0 4 (P = 0.1 vs Plac 26.48 17.92 15.6 hi² = 0.6 4 (P < 0.0	Total ebo 273 189 231 115 693 66, df= 73) ebo 114 273 184 795 200001) 1488 004, df=	Mean 23.1 32.1 27 10.1 2 (P = 0 10.1 16.8 19.7 24.7 3 (P = 0	SD 26.48 15.6 17.92 11.5 .59); * = 11.5 27.83 19.32 39.02 .88); * =	274 184 223 681 :0% 230 538 461 377 1606 :0% 2287	13.1% 14.1% 14.9% 0.0% 42.1% 16.2% 13.6% 15.8% 12.3% 57.9%	M, Random, 95% Cl -1.30 [-5.47, 2.87] 0.30 [-3.40, 4.00] 1.50 [-1.83, 4.83] 7.00 [4.25, 9.75] 0.37 [-1.75, 2.50] 5.80 [3.02, 8.58] 6.30 [2.38, 10.22] 7.30 [4.36, 10.24] 7.40 [2.86, 11.94] 6.59 [4.92, 8.26]	IV, Random, 95% Cl
Study or Subgroup 5.4.1 Galcanezumat Detke 2018 Stauffer 2018 Skijarevski 2018b Sakai 2020 Subtotal (95% C) Heterogeneity: Tau ² : Test for overall effect Sakai 2020 Detke 2018 Skijarevski 2018b Stauffer 2018 Stauffer 2018 Sta	Mean 120 mg 21.8 32.4 28.55 17.1 = 0.00; C : Z = 0.3 ³ 240 mg 23.1 27 32.1 = 0.00; C : Z = 7.7 ⁴ = 8.57; C : Z = 3.0 ²	SD vs Plac 23.13 20.62 18.24 12.65 hi² = 1.0 4 (P = 0.3) vs Plac 26.48 17.92 15.6 hi² = 0.6 4 (P < 0.0	Total ebo 273 189 231 115 693 6, df = 73) ebo 114 274 223 184 795 8, df = 200001) 1488 004, df = 002)	Mean 23.1 32.1 27 10.1 2 (P = 0 10.1 16.8 19.7 24.7 3 (P = 0 = 6 (P =	SD 26.48 15.6 17.92 11.5 .59); I [≠] = 11.5 27.83 19.32 39.02 .88); I [≠] = 0.001);	274 184 223 230 681 : 0% 230 538 461 377 1606 : 0% 2287 ² = 73 ⁴	13.1% 14.1% 14.9% 0.0% 42.1% 16.2% 13.6% 13.6% 13.8% 12.3% 57.9% 1000.0%	M, Random, 95% Cl -1.30 [-5.47, 2.87] 0.30 [-3.40, 4.00] 1.50 [-1.83, 4.83] 7.00 [4.25, 9.75] 0.37 [-1.75, 2.50] 5.80 [3.02, 8.58] 6.30 [2.38, 10.22] 7.30 [4.36, 10.24] 7.40 [2.86, 11.94] 6.59 [4.92, 8.26]	N, Random, 95% Cl
Study or Subgroup 5.4.1 Galcanezumat Detke 2018 Stauffer 2018 Stauffer 2018 Sakai 2020 Subtotal (95% CI) Heterogeneity: Tau ² : Test for overall effect 5.4.2 Galcanezumat Sakai 2020 Detke 2018 Stauffer 2018 Stauffer 2018 Subtotal (95% CI) Heterogeneity: Tau ² : Total (95% CI)	Mean 120 mg 21.8 32.4 28.55 17.1 = 0.00; C : Z = 0.3 ³ 240 mg 23.1 27 32.1 = 0.00; C : Z = 7.7 ⁴ = 8.57; C : Z = 3.0 ²	SD vs Plac 23.13 20.62 18.24 12.65 hi² = 1.0 4 (P = 0.3) vs Plac 26.48 17.92 15.6 hi² = 0.6 4 (P < 0.0	Total ebo 273 189 231 115 693 6, df = 73) ebo 114 274 223 184 795 8, df = 200001) 1488 004, df = 002)	Mean 23.1 32.1 27 10.1 2 (P = 0 10.1 16.8 19.7 24.7 3 (P = 0 = 6 (P =	SD 26.48 15.6 17.92 11.5 .59); I [≠] = 11.5 27.83 19.32 39.02 .88); I [≠] = 0.001);	274 184 223 230 681 : 0% 230 538 461 377 1606 : 0% 2287 ² = 73 ⁴	13.1% 14.1% 14.9% 0.0% 42.1% 16.2% 13.6% 13.6% 13.8% 12.3% 57.9% 1000.0%	M, Random, 95% Cl -1.30 [-5.47, 2.87] 0.30 [-3.40, 4.00] 1.50 [-1.83, 4.83] 7.00 [4.25, 9.75] 0.37 [-1.75, 2.50] 5.80 [3.02, 8.58] 6.30 [2.38, 10.22] 7.30 [4.36, 10.24] 7.40 [2.86, 11.94] 6.59 [4.92, 8.26]	N, Random, 95% Cl

FIGURE 6: Forest plot showing the MSQ RF-R score between galcanezumab and placebo groups before (A) and after (B) sensitivity

analysis using the leave-one-out method.

MSQ RF-R, migraine-specific quality of life questionnaire role function-restrictive

Efficacy outcome: MIDAS score

The overall effect size significantly favored galcanezumab over placebo (MD=6.83; 95% CI [1.35, 12.32]; p<0.001). Pooled results were heterogeneous (I^2 =69%; p=0.01), and the random-effects model was used (Figure 7). Subgroup analysis was performed according to the galcanezumab dose. For galcanezumab 120 mg versus placebo, the overall effect size significantly favored the galcanezumab group (MD=7.06; 95% CI [-3.68, 17.81]; p=0.20). Pooled results were heterogeneous (I^2 =81%; p=0.005). Heterogeneity was best resolved (I^2 =0%; p=0.71) by omitting Mulleners et al.'s study [13], and the overall effect size did not favor any group (MD=1.29; 95% CI [-2.76, 5.35]; p=0.53). For galcanezumab 240 mg versus placebo, the overall effect size significantly favored the galcanezumab group (MD=7.85; 95% CI [4.08, 11.62]; p<0.001). Pooled results were homogeneous (I^2 =0%; p=0.64).

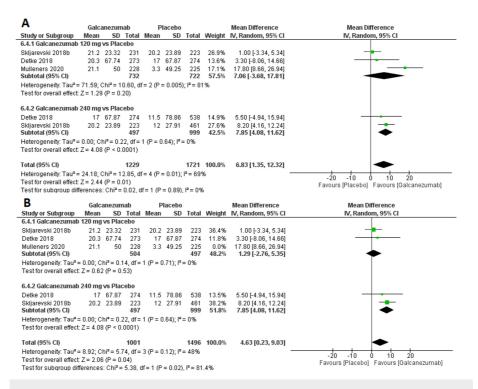


FIGURE 7: Forest plot showing MIDAS between galcanezumab and placebo groups before (A) and after (B) sensitivity analysis using the leave-one-out method.

MIDAS, migraine disability assessment score

Safety outcome: injection-site pain

The overall effect size did not show a significant difference between both groups (RR=1.35; 95% CI [0.98, 1.86]; p=0.06) Pooled results were heterogeneous (I^2 =62%; p=0.005), and the random-effects model was used (Figure 8). Subgroup analysis was performed according to the galcanezumab dose. For galcanezumab 120 mg versus placebo, the overall effect size significantly did not differ between both groups (RR=1.34; 95% CI [0.79, 2.27]; p=0.28). Pooled results were heterogeneous (I^2 =71%; p=0.004). Heterogeneity could not be resolved by performing leave-one-out method. For galcanezumab 240 mg versus placebo, the overall effect size did not significantly differ between both groups (RR=1.40; 95% CI [0.93, 2.11]; p=0.11). Pooled results were homogeneous (I^2 =52%; p=0.10).

	Galcanezu	ımab	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
8.4.1 Galcanezumab	120 mg vs I	Placebo					
Mulleners 2020	5	232	13	230	6.5%	0.38 [0.14, 1.05]	
Stauffer 2018	33	206	75	432	14.9%	0.92 [0.63, 1.34]	
Skljarevski 2018b	21	226	39	461	12.8%	1.10 [0.66, 1.82]	_ -
Detke 2018	17	273	24	558	11.2%	1.45 [0.79, 2.65]	
Sakai 2020	7	115	3	230	4.4%	4.67 [1.23, 17.71]	
Skljarevski 2018a	10	70	4	137	5.7%	4.89 [1.59, 15.04]	
Subtotal (95% CI)		1122		2048	55.6%	1.34 [0.79, 2.27]	
Total events	93		158				
Heterogeneity: Tau ² =	0.28; Chi ² =	17.08,	df = 5 (P	= 0.004	l); l² = 719	6	
Test for overall effect: .	Z = 1.07 (P	= 0.28)					
8.4.2 Galcanezumab 2							
Skljarevski 2018b	20	228	39	461	12.6%	1.04 [0.62, 1.74]	_ _
Stauffer 2018	45	220	75	432	15.6%	1.18 [0.85, 1.64]	- - -
Detke 2018	20	282	24	558	11.7%	1.65 [0.93, 2.93]	—
Sakai 2020	8	114	3	230	4.6%	5.38 [1.45, 19.90]	
Subtotal (95% CI)		844		1681	44.4%	1.40 [0.93, 2.11]	-
Total events	93		141				
Heterogeneity: Tau² =			f=3(P=	0.10);1	l² = 52%		
Test for overall effect: .	Z = 1.62 (P	= 0.11)					
Total (95% CI)		1966		3729	100.0%	1.35 [0.98, 1.86]	•
Total events	186		299				
Heterogeneity: Tau ² =	0.14: Chi ² =	23.84.		= 0.005	5); I ² = 629	6	
Test for overall effect: .			- (0.05 0.2 1 5 20
Test for subaroup diffe							Favours [Galcanezumab] Favours [Placebo]

FIGURE 8: Forest plot showing the rate of injection-site pain between galcanezumab and placebo groups.

Safety outcome: nasopharyngitis

The overall effect size did not show a significant difference between both groups (MD=0.93; 95% CI [0.74, 1.16]; p=0.5). Pooled results were homogenous (I^2 =35%; p=0.15), and the fixed-effects model was used (Figure 9). Subgroup analysis was performed according to the galcanezumab dose. For galcanezumab 120 mg versus placebo, the overall effect size did not significantly differ between both groups (RR=1.11; 95% CI [0.84, 1.47]; p=0.47). Pooled results were homogeneous (I^2 =29%; p=0.23). For galcanezumab 240 mg versus placebo, the overall effect size did not significantly differ between both groups (RR=0.68; 95% CI [0.46, 1.00]; p=0.05). Pooled results were homogeneous (I^2 =53%; p=0.53).

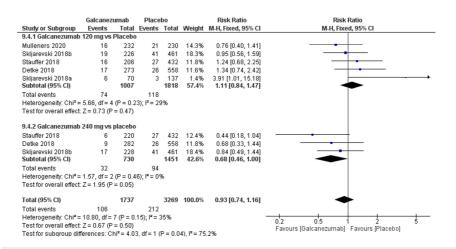


FIGURE 9: Forest plot showing the rate of nasopharyngitis between galcanezumab and placebo groups.

Safety outcome: URTI

The overall effect size significantly showed a significantly higher frequency of URTI in the galcanezumab group (RR=1.61; 95% CI [1.16, 2.24]; p=0.004). Pooled results were homogenous (I^2 =0%; p=0.53), and the fixed-effects model was used (Figure *10*). Subgroup analysis was performed according to the galcanezumab dose. For galcanezumab 120 mg versus placebo, the overall effect size revealed a significantly higher occurrence of URTI in the galcanezumab group (RR=1.79; 95% CI [1.17, 2.72]; p=0.007). Pooled results were homogeneous (I^2 =30%; p=0.23). For galcanezumab 240 mg versus placebo, the overall effect size did not differ between both groups (RR=1.38; 95% CI [0.81, 2.35]; p=0.24). Pooled results were homogeneous (I^2 =0%; p=0.80).

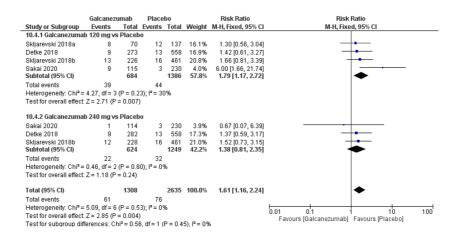


FIGURE 10: Forest plot showing the rate of upper respiratory tract infection between galcanezumab and placebo groups.

Discussion

Our analysis found that galcanezumab was highly effective in the management of migraine attacks. Specifically, galcanezumab succeeded in decreasing monthly MHDs and monthly MHDs with acute medication use. Overall, when compared to placebo, our results revealed that both doses of galcanezumab provided nearly equal therapeutic efficacy for most outcomes, except for MSQ RF-R and MIDAS scores where galcanezumab 240 mg showed a significantly higher efficacy when compared with galcanezumab 120 mg. With regard to side effects, the rates of injection-site pain and nasopharyngitis did not substantially differ between galcanezumab (inclusive of 120 mg and 240 mg) and placebo groups. Nonetheless, when compared to placebo, galcanezumab 120 mg, but not galcanezumab 240 mg, substantially correlated with a higher rate of URTI.

The favorable efficacy of galcanezumab for the management of migraine is somehow anticipated, as galcanezumab has been depicted to be effective in managing other neurological disorders. In a recent review, galcanezumab has demonstrated promising results for both prevention and treatment of cluster headache [6,15,16]. Nonetheless, when administered to patients with osteoarthritis, galcanezumab failed to reduce signs and symptoms in patients with knee osteoarthritis [17].

Similar drugs of the same anti-CGRP monoclonal antibodies have been previously tried for migraine and reported encouraging results. For example, erenumab proved to be effective in the prevention and treatment of migraine [18]. A systematic review and meta-analysis of five randomized placebo-controlled trials revealed the superiority of erenumab over placebo in reducing the monthly MHDs and migraine-specific medication days [19]. Fremanezumab is a humanized monoclonal antibody that targets the CGRP receptor. Fremanezumab showed promising results in the treatment and prevention of migraine, with a very low incidence of side effects [20]. Both fremanezumab and erenumab could advantageously convert patients from chronic migraine status to episodic migraine status [21]. No trials till now have yet compared fremanezumab and galcanezumab to determine which drug is more effective and safer.

Generally, common side effects of anti-CGRP monoclonal antibodies include URTI, nasopharyngitis, urinary tract infection, and injection-site pain. Deng et al. [22] conducted a meta-analysis of 11 randomized placebo-controlled trials comparing anti-CGRP monoclonal antibodies versus placebo. The authors revealed that galcanezumab, fremanezumab, and erenumab significantly resulted in reduction of MHDs and acute migraine-specific medication days, in addition to an enhancement in 50% responder rate. Moreover, the adverse events and treatment discontinuation frequencies secondary to adverse events were not considerably dissimilar between the anti-CGRP monoclonal antibodies and placebo groups. In subgroup analysis, comparable efficacy and tolerability outcomes were achieved for galcanezumab, fremanezumab, and erenumab. Similar findings were reciprocated in other meta-analyses by Zhu et al. [23] and Xu et al. [24]. In the literature, various doses of galcanezumab have been used, ranging from as low as 5 mg to as high as 300 mg. The optimal dose that yields maximum efficacy and minimum adverse events is yet to be determined.

Our study has several strengths. The large number of included trials is the main strength of our study when compared to previous meta-analysis studies [25-27]. We only included randomized placebo-controlled clinical trials to ensure high-quality evidence. Moreover, we performed subgroup analysis according to the two most commonly used galcanezumab doses (120 mg and 240 mg) and excluded the others to ensure consistency with regard to drug dosing. Whenever heterogeneity existed during meta-analysis, we used the

leave-one-out method to resolve the heterogeneity. Nonetheless, our study is not without limitations. The vast majority of studies had an unclear risk of bias regarding two important domains: allocation concealment and blinding of outcome assessment. This observation could negatively impact the quality of the evaluated outcomes. Moreover, some of the reported endpoints revealed significant heterogeneity, which could be ascribed to the varying degrees of migraine severity and duration of treatment. Lastly, not all studies adequately reported our prespecified side effects.

As it stands now, galcanezumab (120 mg and 240 mg) appears to be clinically safe and effective in the management of patients with migraine. Nonetheless, future research directions should be geared toward determining the optimal dose of galcanezumab for the management of patients with migraine. Moreover, head-to-head comparative studies between galcanezumab and other related anti-CGRP receptor monoclonal antibodies are warranted.

Conclusions

In summary, this systematic review and meta-analysis examined the efficacy of galcanezumab (120 mg and 240 mg) versus placebo in patients with migraine. Our findings showed that galcanezumab (120 mg or 240 mg) was superior to placebo in reducing the number of MHDs and MHDs with acute medication use. Moreover, galcanezumab treatment significantly correlated with improved PGI-S, MSQ RF-R, and MIDAS scores. Overall, the rates of side effects did not substantially differ between galcanezumab and placebo groups.

Additional Information

Disclosures

Human subjects: All authors have confirmed that this study did not involve human participants or tissue. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

- 1. Dodick DW: Migraine. Lancet. 2018, 391:1315-1330. 10.1016/s0140-6736(18)30478-1
- Olesen J: International classification of headache disorders. Lancet Neurol. 2018, 17:396-397. 10.1016/s1474-4422(18)30085-1
- Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olesen J: CGRP may play a causative role in migraine. Cephalalgia. 2002, 22:54-61. 10.1046/j.1468-2982.2002.00310.x
- Juhasz G, Zsombok T, Modos EA, et al.: NO-induced migraine attack: strong increase in plasma calcitonin gene-related peptide (CGRP) concentration and negative correlation with platelet serotonin release. Pain. 2003, 106:461-470. 10.1016/j.pain.2003.09.008
- 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. 10.1001/jamaneurol.2018.1212
- 6. Lamb YN: Galcanezumab: first global approval. Drugs. 2018, 78:1769-1775. 10.1007/s40265-018-1002-7
- Moher D, Liberati A, Tetzlaff J, Altman DG: Preferred reporting items for systematic reviews and metaanalyses: the PRISMA statement. PLoS Med. 2009, 6:1000097. 10.1371/journal.pmed.1000097
- Cochrane Collaboration: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. Higgins JPT, Green S (ed): Cochrane Collaboration, Chichester, UK; 2011.
- 9. Higgins JP, Altman DG, Gøtzsche PC, et al.: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011, 343:5928. 10.1136/bmj.d5928
- 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. 10.1001/jamaneurol.2017.3859
- 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. 10.1177/0333102418779543
- Sakai F, Ozeki A, Skljarevski V: Efficacy and safety of galcanezumab for prevention of migraine headache in Japanese patients with episodic migraine: a phase 2 randomized controlled clinical trial. Cephalalgia Rep. 2020, 3:251581632093257. 10.1177/2515816320932573
- Mulleners WM, Kim BK, Láinez MJA, et al.: Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial. Lancet Neurol. 2020, 19:814-825. 10.1016/s1474-4422(20)30279-9
- 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, 91:2211-2221. 10.1212/wnl.00000000006640
- 15. Yuan H, Spare NM, Silberstein SD: Targeting CGRP for the prevention of migraine and cluster headache: a

narrative review. Headache. 2019, 59:20-32. 10.1111/head.13583

- Giani L, Proietti Cecchini A, Leone M: Galcanezumab for the prevention of cluster headache. Expert Opin Biol Ther. 2020, 20:1133-1142. 10.1080/14712598.2020.1800635
- Jin Y, Smith C, Monteith D, et al.: CGRP blockade by galcanezumab was not associated with reductions in signs and symptoms of knee osteoarthritis in a randomized clinical trial. Osteoarthritis Cartilage. 2018, 26:1609-1618. 10.1016/j.joca.2018.08.019
- Ramón C, Cernuda-Morollón E, Pascual J: Calcitonin gene-related peptide in peripheral blood as a biomarker for migraine. Curr Opin Neurol. 2017, 30:281-286. 10.1097/wco.00000000000440
- Zhu C, Guan J, Xiao H, Luo W, Tong R: Erenumab safety and efficacy in migraine: A systematic review and meta-analysis of randomized clinical trials. Medicine (Baltimore). 2019, 98:18483. 10.1097/md.00000000018483
- Lionetto L, Curto M, Cisale GY, Capi M, Cipolla F, Guglielmetti M, Martelletti P: Fremanezumab for the preventive treatment of migraine in adults. Expert Rev Clin Pharmacol. 2019, 12:741-748. 10.1080/17512433.2019.1635452
- Tepper SJ: Anti-calcitonin gene-related peptide (CGRP) therapies: update on a previous review after the American Headache Society 60th Scientific Meeting, San Francisco, June 2018. Headache. 2018, 58:276-290. 10.1111/head.13417
- Deng H, Li GG, Nie H, Feng YY, Guo GY, Guo WL, Tang ZP: Efficacy and safety of calcitonin-gene-related peptide binding monoclonal antibodies for the preventive treatment of episodic migraine - an updated systematic review and meta-analysis. BMC Neurol. 2020, 20:57. 10.1186/s12883-020-01633-3
- Zhu Y, Liu Y, Zhao J, Han Q, Liu L, Shen X: The efficacy and safety of calcitonin gene-related peptide monoclonal antibody for episodic migraine: a meta-analysis. Neurol Sci. 2018, 39:2097-2106. 10.1007/s10072-018-3547-3
- 24. Xu D, Chen D, Zhu LN, Tan G, Wang HJ, Zhang Y, Liu L: Safety and tolerability of calcitonin-gene-related peptide binding monoclonal antibodies for the prevention of episodic migraine - a meta-analysis of randomized controlled trials. Cephalalgia. 2019, 39:1164-1179. 10.1177/0333102419829007
- Gklinos P, Mitsikostas DD: Galcanezumab in migraine prevention: a systematic review and meta-analysis of randomized controlled trials. Ther Adv Neurol Disord. 2020, 13:1756286420918088. 10.1177/1756286420918088
- 26. Zhao X, Xu X, Li Q: Efficacy and safety of galcanezumab for preventive treatment of migraine: a systematic review and meta-analysis [Online ahead of print]. J Neurol. 2020, 10.1007/s00415-020-09707-5
- Yang Y, Wang Z, Gao B, Xuan H, Zhu Y, Chen Z: Different doses of galcanezumab versus placebo in patients with migraine and cluster headache: a meta-analysis of randomized controlled trials. J Headache Pain. 2020, 21:14. 10.1186/s10194-020-1085-x