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Adverse and serious adverse events incidence of pharmacological interventions for managing chronic and episodic migraine in adults: a systematic review

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ABSTRACT

Background Migraine is the second most common prevalent disorder worldwide and is a top cause of disability with a substantial economic burden. Many preventive migraine medications have notable side effects that affect different body organs.

Method We systematically searched for published randomised controlled trials (RCTs) using terms for migraine/headache and preventive medications. Using eligibility criteria, two reviewers independently assessed the articles. Cochrane risk-of-bias tool was applied to assess the quality of the studies. Data were classified by system organ class (SOC).

Results Thirty-two RCTs with 21 780 participants met the eligibility criteria for the incidence of adverse events (AEs). Additionally, 33 RCTs with 22 615 participants were included to synthesise the incidence of serious AEs (SAEs). The percentage of attributed AEs and SAEs to each SOC for 10 preventive drugs with different dosing regimens was calculated. Amitriptyline and topiramate had a higher incidence of nervous system disorders; Topiramate was also associated with a higher incidence of psychiatric disorders. All drugs showed a certain incidence of infections and infestations, with Onabotulinumtoxin A (BTA) having the lowest rate. BTA had a higher incidence of musculoskeletal disorders than the other drugs. Calcitonin gene-related peptide (CGRP) monoclonal antibodies (MAbs) such as fremanezumab and galcanezumab were linked to more general disorders and administration site conditions than other drugs.

Conclusion Notably, the observed harm to SOCs varies among these preventive drugs. We suggest conducting head-to-head RCTs to evaluate the safety profile of oral medications, BTA, and CGRP MAbs in episodic and/or chronic migraine populations.

PROSPERO registration number CRD42021265993.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The current landscape of migraine management involves preventive medications with notable side effects, contributing to challenges in adherence and treatment discontinuation. While previous reviews have explored the safety of migraine medications, there remains a gap in understanding how these pharmacological treatments affect specific organs in the body.

WHAT THIS STUDY ADDS

⇒ This study contributes by systematically evaluating adverse events and serious adverse events associated with 10 preventive migraine medications. Notably, it identifies varying safety profiles, with amitriptyline and topiramate showing higher adverse event incidence particularly in the nervous system, while newer treatments exhibit limited adverse events, emphasising the need for head-to-head trials.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further head-to-head randomised controlled trials to evaluate the safety profile of oral medications, Onabotulinumtoxin A and calcitonin gene-related peptide monoclonal antibodies in episodic and/or chronic migraine populations is encouraged.

BACKGROUND

Migraine ranks as the second most prevalent disabling condition worldwide, and it is the top cause of years lived with disability among individuals aged 15–49 years.[1] Migraine is a recurrent condition characterised by headaches lasting from 4 hours to 72 hours. These headaches are described as pulsating, typically unilateral, and can be moderate to severe in intensity. Migraine symptoms include nausea and/or vomiting, sensitivity to light and/or sound and can be aggravated from routine physical activity.[2] Migraine can significantly impact the patient's work–life, social and leisure activities as well as their physical and emotional well-being. This, in turn, can result in a considerable burden on

patients and their families and also an increase in healthcare expenditure.[3] The frequency of migraine episodes determines its classification: up to 14 migraine days per month is classified as 'episodic', while a headache occurring on 15 or more days per month, with at least 8 days meeting migraine criteria, is classified as 'chronic'.[4]

Currently, various migraine preventive therapies are recommended for individuals who experience four or more migraine attacks per month, have overused or failed on acute medication or suffer from significant migraine-related impairment in daily functioning or quality of life.[5] Many preventive migraine medications have notable side effects, including fatigue, memory problems, mental confusion, weight gain and sexual dysfunction. Poor adherence and persistence with preventive treatments for migraine are common, and adverse events frequently lead to treatment discontinuation.[5]

The published literature reveals a complex view regarding patient preferences and side effects related to migraine preventive drugs. Among the side effects, depression, memory loss and weight gain are the least accepted.[6] Women show a greater aversion to weight gain.[6] A 2019 choice experiment demonstrated that avoiding a 10% increase in weight was more desired by participants than avoiding issues with memory and reasoning.[5] Thus, it is important to have a picture of the side effects of each of these preventive drugs.

Although systematic reviews and meta-analyses have been conducted to assess the safety of head-to-head medications,[7–14] there is currently no evidence available to compare the safety profiles of pharmacological medications for migraine and determine which organs in the body are affected. This review aims to synthesise evidence on the incidence of adverse events (AEs) and serious AEs (SAEs) in people with chronic or episodic migraine.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews.[15] No ethical approval was required. We considered the following standard definitions for AEs and SAEs (table 1).

Search strategy

The search strategy was constructed in MEDLINE by an information specialist and checked by another information specialist for any errors before being translated to other bibliographic databases. No date or language limits were applied. The following databases were searched in September 2021: MEDLINE (Ovid), Embase (Ovid), Cochrane CENTRAL, Science Citation Index Expanded (Web of Science), Global Index Medicus, ClinicalTrials.gov and WHO's International Clinical Trials Registry Platform.

A supplemental search was performed in February 2022 for three medicines which are currently used in the UK which were not included in the original search: riboflavin, magnesium & CoQ-10. An additional, pragmatic search was also conducted to identify recent systematic reviews of migraine preventive drugs. The reference lists of the outputs of this search, those of the National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN) and American Headache Society guidelines were checked for relevant literature. Authors of key studies were contacted and forward and backward citation tracking was conducted on all included papers.

We reran all searches in November 2022 and in June 2023 to identify any new publications. Full details of all searches are provided in online supplemental appendix 1. We used EndNote V.X20[16] to manage references including the removal of duplicates.

Eligibility and study selection

We only included randomised controlled trials (RCTs) with more than 100 participants per arm and defined AEs and SAEs according to the standard definitions in table 1. Our focus was on adult participants aged 18 years or older with chronic or episodic migraine. We considered pharmacological medications available in the UK or expected to become available, and compared them with placebo, usual care or other preventative drugs. We excluded traditional Chinese medicines, non-UK herbal remedies, non-pharmacological interventions, dose–response trials and drugs not recommended by NICE or SIGN. We did not include data on discontinuation or withdrawal from trials.

Table 1 : Definitions of key terms

Adverse events (AEs)	An AE that is not a SAE, meaning that it does not result in death, is not life-threatening, does not require inpatient hospitalisation or extend a current hospital stay, does not result in an ongoing or significant incapacity or interfere substantially with normal life functions, and does not cause a congenital anomaly or birth defect; it also does not put the participant in danger and does not require medical or surgical intervention to prevent one of the results listed above.[17]
Serious adverse events (SAEs)	An adverse event that results in death, is life-threatening, requires inpatient hospitalisation or extends a current hospital stay, results in an ongoing or significant incapacity or interferes substantially with normal life functions, or causes a congenital anomaly or birth defect. Medical events that do not result in death, are not life-threatening, or do not require hospitalisation may be considered SAEs if they put the participant in danger or require medical or surgical intervention to prevent one of the results listed above.[17]

Our outcomes of interest were AEs, treatment-related AEs (TAEs), SAEs and treatment-related SAEs (TSAEs).

Two reviewers (AB and SN) assessed title and abstract screening first, and then abstract and full text screening were conducted by a combination of four reviewers (MU, SN, AA and ND). Discrepancies were resolved through discussion by a third reviewer (CD or MM).

Data extraction and synthesis

Data from included studies were extracted by one reviewer (SN) using a predetermined data extraction form in Microsoft Excel and checked for accuracy and completeness by a second reviewer (SK). Information collected included study characteristics, participant demographics, treatment details and adverse event definitions as well as data on adverse events, TAEs, serious adverse events and TSAEs.

We applied the Common Terminology Criteria for Adverse Events (CTCAE) V.5.0[17] to classify the adverse events and serious adverse events and calculated their proportion for each system organ class (SOC) and preventive drug.

Quality assessment

The Cochrane risk-of-bias tool for RCTs[18] was applied to assess the risk of bias by SN. To ensure the accuracy, 20% of studies was checked by SK.

RESULTS

Study selection

Out of 19 111 initial records after removal of duplicates, 18 777 were excluded during title and abstract screening. Three-hundred and thirty-four records were assessed for eligibility and 59 articles reporting data from 33 trials were included after full text assessment (see online supplemental appendix 2 for excluded studies).[19–57] Although many of these linked articles were cited, we only used the main trial paper for the main citation, as the other linked papers only reported some subgroup analyses, were either repetitive or combined the data. The PRISMA flow diagram summarises study selection results (figure 1).

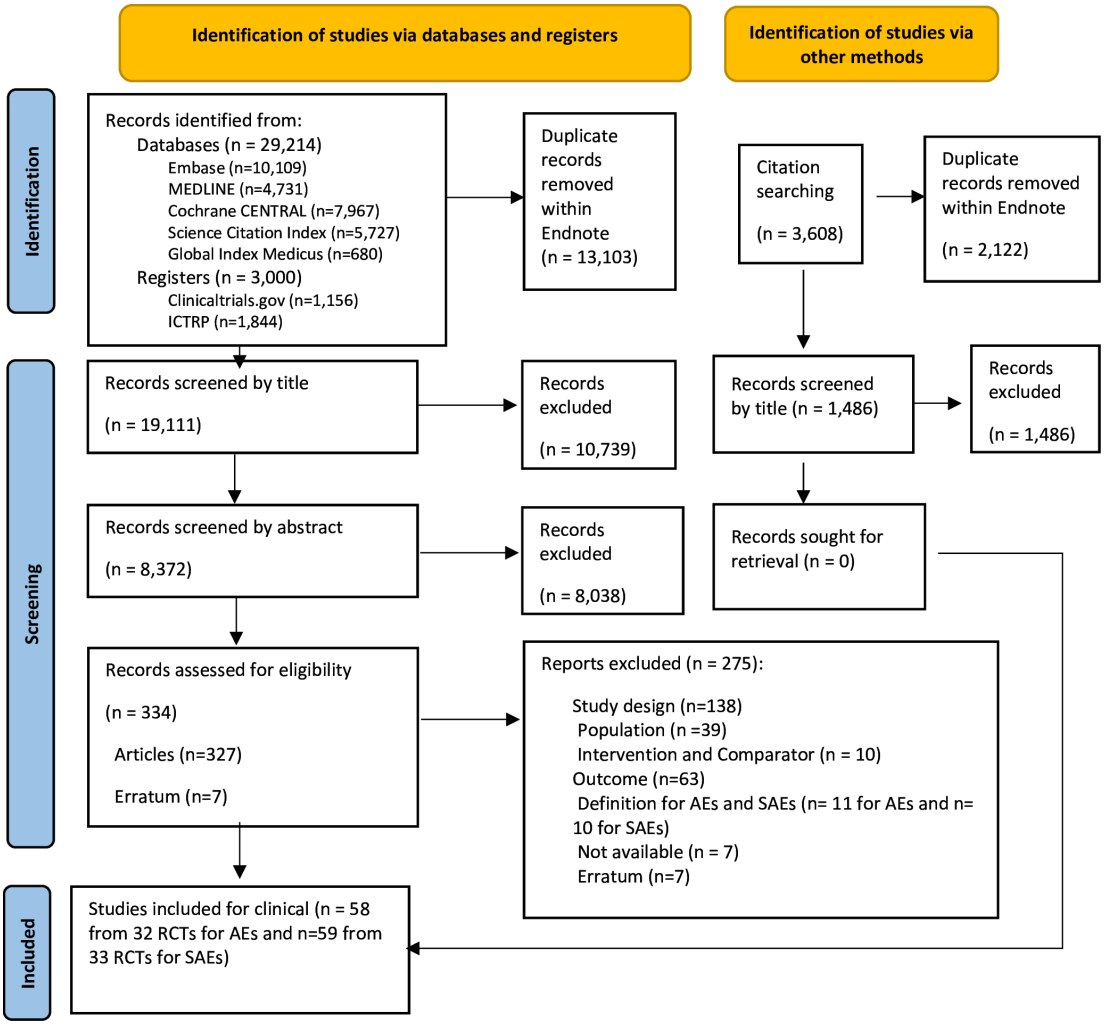


Figure 1 PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs, randomised controlled trials; SAEs, serious adverse events.

Study characteristics

The patients in each of the included studies satisfied the diagnostic criteria of chronic or episodic migraine in accordance with the International Classification of Headache Disorders.[58] Nineteen RCTs included only participants with episodic migraine,[19 21 36–45 47–49 51–53 55] nine RCTs enrolled participants exclusively with chronic migraine,[20 22–26 29–31 35 57] and five RCTs had a mixed population of both chronic or episodic migraine participants.[34 46 50 54 56] All of the RCTs were conducted across multiple centres. The number of participants randomised across the 33 trials evaluating the safety of pharmacological treatment ranged from 217[39] to 1379[25] with a total of 22 615 participants. The mean age of trial participants ranged from 36[30] to 46[34] years; and the percentage of female participants ranged from 74%[53] to 91%.[54]

Most of the trials utilised double-blinded designs except two trials that were classed as open-label.[35 55] Treatment duration varied across the trials; one trial had a 4-week treatment duration,[52] while 19 trials reported 12 weeks.[20–22 29–31 34 36 37 39 40 42 47–51 53 57] Additionally, one trial had a treatment duration of 22 weeks,[41] 11 trials reported a 24-week treatment duration,[21 25 26 35 38 43–46 54 56] and for one trial the treatment duration was 52 weeks.[55]

The included studies evaluated 20 different dosing regimens of nine drugs, including calcitonin gene-related peptide (CGRP) monoclonal antibodies (MAbs) (eptinezumab 100 mg and 300 mg, erenumab 70 mg and 140 mg, fremanezumab 225 mg and 675 mg and galcanezumab 120 mg, 150 mg and 240 mg), onabotulinumtoxin A (BTA) 7U, 25U, 50U, 155U and 195U, topiramate 100 mg, atogepant 10 mg, 30 mg and 60 mg, amitriptyline 25 mg to 100 mg and rimegepant 75 mg. Further details of included characteristics of these studies are presented in online supplemental table 1 and online supplemental appendix 3.

Adverse events

Thirty-two studies reported adverse events for 20 different dosing regimens of nine drugs with 21 780 participants.[19–57] The most reported adverse events belonged to Amitriptyline 25 mg to 100 mg and galcanezumab 150 mg with 89%[39 41] and 72.0%,[39] respectively. The lowest number of any adverse events are for erenumab 140 mg (33%).[31 43 46–48] Online supplemental table 2 summarises the pooled adverse events as reported in the 32 trials; we have highlighted in bold for each SOC the medication, which contributed to the largest percentage of AEs. For example, for gastrointestinal disorders, amitriptyline (25 mg to 100 mg) had the highest percentage of adverse events (59%); and for nervous system disorders, topiramate 100 mg was attributed with the highest percentage of AEs at 60%. Table 2 presents the most common adverse events for each medication. For example, participants in the amitriptyline (25 mg to 100 mg) group experienced dry mouth (36%), and participants in the topiramate 100 mg group suffered from paraesthesia (36%). Further details of adverse events for each individual study categorised according to SOC are presented in online supplemental appendix 4, online supplemental tables 2–17.

Serious adverse events

Serious adverse events were reported in 33 trials, evaluating 20 different dosing regimens of nine drugs with data from 22 615 participants.[19–57] One trial did not report the number of people with SAEs, but the results indicated no treatment-related SAEs.[49] Thus, SAEs from 32 trials with 21 643 participants were combined, and online supplemental table 3 shows the percentage of attributed SAEs for each SOC. In online supplemental table 3, we have highlighted in bold for each SOC the medication, which contributed to the largest percentage of SAEs. For example, for infections and infestations, topiramate 100 mg had the highest percentage of serious adverse events (1.13%); and for neoplasm-benign malignant and unspecified, BTA was attributed with the highest percentage of SAEs at 1.21%. Further information on the incidence of SAEs for each dosing regimen is found in online supplemental appendix 5, online supplemental tables 19 to 40.

Risk of bias assessment

Figure 2 and online supplemental table 1 provide a summary of the risk of bias results. In terms of overall risk of bias, two trials were rated as being at high risk of bias,[35 55] 16 trials at medium risk of bias[22 29 30 38 39 41 44–47 49–51 53 54 57] and 15 trials at low risk of bias.[19–21 25 26 31 34 36 37 40 42 43 48 52 56] Overall, there were no major concerns that the studies were not applicable to the research question for this review.

DISCUSSION

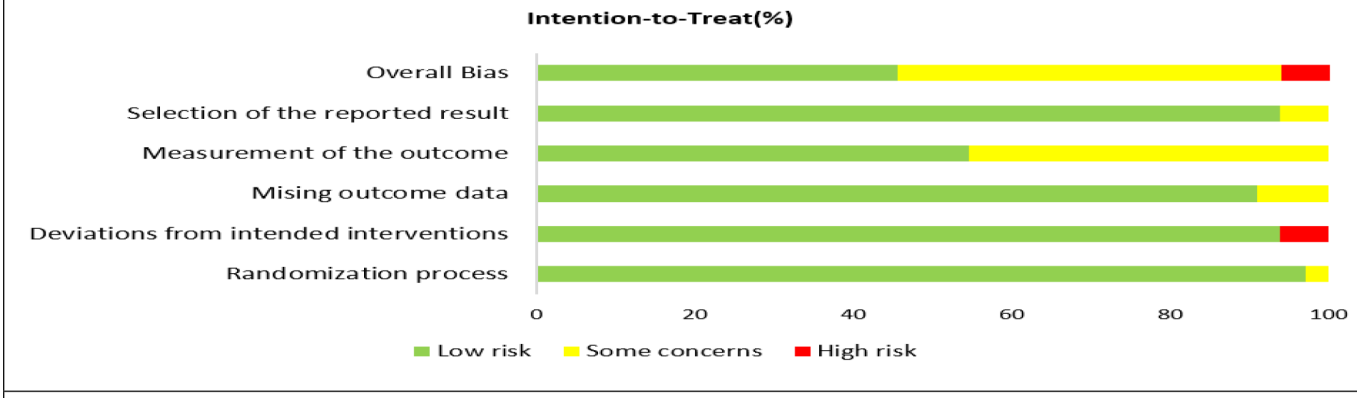
Overview and key findings

We systematically reviewed and narratively synthesised the incidence of adverse and serious adverse events from 33 clinical trials involving 22 615 participants with chronic or episodic migraine.[19–57] Our findings suggest that all the pharmacological interventions reviewed were well tolerated, although the incidence of adverse events varied among the drugs. For instance, amitriptyline and topiramate had a higher incidence of adverse events in nervous system disorders, while rimegepant did not cause such disorders in any of the trials. Topiramate was associated with a higher incidence of psychiatric disorders. All drugs caused some infections and infestations, with erenumab and eptinezumab having the highest rates and BTA having the lowest rates. BTA had a higher incidence of musculoskeletal and connective tissue disorders compared with other medications. Amitriptyline and topiramate were associated with more gastrointestinal disorders in participants, while fremanezumab and Galcanezumab were linked to more general disorders and administration site conditions than other drugs.

Table 2 Most common adverse events for each medication (%)

Medications	Doses	Participants (N)	Most common adverse events (%)
Amitriptyline[41]	25 mg to 100 mg	169	Dry mouth (36), somnolence (18), dizziness (11), dyspepsia and constipation (8) and nausea (7).
Atogepant[36 55]	10 mg	221	Constipation (8), nausea (5) and upper respiratory tract infection (4).
	30 mg	228	Constipation (7), upper respiratory tract infection (6) and nausea (4).
	60 mg	774	Nasopharyngitis (4), influenza, upper respiratory tract infection and urinary tract infection (3) and constipation (2).
BTA[25 35]	155 U	907	Neck pain (6), muscular weakness, cognitive disorder (4) and migraine, headache and dizziness (2).
Eptinezumab[26 30 38 52 54]	100 mg	1238	Nasopharyngitis and upper respiratory tract infection (4) and dizziness, nausea, fatigue (2).
Eptinezumab[26 30 38 54]	300 mg	989	Nasopharyngitis (7), upper respiratory tract infection (6) and nausea (3)
Erenumab[37]	21 mg	105	Nasopharyngitis (5), influenza (4), headache (3) and upper respiratory tract infection (2).
Erenumab[37]	7 mg	108	Nasopharyngitis (9), migraine (4) and upper respiratory tract infection and influenza (2).
Erenumab[31 37 40 43 48 56 57]	70 mg	1637	Nasopharyngitis (6), upper respiratory tract infection and constipation (4) and injection site pain (2).
Erenumab[31 43 46–48]	140 mg	1238	Constipation (6), nasopharyngitis and fatigue (4), upper respiratory tract infection (2).
Fremanezumab[19 20 22 34 42]	Monthly	1263	Injection site induration (18), injection site pain (17), injection site erythema (15), injection site reaction (7), nasopharyngitis (6).
	Quarterly	1251	Injection site pain (20), injection site erythema and injection site induration (14), nasopharyngitis (8), injection site reaction (7).
Galcanezumab[21 29 44 45 50 53]	120 mg	1313	Injection site pain (8), nasopharyngitis (6), injection site erythema (4), injection site reaction and injection site pruritus (3).
Galcanezumab[21 29 44 45]	240 mg	844	Injection site pain (11), injection site erythema (7), injection site reaction and injection site pruritus (5), nasopharyngitis (4).
Galcanezumab (LY2951742)[39]	150 mg	107	Injection site pain and upper respiratory tract infection (17), back pain (7), abdominal pain and arthralgia (6), injection site erythema, dizziness, rash, and hypertension (5).
Rimegepant[51]	75 mg	370	Nasopharyngitis (4), nausea (3), upper respiratory tract infection and urinary tract infection (2).
Topiramate[35 41 46]	100 mg	707	Paraesthesia (36), difficulty with concentration, dizziness and fatigue (12), nausea (9), hypoesthesia and dry mouth (5), depression, somnolence and vertigo (3)

BTA, Onabotulinumtoxin A.



A Summary of risk of bias assessment

Study ID	D1	D2	D3	D4	D5	Overall
Sakai, 2021	+	+	+	+	+	+
Silberstein, 2017	+	+	!	+	+	!
Dodick, 2010	+	+	+	+	+	+
Lipton, 2020	+	+	+	+	+	+
Detke, 2018	+	+	!	+	+	!
Dodick, 2019	+	+	+	!	+	!
Tepper, 2017	+	+	+	+	+	+
Ferrari, 2019	+	+	+	+	+	+
Rothrock, 2019	!	-	+	!	+	-
Ailani, 2021	+	+	+	+	+	+
Sun, 2016	+	+	+	+	+	+
Ashina, 2020	+	+	!	+	+	!
Dodick, 2014	+	+	+	!	+	!
Dodick, 2018	+	+	+	+	+	+
Dodick, 2009	+	+	+	!	!	!
Dodick, 2018	+	+	+	+	+	+
Goadsby, 2017	+	+	+	+	+	+
Sakai, 2021	+	+	+	+	+	+
Stauffer, 2018	+	+	+	!	+	!
Skljarevski, 2018	+	+	+	!	+	!
Reuter, 2018	+	+	+	!	+	!
Reuter, 2022	+	+	+	!	+	!
Wang, 2021	+	+	+	+	+	+
Mulleners, 2020	+	+	+	!	+	!
Elkind, 2006	+	+	+	!	!	!
Croop, 2021	+	+	+	!	+	!
Winner, 2021	+	+	+	+	+	+
Bo Hu, 2022	+	+	+	!	+	!
Ashina, 2022	+	+	+	!	+	!
Sakai, 2020	+	+	+	+	+	+
Takeshima, 2021	+	+	+	+	+	+
Yu, 2022	+	+	+	!	+	!
Ashina, 2023	+	-	+	!	+	-

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

B Traffic lights for the risk of bias for each included study

Figure 2 Risk of bias assessment result.

It should be noted that the number of included trials for each drug are different. Safety profiles for erenumab, topiramate and galcanezumab were investigated more extensively than other medications. Additionally, almost half of the included trials were potentially biased (medium or high risk), which should be taken into consideration when interpreting the results. Many of these trials raised concerns due to their outcome assessors being aware of the interventions received by study participants. It remained unclear whether the assessment of outcomes had been influenced by knowledge of whether interventions were received or not.

RCTs are not typically powered to show adverse events. Even in this systematic review, there is likely to be insufficient statistical power to identify differences in the incidence of uncommon adverse events. These are best identified in observational studies.

Our review found that placebo-related adverse events were more frequent than those observed in patients who were receiving various doses of erenumab, rimegepant, topiramate and eptinezumab. Reported AE percentages for placebo were similar to those for atogepant, while they were lower for the other medications.

Generalisibilty and other studies

Some trials have exclusively investigated the safety profiles of certain medications in patients with either episodic or chronic migraine, while others have included a mix of both. Despite these differences, the incidence of AEs and SAEs appears to be generally consistent across all types of migraine, suggesting that the type of migraine is not a critical determinant of the safety profiles of these medications.

In our comparisons with other studies, we have identified some evidence that support our findings, while others do not align with the conclusions we have drawn about the adverse events and standard adverse events in this review. We have compared our findings with the other studies for each drug separately:

- Topiramate: overall, three trials[35 41 46] reported that topiramate was poorly tolerated, with the most common AEs related to the nervous system and gastrointestinal disorders. The results of a meta-analysis showed that the safety profile favoured the CGRP MAbs, with a higher likelihood of benefit compared with harm when compared with topiramate.[59]
- BTA: the results of three trials[25 35] indicated that BTA is well tolerated with the most common adverse events limited to musculoskeletal and connective tissue disorders. Furthermore, a pairwise meta-analysis revealed that the total AEs for BTA were higher than placebo, with a relative risk ratio of 1.22 (95% CI 1.07 to 1.14).[7] This is consistent with our findings.
- Eptinezumab: all doses of eptinezumab were generally well tolerated and acceptable in the three trials[38 52 54] it was reported. Eptinezumab at 100 mg dose exhibited a smaller proportion of AEs, which may be attributed to the short treatment duration of 4 weeks in one study.[52] Results of a meta-analysis showed that CGRP MAbs safety profiles were not significantly different from placebo (OR 1.17, 95% CI 0.91 to 1.51).[8] The most common AEs for all doses were related to infections and infestations[8] which is in line with our results.
- Erenumab: two meta-analyses yielded results consistent with our review, indicating no significant differences in the occurrence of AEs and SAEs between the erenumab and placebo.[9 10] According to our findings from nine trials,[31 37 40 43 46–48 56 57] the lowest incidence of AEs occurred in patients taking 140 mg of erenumab. Patients who were prescribed 70 mg of erenumab reported a higher incidence of infection and infestation, which was consistent with another review.[8]
- Fremanezumab: five trials reported the incidence of adverse events, which was reported to be lower in the monthly groups compared with the quarterly groups.[19 20 22 34 42] Statistical analysis of a meta-analysis showed that the fremanezumab group is more likely to suffer from adverse events related to the trial regimen rather than placebo (RR=1.21, 95% CI 1.09 to 1.34, p=0.0005).[60] However, the most common adverse event remained as injection-site reactions, which is in line with our results.[60]
- Galcanezumab: seven trials found that the incidence of adverse events was lower for the 12-week treatment period[29 39 50 53] compared with the 24-week period.[21 44 45] General disorders and administration site conditions, followed by infection and infestations, were the most frequent AEs for all doses. While Hou *et al* presented upper respiratory infections and viral infections (infection and infestations) as the most common AEs,[8] this was not consistent with our finding, perhaps due to the fact they only reported safety data on galcanezumab from one trial.
- Rimegepant: the results for rimegepant 75 mg from one small trial showed similar tolerability to placebo, and there were no unexpected or serious safety issues noted.[51 61] In line with our findings, Gao *et al* demonstrated that rimegepant 75 mg was safe for treating episodic migraine.[11]
- Atogepant: the AEs for all doses from two studies were approximately the same and well tolerable,[36 55] which is supported by results of another systematic review.[12] Infection was more common in all doses.
- Amitriptyline 25 mg to 100 mg: the results of a small trial indicated poor tolerability, with gastrointestinal disorders being the most commonly experienced adverse events, followed by nervous system disorders.[41] We could not find any evidence for the safety profile of Amitriptyline that had been synthesised through systematic review or meta-analysis.

Strengths and limitations

The main strength of our review is the analysis of adequately powered studies of the wide range of medications, as most systematic reviews in the literature focus

on only one or a few drugs. We included the CGRP MAbs namely fremanezumab, eptinezumab, galcanezumab and erenumab, along with BTA, topiramate, amitriptyline, atogepant and rimegepant. This diversity provides a comprehensive overview of medication safety, enabling decision-makers to compare treatments and obtain a more accurate reflection of clinical practice. We used a comprehensive search strategy across a wide range of electronic databases, without imposing any restrictions on date or language.

It is important to mention additional limitations of some included trials in this review. Specifically, atogepant and rimegepant have product licenses but are not yet approved by NICE. However, Scottish Medicine Consortium in 2023 approved atogepant for chronic and episodic migraine and rimegepant for episodic migraine. The BTA trial for episodic migraine patients used non-standard doses, while the standard dose for chronic migraine patients is 155U. Additionally, the 150 mg dose of galcanezumab, which is not commonly used, had a noticeably higher adverse events profile.

Excluding studies with fewer than 100 participants per arm and also excluding studies without reporting AEs and SAEs according to the standard definition have limited our analyses to more recently investigated treatments where the trial methodology is more precise, at the risk that we might exclude pertinent data from smaller, usually older, trials. Because of this, we were unable to identify any eligible studies of adequate quality for other commonly used oral drugs used in the management of migraine, such as candesartan, flunarizine and Propranolol.

Furthermore, the results must be viewed cautiously due to limitations. It is important to note that differences in the definition and measurement of side effects may have influenced reporting. To manage this variability, we opted to include trials adhering to the standard definition AEs and SAEs, enabling categorisation within the SOC. However, we acknowledge that variations in the measurement and reporting of side effects exist among the included trials, and this aspect remains unclear in some original papers. Also, we used CTCAE V.5.0 to classify AEs and SAEs, but some events in the studies were not classified in the CTCAE. To address this, our clinical experts determined the appropriate category for those events, such as categorising panic attacks as a psychiatric disorder (further details in online supplemental table 18 and 41, online supplemental appendix 4 and 5).

Other systematic reviews we compared with ours noted limitations in the RCTs and recommended further head-to-head RCTs to obtain more robust results for AEs. Similarly, we suggest conducting additional head-to-head RCTs to evaluate the safety profile of oral medications, BTA and CGRP MAbs in episodic and/or chronic migraine populations.

While assessing the incidence of AEs and SAEs from these drugs is important and gives important new insights, there is a wider literature related to known adverse effects of these drugs when used in the general population. For example, the SAEs of sodium valproate (teratogenicity and developmental delay) when used in women of childbearing potential are well documented. To a lesser extent, there are similar concerns about teratogenicity and developmental delay, and effects on the efficacy of hormonal contraceptives, in topiramate and so it should be used with caution in women of childbearing age. These effects are unlikely to be captured in RCTs.

CONCLUSION

To the best of our knowledge, our study is the most comprehensive review of the safety profile of preventive medications for adults with chronic or episodic migraine classified by SOC. Only a minimal number of SAEs were observed, with no treatment-related SAEs to the drugs were reported. Minor adverse events were prevalent, and the findings indicated that amitriptyline and topiramate are associated with a higher frequency of adverse events, especially in the context of nervous system disorders and exhibit lower overall tolerance levels. Conversely, emerging treatments such as BTA, CGRP MAbs and the gepants demonstrate a reduced incidence of adverse events and enhanced tolerance. Notably, the observed harm to SOCs differs among these drugs. It should be noted that the trial numbers are poor with amitriptyline, better with Topiramate and good for the others.

Disparities in the occurrence of adverse events were identified among the CGRP MAbs. The majority of fremanezumab users and one out of four galcanezumab users reported problems at the injection site, a concern far less frequently noted among eptinezumab or erenumab users. Nervous system or gastrointestinal side effects such as paraesthesia and dry mouth were commonly experienced by those taking topiramate or amitriptyline. Notably, topiramate showed a higher association with psychiatric disorders, particularly depression, while adverse events linked to BTA were uncommon. We suggest conducting additional head-to-head RCTs to evaluate the safety profile of oral medications, BTA and CGRP MAbs in episodic and/or chronic migraine populations.

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MU. HM and SN wrote the first draft of the manuscript, which all authors revised. All authors reviewed and agreed with the final version. All authors had access to all the data in the study and had final responsibility for the decision to submit for publication. HM is guarantor.

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Competing interests Martin Underwood is chief investigator or co-investigator on multiple previous and current research grants from the UK National Institute for Health Research and is a co-investigator on grants funded by the Australian NHMRC and Norwegian MRC. He was an NIHR Senior Investigator until March 2021. He is a director and shareholder of Clinvivo Ltd which provides electronic data collection for health services research. He is part of an academic partnership with Serco Ltd, funded by the European Social Fund, related to return-to-work initiatives. He receives some salary support from University Hospitals Coventry and Warwickshire. He is a co-investigator on two current and one completed NIHR-funded studies that have, or have had, additional support from Stryker Ltd. Callum Duncan is chair of Scottish Intercollegiate Guideline Network (SIGN) 155 and has provided advice on the use of Botox, CGRP monoclonal antibodies and CGRP antagonists to the Scottish Medicines Consortium and on Eptinezumab to NICE. He was the Secretary for the British Association for the Study of Headache 2015-2022 and is a Board member of Anglo Dutch Migraine Association. Manjit Matharu is the President of the medical advisory board of the CSF Leak Association. He has received consulting fees from AbbVie, TEVA, Lundbeck, Eli Lilly, Salvia, and Pfizer. He has received payment for the development of educational presentations from AbbVie, Pfizer and Eli Lilly and support for attending a meeting from Pfizer. He is on the advisory board for AbbVie, TEVA, Lunbeck, Eli Lilly, Salvia, and Pfizer. He has the following patent issued WO2018051103A1: System and method for diagnosing and treating headaches. He has stock options with Tesla, Adobe, Nvidia, META and Microsoft. He has received grants from Abbott, Medtronic and Ehlers Danlos Society.

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Appendix 1-5

Appendix 1: Literature searches

Overview

Bibliographic databases and clinical trials registers		
Database	**Date searched**	**Number of records**
MEDLINE All (via Ovid)	08/09/21	4,029
Embase (via Ovid)	08/09/21	8,404
Cochrane CENTRAL (via Cochrane Library)	08/09/21	6,754
Science Citation Index (via Web of Science)	08/09/21	4,737
Global Index Medicus (via World Health Organization)	14/09/21	200
Clinicaltrials.gov	15/09/21	338
International Clinical Trials Registry Platform (ICTRP) (World Health Organization)	15/09/21	512
Total number of records retrieved: 24,974 **Duplicates removed (EndNote): 8,368** **Final number for screening: 16,606**		
Bibliographic databases and clinical trials registers; additional search for riboflavin, magnesium and coenzyme Q10		
Source	**Date searched**	**Number of records**
MEDLINE All (via Ovid)	08/02/22	163
Embase (via Ovid)	08/02/22	587
Cochrane CENTRAL (via Cochrane Library)	08/02/22	331
Science Citation Index (via Web of Science)	08/02/22	359
Global Index Medicus (via World Health Organization)	08/02/22	24
Clinicaltrials.gov	08/02/22	15
International Clinical Trials Registry Platform (ICTRP) (World Health Organization)	08/02/22	38
Total number of records retrieved: 1,517 **Duplicates removed within this set (EndNote): 481** **Duplicates removed against original search (EndNote): 448** **Final number for screening: 588**		
Pragmatic search for recent systematic reviews, to check reference lists/included studies		
Database	**Date searched**	**Number of records**
MEDLINE All (via Ovid)	14/02/22	114
Embase (via Ovid)	14/02/22	164
Cochrane Database of Systematic Reviews (via Cochrane Library)	14/02/22	4
Total number of records retrieved: 282 **Duplicates removed within this set (EndNote): 103** **Final number for screening: 179**		
Bibliographic databases and clinical trials registers; search update November 2022 (including all relevant drug terms)		
Database	**Date searched**	**Number of records**
MEDLINE All (via Ovid)	07/11/22	390
Embase (via Ovid)	07/11/22	710
Cochrane CENTRAL (via Cochrane Library)	07/11/22	713
Science Citation Index (via Web of Science)	07/11/22	440
Global Index Medicus (via World Health Organization)	07/11/22	222
Clinicaltrials.gov	08/11/22	390
International Clinical Trials Registry Platform (ICTRP) (World Health Organization)	08/11/22	631
Total number of records retrieved: 3,496 **Duplicates removed within this set (EndNote): 1,096**		

Duplicates removed against previous searches (EndNote): 1,066 **Final number for screening: 1,334**		
Other sources; citation tracking		
Source	**Date searched**	**Number of records**
Reference lists – included studies (Web of Science)	23/11/22	875
Forwards citation tracking: Science Citation Index (Web of Science)	22-23/11/22	2,710
Forwards citation tracking: Google Scholar (for studies not found in Web of Science only)	23/11/22	23
Total number of records retrieved: 3,608 **Duplicates removed (both within this set and against previous searches) (Endnote): 2,122** **Final number for screening: 1,486**		
Checking for retraction notices, errata and comments relating to included studies		
Source	**Date searched**	**Number of records**
MEDLINE All (via Ovid)	22/11/22	23
Embase (via Ovid)	22/11/22	0
Retraction Watch website	22/11/22	0
Total number of records retrieved: 23		
Bibliographic databases and clinical trials registers; search update June 2023 (including all relevant drug terms)		
Database	**Date searched**	**Number of records**
MEDLINE All (via Ovid)	15/06/23	149
Embase (via Ovid)	15/06/23	408
Cochrane CENTRAL (via Cochrane Library)	15/06/23	169
Science Citation Index (via Web of Science)	15/06/23	191
Global Index Medicus (via World Health Organization)	15/06/23	234
Clinicaltrials.gov	15/06/23	413
International Clinical Trials Registry Platform (ICTRP) (World Health Organization)	15/06/23	663
Total number of records retrieved: 2,227 **Duplicates removed (both within this set and against previous searches) (EndNote): 1,644** **Final number for screening: 583**		

MEDLINE search strategy: original searches, September 2021

Date searched: 08/09/21

Database: Ovid MEDLINE(R) ALL <1946 to September 07, 2021>

Search Strategy:

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1 (headache* or head ache* or migrain* or cephalgi* or cephalalgi* or hemicrani*).ab,kf,ti. (112921)
2 Headache/ or exp Headache Disorders/ (61239)
3 1 or 2 [population: migraine/headache] (124144)
4 (((calcitonin gene-related peptide or CGRP) adj5 (antibod* or antagon* or inhibit* or block*)) or anti-CGRP or anti-calcitonin gene-related peptide or monoclonal antibod* or mAb or mAbs or moAb or moAbs).ab,kf,ti. (216437)
5 Calcitonin Gene-Related Peptide/ai (436)
6 Antibodies, Monoclonal/ or Antibodies, Monoclonal, Humanized/ (217039)
7 Calcitonin Gene-Related Peptide Receptor Antagonists/ (701)
8 (erenumab or galcanezumab or fremanezumab or eptinezumab).ab,kf,ti,nm. (507)
9 (rimegepant or ubrogepant or atogepant or gepant?).ab,kf,ti,nm. (214)
10 exp Botulinum Toxins/ (17105)
11 (botulin* adj toxin*).ab,kf,ti,nm. (21943)
12 (botulinum* or botox* or onabotulinum*).ab,kf,ti,nm. (25159)
13 (antidepress* or anti depress*).ab,kf,ti. (73890)
14 exp Antidepressive Agents/ (153122)
15 (amitriptyline or venlafaxine or mirtazapine or duloxetine).ab,kf,ti,nm. (17955)
16 exp "Serotonin and Noradrenaline Reuptake Inhibitors"/ (5005)
17 (SNRI or SNRIs or (serotonin adj2 (noradrenaline or norepinephrine) adj reuptake inhib*)).ab,kf,ti. (2908)
18 exp Angiotensin-Converting Enzyme Inhibitors/ (45324)
19 (Angiotensin Converting Enzyme Inhibit* or ACE inhibit*).ab,kf,ti. (37937)
20 acei.ab,kf,ti. (4344)
21 lisinopril.ab,kf,ti,nm. (3086)
22 ((angiotensin receptor or angiotensin II receptor) adj (block* or antagon*)).ab,kf,ti. (14474)
23 (ARB or ARBs).ab,kf,ti. (7873)
24 exp Angiotensin Receptor Antagonists/ (25403)
25 candesartan.ab,kf,ti,nm. (3374)
26 ((beta adj3 block*) or betablock*).ab,kf,ti. (55697)
27 ((adrenergic or adrenoreceptor* or adrenoceptor*) adj3 (antagon* or block*)).ab,kf,ti. (34997)
28 exp Adrenergic beta-Antagonists/ (85444)
29 (propranolol or metoprolol or timolol or atenolol or nadolol or nebivolol or pindolol).ab,kf,ti,nm. (67114)
30 (calcium adj2 (block* or antagon* or inhibit*)).ab,kf,ti. (41676)
31 (CCB or CCBs).ab,kf,ti. (2619)
32 exp Calcium Channel Blockers/ (88532)
33 (flunarizine or verapamil).ab,kf,ti,nm. (27700)
34 (anticonvuls* or antiepilep* or anti convuls* or anti epilep*).ab,kf,ti. (53599)
35 exp Anticonvulsants/ (147158)
36 (topiramate or valproate or divalproex or valproic acid or gabapentin).ab,kf,ti,nm. (31200)
37 Pizotyline/ (250)
38 (pizotifen or pizotyline).ab,kf,ti,nm. (418)
39 (alpha adj4 agonist*).ab,kf,ti. (15369)
40 exp Adrenergic alpha-Agonists/ (164069)
41 (clonidine or guanfacine).ab,kf,ti,nm. (19180)
42 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 [Interventions: named drugs/drug classes or types] (1098623)
43 randomized controlled trial.pt. (542809)
44 controlled clinical trial.pt. (94373)
45 randomized.ab. (533045)
46 placebo.ab. (221237)

47 clinical trials as topic.sh. (197235)
48 randomly.ab. (365421)
49 trial.ti. (247114)
50 43 or 44 or 45 or 46 or 47 or 48 or 49 (1392358)
51 exp animals/ not humans.sh. (4882975)
52 50 not 51 [RCTs filter] (1281368)
53 3 and 42 and 52 [population and interventions and RCTs filter] (3949)
54 ("in data review" or in process or publisher or "pubmed not medline").st. (4677722)
55 (random* or controlled trial* or clinical trial* or rct).ab,kf,ti. (1547833)
56 54 and 55 [pragmatic filter to pick up RCTs that have not been fully indexed for MEDLINE yet] (236445)
57 3 and 42 and 56 [population and interventions and non-MEDLINE RCT filter] (365)
58 53 or 57 (4029)

The migraine/headache search terms (lines 1-3) and botox search terms (lines 10-12) are based on those used in:
Herd CP, Tomlinson CL, Rick C, Scotton WJ, Edwards J, Ives N, Clarke CE, Sinclair A. Botulinum toxins for the prevention of migraine in adults. Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD011616. DOI: 10.1002/14651858.CD011616.pub2.

The search filter for RCTs (lines 43-52) is the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format: Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from: www.training.cochrane.org/handbook.

MEDLINE search strategy: additional searches for riboflavin, magnesium and coenzyme Q10, February 2022

Date searched: 08/02/22
Ovid MEDLINE(R) ALL <1946 to February 07, 2022>

1 (headache* or head ache* or migrain* or cephalgi* or cephalalgi* or hemicrani*).ab,kf,ti. 115846
2 Headache/ or exp Headache Disorders/ 62888
3 1 or 2 [population: migraine/headache] 127140
4 Riboflavin/ 9019
5 (riboflavin or vitamin b2 or vitamin b 2).ab,kf,ti,nm. 14667
6 Ubiquinone/ 9986
7 (coenzyme q* or co enzyme q* or ubidecarenone or ubiquino* or coq10 or co q10).ab,kf,ti,nm. 17133
8 Magnesium/ or exp Magnesium Compounds/ 83822
9 magnesium.ab,kf,ti,nm. 113129
10 4 or 5 or 6 or 7 or 8 or 9 [interventions: 3 drugs added February 2022] 147736
11 randomized controlled trial.pt. 558117
12 controlled clinical trial.pt. 94685
13 randomized.ab. 550007
14 placebo.ab. 225467
15 clinical trials as topic.sh. 199113
16 randomly.ab. 375668
17 trial.ti. 256318
18 11 or 12 or 13 or 14 or 15 or 16 or 17 1425517
19 exp animals/ not humans.sh. 4955382
20 18 not 19 [Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)] 1311348
21 3 and 10 and 20 [population + interventions + RCT filter] 161
22 ("in data review" or in process or publisher or "pubmed not medline").st. 4673502
23 (random* or controlled trial* or clinical trial* or rct).ab,kf,ti. 1597122

24 22 and 23 [filter to pick up RCTs that have not been fully indexed for MEDLINE yet] 231267
25 3 and 10 and 24 [population + interventions + RCT filter for non indexed studies] 18
26 21 or 25 163

MEDLINE search strategy: pragmatic search for recent systematic reviews, to check reference lists/included studies, February 2022

Date searched: 14/02/22
Ovid MEDLINE(R) ALL <1946 to February 11, 2022>
1 exp Migraine Disorders/pc 2569
2 "migrain*".ab,hw,kf,ti. 43508
3 ((prevent* or prophyla*) adj2 (treatment? or therap* or medication? or drug?)).ab,hw,kf,ti. 179039
4 2 and 3 3218
5 (migrain* adj4 (prevent* or prophyla*)).ab,hw,kf,ti. 3883
6 1 or 4 or 5 5846
7 (metaanalys* or "meta analys*").tw. 222321
8 (systematic* adj3 review*).mp. 276043
9 meta analysis.pt. 152804
10 7 or 8 or 9 [pragmatic systematic review filter] 392108
11 (((calcitonin gene-related peptide or CGRP) adj5 (antibod* or antagon* or inhibit* or block*)) or anti-CGRP or anti-calcitonin gene-related peptide or monoclonal antibod* or mAb or mAbs or moAb or moAbs).ab,kf,ti. 219332
12 Calcitonin Gene-Related Peptide/ai 452
13 Antibodies, Monoclonal/ or Antibodies, Monoclonal, Humanized/ 221635
14 Calcitonin Gene-Related Peptide Receptor Antagonists/ 781
15 (erenumab or galcanezumab or fremanezumab or eptinezumab).ab,kf,ti,nm. 588
16 (rimegepant or ubrogepant or atogepant or gepant?).ab,kf,ti,nm. 247
17 exp Botulinum Toxins/ 17563
18 (botulin* adj toxin*).ab,kf,ti,nm. 22444
19 (botulinum* or botox* or onabotulinum*).ab,kf,ti,nm. 25677
20 (antidepress* or anti depress*).ab,kf,ti. 75518
21 exp Antidepressive Agents/ 155320
22 (amitriptyline or venlafaxine or mirtazapine or duloxetine).ab,kf,ti,nm. 18204
23 exp "Serotonin and Noradrenaline Reuptake Inhibitors"/ 5141
24 (SNRI or SNRIs or (serotonin adj2 (noradrenaline or norepinephrine) adj reuptake inhib*)).ab,kf,ti. 2996
25 exp Angiotensin-Converting Enzyme Inhibitors/ 45974
26 (Angiotensin Converting Enzyme Inhibit* or ACE inhibit*).ab,kf,ti. 38458
27 acei.ab,kf,ti. 4519
28 lisinopril.ab,kf,ti,nm. 3114
29 ((angiotensin receptor or angiotensin II receptor) adj (block* or antagon*)).ab,kf,ti. 14830
30 (ARB or ARBs).ab,kf,ti. 8220
31 exp Angiotensin Receptor Antagonists/ 26157
32 candesartan.ab,kf,ti,nm. 3407
33 ((beta adj3 block*) or betablock*).ab,kf,ti. 56350
34 ((adrenergic or adrenoreceptor* or adrenoceptor*) adj3 (antagon* or block*)).ab,kf,ti. 35141
35 exp Adrenergic beta-Antagonists/ 85957
36 (propranolol or metoprolol or timolol or atenolol or nadolol or nebivolol or pindolol).ab,kf,ti,nm. 67483
37 (calcium adj2 (block* or antagon* or inhibit*)).ab,kf,ti. 41979
38 (CCB or CCBs).ab,kf,ti. 2692
39 exp Calcium Channel Blockers/ 89276
40 (flunarizine or verapamil).ab,kf,ti,nm. 27822
41 (anticonvuls* or antiepilep* or anti convuls* or anti epilep*).ab,kf,ti. 54399
42 exp Anticonvulsants/ 149062

43 (topiramate or valproate or divalproex or valproic acid or gabapentin).ab,kf,ti,nm. 31789
44 Pizotyline/ 250
45 (pizotifen or pizotyline).ab,kf,ti,nm. 420
46 (alpha adj4 agonist*).ab,kf,ti. 15482
47 exp Adrenergic alpha-Agonists/ 165206
48 (clonidine or guanfacine).ab,kf,ti,nm. 19260
49 Riboflavin/ 9020
50 (riboflavin or vitamin b2 or vitamin b 2).ab,kf,ti,nm. 14670
51 Ubiquinone/ 9995
52 (coenzyme q* or co enzyme q* or ubidecarenone or ubiquino* or coq10 or co q10).ab,kf,ti,nm. 17147
53 Magnesium/ or exp Magnesium Compounds/ 83845
54 magnesium.ab,kf,ti,nm. 113174
55 or/11-54 1249348
56 6 and 10 and 55 182
57 limit 56 to yr="2017 - 2022" 114

MEDLINE search strategy: update searches, November 2022 & June 2023

Date searched: 07/11/22

Ovid MEDLINE(R) ALL <1946 to November 04, 2022>

1 (headache* or head ache* or migrain* or cephalgi* or cephalalgi* or hemicrani*).ab,kf,ti. 121076
2 Headache/ or exp Headache Disorders/ 64821
3 1 or 2 [population: migraine/headache, based on Cochrane botox review] 132425
4 (((calcitonin gene-related peptide or CGRP) adj5 (antibod* or antagon* or inhibit* or block*)) or anti-CGRP or anti-calcitonin gene-related peptide or monoclonal antibod* or mAb or mAbs or moAb or moAbs).ab,kf,ti. 224346
5 Calcitonin Gene-Related Peptide/ai 463
6 Antibodies, Monoclonal/ or Antibodies, Monoclonal, Humanized/ 227720
7 Calcitonin Gene-Related Peptide Receptor Antagonists/ 887
8 (erenumab or galcanezumab or fremanezumab or eptinezumab).ab,kf,ti,nm. 730
9 (rimegepant or ubrogepant or atogepant or gepant?).ab,kf,ti,nm. 300
10 exp Botulinum Toxins/ 18153
11 (botulin* adj toxin*).ab,kf,ti,nm. 23232
12 (botulinum* or botox* or onabotulinum*).ab,kf,ti,nm. 26565
13 (antidepress* or anti depress*).ab,kf,ti. 78168
14 exp Antidepressive Agents/ 158352
15 (amitriptyline or venlafaxine or mirtazapine or duloxetine).ab,kf,ti,nm. 18641
16 exp "Serotonin and Noradrenaline Reuptake Inhibitors"/ 5336
17 (SNRI or SNRIs or (serotonin adj2 (noradrenaline or norepinephrine) adj reuptake inhib*)).ab,kf,ti. 3138
18 exp Angiotensin-Converting Enzyme Inhibitors/ 46764
19 (Angiotensin Converting Enzyme Inhibit* or ACE inhibit*).ab,kf,ti. 39244
20 acei.ab,kf,ti. 4749
21 lisinopril.ab,kf,ti,nm. 3155
22 ((angiotensin receptor or angiotensin II receptor) adj (block* or antagon*)).ab,kf,ti. 15370
23 (ARB or ARBs).ab,kf,ti. 8687
24 exp Angiotensin Receptor Antagonists/ 27181
25 candesartan.ab,kf,ti,nm. 3449
26 ((beta adj3 block*) or betablock*).ab,kf,ti. 57470
27 ((adrenergic or adrenoreceptor* or adrenoceptor*) adj3 (antagon* or block*)).ab,kf,ti. 35378
28 exp Adrenergic beta-Antagonists/ 86663
29 (propranolol or metoprolol or timolol or atenolol or nadolol or nebivolol or pindolol).ab,kf,ti,nm. 68123
30 (calcium adj2 (block* or antagon* or inhibit*)).ab,kf,ti. 42541
31 (CCB or CCBs).ab,kf,ti. 2828

32 exp Calcium Channel Blockers/ 90326
33 (flunarizine or verapamil).ab,kf,ti,nm. 28045
34 (anticonvuls* or antiepilep* or anti convuls* or anti epilep*).ab,kf,ti. 55690
35 exp Anticonvulsants/ 152010
36 (topiramate or valproate or divalproex or valproic acid or gabapentin).ab,kf,ti,nm. 32842
37 Pizotyline/ 252
38 (pizotifen or pizotyline).ab,kf,ti,nm. 425
39 (alpha adj4 agonist*).ab,kf,ti. 15644
40 exp Adrenergic alpha-Agonists/ 166795
41 (clonidine or guanfacine).ab,kf,ti,nm. 19418
42 Riboflavin/ 9260
43 (riboflavin or vitamin b2 or vitamin b 2).ab,kf,ti,nm. 15160
44 Ubiquinone/ 10256
45 (coenzyme q* or co enzyme q* or ubidecarenone or ubiquino* or coq10 or co q10).ab,kf,ti,nm. 17694
46 Magnesium/ or exp Magnesium Compounds/ 85028
47 magnesium.ab,kf,ti,nm. 115926
48 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 [Interventions: named drugs/drug classes or types] 1275840
49 randomized controlled trial.pt. 579949
50 controlled clinical trial.pt. 95083
51 randomized.ab. 580977
52 placebo.ab. 232922
53 clinical trials as topic.sh. 200534
54 randomly.ab. 394586
55 trial.ti. 273031
56 49 or 50 or 51 or 52 or 53 or 54 or 55 1482588
57 exp animals/ not humans.sh. 5060853
58 56 not 57 [Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)] 1364006
59 3 and 48 and 58 [population and interventions and RCT filter] 4313
60 ("in data review" or in process or publisher or "pubmed not medline").st. 4897386
61 (random* or controlled trial* or clinical trial* or rct).ab,kf,ti. 1688331
62 60 and 61 [filter to pick up RCTs that have not been fully indexed for MEDLINE yet] 242577
63 3 and 48 and 62 [population and interventions and non-MEDLINE RCT filter] 328
64 59 or 63 4390
65 limit 64 to ed=20210908-20221107 303
66 limit 64 to ep=20210908-20221107 211
67 limit 64 to dt=20210908-20221107 259
68 limit 64 to ez=20210908-20221107 259
69 limit 64 to da=20210908-20221107 366
70 65 or 66 or 67 or 68 or 69 390

Date searched: 15/06/23
Ovid MEDLINE(R) ALL <1946 to June 14, 2023>
As above, but lines 64-70 are:
64 59 or 63 4509
65 limit 64 to ed=20221107-20230615 101
66 limit 64 to ep=20221107-20230615 98
67 limit 64 to dt=20221107-20230615 127
68 limit 64 to ez=20221107-20230615 127
69 limit 64 to da=20221107-20230615 147
70 65 or 66 or 67 or 68 or 69 149

Appendix 2: The list of excluded studies

Publications	Reason(s) for exclusion
1.Pradalier A, Rancurel G, Dordain G, Verdure L, Rascol A, Dry J. Acute Migraine Attack Therapy: Comparison of Naproxen Sodium and an Ergotamine Tartrate Compound. Cephalalgia. 1985;5(2):107-113. [1] doi:10.1046/j.1468-2982.1985.0502107.x	Acute Migraine
2.Abbasi V, Atalu A, Seddighnia P. Comparison of Levetiracetam and sodium Valproate in the prevention of migraine: a randomized clinical trial study. International Journal of Basic & Clinical Pharmacology. 2018 Aug;7(8):1460. [2]	Small sample size of episodic migraine
3.Krakowski AJ, Engisch R. A new agent for chemotherapy of migraine headaches: a controlled study. Psychosomatics: Journal of Consultation and Liaison Psychiatry. 1973 Sep. [3]	Small sample size of episodic migraine
4.Adam EI, Gore SM, Price WH. Double blind trial of clonidine in the treatment of migraine in a general practice. The Journal of the Royal College of General Practitioners. 1978 Oct 1;28(195):587-90. [4]	Small sample size of episodic migraine
5.Soares AD, Louçana PM, Nasi EP, Sousa KM, Sá OM, Silva-Néto RP. A double-blind, randomized, and placebo-controlled clinical trial with omega-3 polyunsaturated fatty acids (OPFA ω-3) for the prevention of migraine in chronic migraine patients using amitriptyline. Nutritional neuroscience. 2018 Mar 16;21(3):219-23. [5]	Small sample size of chronic migraine
6.Afshari D, Rafizadeh S, Rezaei M. A comparative study of the effects of low-dose topiramate versus sodium valproate in migraine prophylaxis. International journal of Neuroscience. 2012 Jan 1;122(2):60-8. [6]	Small sample size of episodic migraine
7.Allais G, De Lorenzo C, Quirico PE, Airola G, Tolardo G, Mana O, Benedetto C. Acupuncture in the prophylactic treatment of migraine without aura: a comparison with flunarizine. Headache: The Journal of Head and Face Pain. 2002 Oct;42(9):855-61. [7]	Small sample size of episodic migraine
8. Chabi A, Zhang Y, Jackson S, Cady R, Lines C, Herring WJ, Connor KM, Michelson D. Randomized controlled trial of the orexin receptor antagonist filorexant for migraine prophylaxis. Cephalalgia. 2015 Apr;35(5):379-88. [8]	Not available in the market
9. Andersson PG, Dahl S, Hansen JH, Hansen PE, Hedman C, Nygaard Kristensen T, de Fine Olivarius B. Prophylactic treatment of classical and non-classical migraine with metoprolol—a comparison with placebo. Cephalalgia. 1983 Dec;3(4):207-12. [9]	Small sample size of episodic migraine
10. Camporeale A, Kudrow D, Sides R, Wang S, Van Dycke A, Selzler KJ, Stauffer VL. A phase 3, long-term, open-label safety study of Galcanezumab in patients with migraine. BMC neurology. 2018 Dec;18(1):1-2. [10]	A safety study, different Galcanezumab doses.
11.Ansell E, Fazzone T, Festenstein R, Johnson ES, Thavapalan M, Wilkinson M, Wozniak I. Nimodipine in migraine prophylaxis. Cephalalgia. 1988 Dec;8(4):269-72. [11]	Small sample size of episodic migraine
12.Bostani A, Rajabi A, Moradian N, Razazian N, Rezaei M. The effects of cinnarizine versus sodium valproate in migraine prophylaxis. International Journal of Neuroscience. 2013 Jul 1;123(7):487-93. [12]	Not clear if chronic, small sample size
13.Ashina M, Doležil D, Bonner JH, Zhou L, Klatt J, Picard H, Mikol DD. A phase 2, randomized, double-blind, placebo-controlled trial of AMG 301, a pituitary adenylate cyclase-activating polypeptide PAC1 receptor monoclonal antibody for migraine prevention. Cephalalgia. 2021 Jan;41(1):33-44. [13]	Not available in the market

14.Assarzadegan F, Tabesh H, Hosseini-Zijoud SM, Beale AD, Shoghli A, Yazdi MG, Mansouri B, Hesami O, Moghadam NB, Kasmaei HD. Comparing zonisamide with sodium valproate in the management of migraine headaches: double-blind randomized clinical trial of efficacy and safety. Iranian Red Crescent Medical Journal. 2016 Sep;18(9). [14]	Small sample size of episodic migraine
15. Barrientos N, Chana P. Botulinum toxin type A in prophylactic treatment of migraine headaches: a preliminary study. The Journal of headache and pain. 2003 Dec;4(3):146-51. [15]	Small sample size of episodic migraine
16.Bavrasad R, Nejad SE, Yarahmadi AR, Sajedi SI, Rahim F. Assessment of the middle dose of topiramate in comparison with sodium valproate for migraine prophylaxis: a randomized-double-blind study. International Journal of Pharmacology. 2010 Sep 1;6(5):670-5. [16]	Small sample size of episodic migraine
17.Beran RG, Spira PJ. Levetiracetam in chronic daily headache: A double-blind, randomised placebo-controlled study: (The Australian KEPPRA Headache Trial [AUS-KHT]). Cephalalgia. 2011 Apr;31(5):530-6. [17]	Small sample size of chronic headache day
18. Bigal ME, Dodick DW, Krymchantowski AV, VanderPluym JH, Tepper SJ, Aycardi E, Loupe PS, Ma Y, Goadsby PJ. TEV-48125 for the preventive treatment of chronic migraine: efficacy at early time points. Neurology. 2016 Jul 5;87(1):41-8. [18]	Small sample size of chronic migraine and no outcome of interests
19. Blumenfeld AM, Stevanovic DM, Ortega M, Cohen JM, Seminerio MJ, Yang R, Jiang B, Tepper SJ. No "Wearing-Off Effect" Seen in Quarterly or Monthly Dosing of Fremanezumab: Subanalysis of a Randomized Long-Term Study. Headache: The Journal of Head and Face Pain. 2020 Nov;60(10):2431-43. [19]	Wearing-Off Effect study
20. Blumenfeld AM, Schim JD, Chippendale TJ. Botulinum toxin type A and divalproex sodium for prophylactic treatment of episodic or chronic migraine. Headache: The Journal of Head and Face Pain. 2008 Feb;48(2):210-20. [20]	Small size of mixed population
21. Brandes JL, Saper JR, Diamond M, Couch JR, Lewis DW, Schmitt J, Neto W, Schwabe S, Jacobs D, MIGR-002 Study Group, MIGR-002 Study Group. Topiramate for migraine prevention: a randomized controlled trial. Jama. 2004 Feb 25;291(8):965-73. [21]	The mixed population of adults and adolescence
22. Standnes B. The prophylactic effect of timolol versus propranolol and placebo in common migraine: beta-blockers in migraine. Cephalalgia. 1982 Sep;2(3):165-70. [22]	Small sample size of episodic migraine
23. Broessner G, Reuter U, Bonner JH, Dodick DW, Hallström Y, Picard H, Zhang F, Lenz RA, Klatt J, Mikol DD. The spectrum of response to erenumab in patients with episodic migraine and subgroup analysis of patients achieving≥ 50%,≥ 75%, and 100% response. Headache: The Journal of Head and Face Pain. 2020 Oct;60(9):2026-40. [23]	No report of Adverse Events
24. Bruno MA, Krymchantowski AV. Amitriptyline and intraoral devices for migraine prevention: a randomized comparative trial. Arquivos de Neuro-Psiquiatria. 2018;76:213-8. [24]	Small sample size of episodic migraine
25. R. K. Cady, C. P. Schreiber, J. A. H. Porter, A. M. Blumenfeld, and K. U. Farmer, "A multi-center double-blind pilot comparison of onabotulinumtoxinA and topiramate for the prophylactic treatment of chronic migraine," *Headache: The Journal of Head and Face Pain*, vol. 51, no. 1, pp. 21–32, 2011. [25]	Pilot study, small sample size of chronic migraine
26.Cady RK, Voirin J, Farmer K, Browning R, Beach ME, Tarrasch J. Two center, randomized pilot study of migraine prophylaxis comparing paradigms using pre-emptive frovatriptan or daily topiramate: research and clinical implications. Headache: The Journal of Head and Face Pain. 2012 May;52(5):749-64. [26]	Small sample size of episodic migraine

27.Cao K, Han F, Lin A, Yang W, Zhao J, Zhang H, Ding Y, Xie W, Xu Y, Yu T, Wang X. Zhengtian Capsule versus flunarizine in patients with migraine: a multi-center, double-blind, double-dummy, randomized controlled, non-inferior clinical trial. BMC complementary and alternative medicine. 2016 Dec;16(1):1-0. [27]	Herbal remedy
28. Chankrachang S, Arayawichanont A, Poungvarin N, Nidhinandana S, Boonkongchuen P, Towanabut S, Sithinamsuwan P, Kongsaengdao S. Prophylactic botulinum type A toxin complex (Dysport®) for migraine without aura. Headache: The Journal of Head and Face Pain. 2011 Jan;51(1):52-63. [28]	Small sample size of episodic migraine
29.Charles JA, Jotkowitz S, Byrd LH. Prevention of migraine with olmesartan in patients with hypertension/prehypertension. Headache: The Journal of Head and Face Pain. 2006 Mar;46(3):503-7. [29]	Small sample size of different doses of the same drug, no placebo/control
30. Christensen CE, Younis S, Deen M, Khan S, Ghanizada H, Ashina M. Migraine induction with calcitonin gene-related peptide in patients from erenumab trials. The Journal of Headache and Pain. 2018 Dec;19(1):1-9. [30]	question not relevant, not a trial of migraine prevention
31. Couch JR, Amitriptyline Versus Placebo Study Group. Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. Headache: The Journal of Head and Face Pain. 2011 Jan;51(1):33-51. [31]	Small sample size of episodic and chronic migraine
32. Yang CP, Chang MH, Liu PE, Li TC, Hsieh CL, Hwang KL, Chang HH. Acupuncture versus topiramate in chronic migraine prophylaxis: a randomized clinical trial. Cephalalgia. 2011 Nov;31(15):1510-21. [32]	Small sample size of chronic migraine, and compared with Chinese traditional medicines
33.d'Amato CC, Pizza V, Marmolo T, Giordano E, Alfano V, Nasta A. Fluoxetine for migraine prophylaxis: a double-blind trial. Headache: The Journal of Head and Face Pain. 1999 Nov;39(10):716-9. [33]	Small sample size of migraine
34.Buse DC, Lipton RB, Hallström Y, Reuter U, Tepper SJ, Zhang F, Sapra S, Picard H, Mikol DD, Lenz RA. Migraine-related disability, impact, and health-related quality of life among patients with episodic migraine receiving preventive treatment with Erenumab. Cephalalgia. 2018 Sep;38(10):1622-31. [34]	No report of Adverse Events
35. Diener HC, Krupp P, Schmitt T, Steitz G, Milde K, Freytag S, Study Group. Cyclandelate in the prophylaxis of migraine: a placebo-controlled study. Cephalalgia. 2001 Feb;21(1):66-70. [35]	No report of Adverse Events
36. Diener HC, F" h M, Laccarino C, Wessely P, Isler H, Stienge H, Fischer M, Wedekind W, Taneri Z. Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. Cephalalgia. 1996 Oct;16(6):441-7. [36]	Small sample size of episodic or chronic migraine
37.Diener HC, Hartung E, Chrubasik JO, Evers S, Schoenen J, Eikermann A, Latta G, Hauke W, Study Group. A comparative study of oral acetylsalicyclic acid and metoprolol for the prophylactic treatment of migraine. A randomized, controlled, double-blind, parallel group phase III study. Cephalalgia. 2001 Mar;21(2):120-8. [37]	No report of Adverse Events
38. Diener HC, Bussone G, Oene JV, Lahaye M, Schwalen S, Goadsby PJ. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. Cephalalgia. 2007 Jul;27(7):814-23. [38]	Small sample size of chronic migraine
39. Dodick DW, Mauskop A, Elkind AH, DeGryse R, Brin MF, Silberstein SD, Botox CDH Study Group. Botulinum toxin type A for the prophylaxis of chronic daily headache: Subgroup analysis of patients not receiving other prophylactic medications: A randomized double-	Chronic daily headache

blind, placebo-controlled study. Headache: The Journal of Head and Face Pain. 2005 Apr;45(4):315-24. [39]	
40. Domingues RB, Silva AL, Domingues SA, Aquino CC, Kuster GW. A double-blind randomized controlled trial of low doses of propranolol, nortriptyline, and the combination of propranolol and nortriptyline for the preventive treatment of migraine. Arquivos de neuro-psiquiatria. 2009;67:973-7. [40]	Small sample size of episodic or chronic migraine
41. Magalhães E, Menezes C, Cardeal M, Melo A. Botulinum toxin type A versus amitriptyline for the treatment of chronic daily migraine. Clinical neurology and neurosurgery. 2010 Jul 1;112(6):463-6. [41]	Small sample size of chronic migraine, and no outcomes of interest
42. Lipton RB, Pozo-Rosich P, Blumenfeld AM, Dodick DW, McAllister P, Li Y, Lu K, Dabruzzo B, Miceli R, Severt L, Finnegan M. Rates of response to atogepant for migraine prophylaxis among adults: a secondary analysis of a randomized clinical trial. JAMA Network Open. 2022 Jun 1;5(6):e2215499-. [42]	Episodic migraine
43. Faraji F, Zarinfar N, Zanjani AT, Morteza A. The effect of Helicobacter pylori eradication on migraine: a randomized, double blind, controlled trial. Pain physician. 2012;15(6):495. [43]	This is the eradication of HP not use of a prophylactic treatment
44. Ford JH, Ayer DW, Zhang Q, Carter JN, Leroux E, Skljarevski V, Aurora SK, Tockhorn-Heidenreich A, Lipton RB. Two randomized migraine studies of galcanezumab: effects on patient functioning and disability. Neurology. 2019 Jul 30;93(5):e508-17. [44]	No report of Adverse Events
45. Freitag FG, Diamond S, Diamond M, Urban G. Botulinum toxin type A in the treatment of chronic migraine without medication overuse. Headache: The Journal of Head and Face Pain. 2008 Feb;48(2):201-9. [45]	Small sample size of chronic migraine
46. Lauretti GR, Rosa CP, Kitayama A, Lopes BC. Comparison of botox® or prosigne® and facial nerve blockade as adjuvant in chronic migraine. Journal of Biomedical Science and Engineering. 2014 Jun 26;2014. [46]	Small sample size of chronic migraine
47. Ganji R, Majdinasab N, Hesam S, Rostami N, Sayyah M, Sahebnasagh A. Does atorvastatin have augmentative effects with sodium valproate in prevention of migraine with aura attacks? A triple-blind controlled clinical trial. Journal of pharmaceutical health care and sciences. 2021 Dec;7(1):1-0. [47]	Small sample size of episodic migraine
48. Gawel MJ, Kreeft J, Nelson RF, Simard D, Arnott WS. Comparison of the efficacy and safety of flunarizine to propranolol in the prophylaxis of migraine. Canadian journal of neurological sciences. 1992 Aug;19(3):340-5. [48]	Small sample size of episodic migraine
49. Keyvan G, Abolfazl MB. Comparison of treatment effect of sodium valproate, propranolol and tricyclic antidepressants in migraine. Pakistan journal of biological sciences: PJBS. 2009 Aug 1;12(15):1098-101. [49]	Small sample size of episodic or chronic migraine
50. Hussein HS, Alsalihi NJ, Al Gawwam G. Flunarizine Vs Propranolol in the Prevention of Migrainous Headache Attacks. Age (years). 2021;30(9):30-4. [50]	Small sample size of migraine
51. Ghose K, Niven BE, Berry D. A double-blind crossover comparison of the effects of vigabatrin with placebo in the prevention of migraine headache. The Journal of Headache and Pain. 2002 Sep;3(2):79-85. [51]	Small sample size of migraine
52. Goadsby PJ, Silberstein SD, Yeung PP, Cohen JM, Ning X, Yang R, Dodick DW. Long-term safety, tolerability, and efficacy of fremanezumab in migraine: a randomized study. Neurology. 2020 Nov 3;95(18):e2487-99. [52]	Comparing the dosing regime of same drug

53. Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, Wright IK, Chou DE, Klatt J, Picard H, Lenz RA. One-year sustained efficacy of erenumab in episodic migraine: results of the STRIVE study. Neurology. 2020 Aug 4;95(5):e469-79. [53]	Reporting the active treatment phase with dose blinding not the RCT part
54. Goadsby PJ, Reuter U, Lanteri-Minet M, da Silva Lima GP, Hours-Zesiger P, Fernandes C, Wen S, Tenenbaum N, Kataria A, Ferrari MD, Klatt J. Long-Term efficacy and safety of Erenumab: results from 64 weeks of the liberty study. Neurology. 2021 Jun 1;96(22):e2724-35. [54]	Not RCT
55. Grahame R. Drug prophylaxis in migraine. British Medical Journal. 1960 Oct 10;2(5207):1203. [55]	Small sample size of episodic migraine
56. Rompel, H. & Bauermeister PW. Aetiology of migraine and prevention with carbamazepine (Tegretol): results of a double-blind, cross-over study. South African Medical Journal. 1970 Jan 1;44(4):75-80. [56]	Small sample size of episodic migraine
57. Havanka-Kanniainen H, Hokkanen E, Myllylä VV. Efficacy of nimodipine in comparison with pizotifen in the prophylaxis of migraine. Cephalalgia. 1987 Mar;7(1):7-13. [57]	Small sample size of episodic migraine
58. Silberstein SD, Rapoport AM, Loupe PS, Aycardi E, McDonald M, Yang R, Bigal ME. The effect of beginning treatment with fremanezumab on headache and associated symptoms in the randomized phase 2 study of high frequency episodic migraine: Post-hoc analyses on the first 3 weeks of treatment. Headache: The Journal of Head and Face Pain. 2019 Mar;59(3):383-93. [58]	Small sample size of episodic migraine
59. Hering R, Kuritzky A. Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. Cephalalgia. 1992 Apr;12(2):81-4. [59]	Small sample size of episodic migraine
60. Hirata K, Takeshima T, Sakai F, Tatsuoka Y, Suzuki N, Igarashi H, Nakamura T, Ozeki A, Yamazaki H, Skljarevski V. A long-term open-label safety study of galcanezumab in Japanese patients with migraine. Expert Opinion on Drug Safety. 2021 Jun 3;20(6):721-33. [60]	Not RCT
61. Hollanda L, Monteiro L, Melo A. Botulinum toxin type a for cephalic cutaneous allodynia in chronic migraine: a randomized, double-blinded, placebo-controlled trial. Neurology International. 2014 Dec 5;6(4):5133. [61]	Assesses cutaneous allodynia rather than headache improvement
62. Hou M, Xie JF, Kong XP, Zhang Y, Shao YF, Wang C, Ren WT, Cui GF, Xin L, Hou YP. Acupoint injection of onabotulinumtoxin A for migraines. Toxins. 2015 Oct 30;7(11):4442-54. [62]	Small sample size of episodic migraine
63. Mehvari J, Rafieian-Kopaei M. Prophylactic activity of cyproheptadine and Bellergal on migraine headache. Iranian Journal of Medical Sciences. 2005 Jun 1;30(2). [63]	Small sample size of episodic migraine
64. Song JH, Zhang GB, Ding XD, Huang L, Hong Y, Chen HX. Efficacy of type a botulinum toxin injections and infrared polarized light on treating chronic migraine. Eur Rev Med Pharmacol Sci. 2015 Jan 1;19(11):1976-82. [64]	Small sample size of chronic migraine
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67. Grotemeyer KH, Schlake HP, Husstedt IW. Etilefrine Pivalate vs. Dihydroergotamin and Flunarizin in Prophylactic Treatment of	Small sample size of episodic migraine

Migraine in Patients with Low Blood Pressure—A Randomized Double-Blind-Study. Cephalalgia. 1989 Oct;9(10_suppl):433-4. [67]	
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69. Kuruppu DK, Tobin J, Dong Y, Aurora SK, Yunes-Medina L, Green AL. Efficacy of galcanezumab in patients with migraine who did not benefit from commonly prescribed preventive treatments. BMC neurology. 2021 Dec;21(1):1-9. [69]	No report of Adverse Events
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80. Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C, Botox CDH Study Group. Botulinum toxin type A (BOTOX®) for the prophylactic treatment of chronic daily headache: A randomized, double-blind, placebo-controlled trial. Headache: The Journal of Head and Face Pain. 2005 Apr;45(4):293-307. [80]	Chronic daily headache

81. Mathew NT, Jaffri SF. A double-blind comparison of onabotulinumtoxina (BOTOX®) and topiramate (TOPAMAX®) for the prophylactic treatment of chronic migraine: A pilot study. Headache: The Journal of Head and Face Pain. 2009 Nov;49(10):1466-78. [81]	Small sample size of chronic migraine
82. Mazdeh M, Mahmudian R, Vafaei SY, Taheri M, Ghafouri-Fard S. Effect of propranolol with and without rosuvastatin on migraine attacks: a triple blind randomized clinical trial. Future Neurology. 2020 May;15(2):FNL44. [82]	Small sample size of episodic or chronic migraine
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87. Hasan MK, Khan I, Salam T, Sharmin M. The Sociodemographic Characteristics of Migraine Patients in Bangladesh. Int J Med Res Prof. 2019:59-62. [87]	Small sample size of episodic migraine
88. Choudhary MU, Nawaz J, Saddique MU, Zameer A. Comparison between topiramate and sodium valproate efficacy in the treatment of migraine. Pak J Med Health Sci. 2017 Jul 1;11(3):1005-7. [88]	Small sample size of episodic migraine
89. Naderinabi B, Saberi A, Hashemi M, Haghighi M, Biazar G, Gharehdaghi FA, Sedighinejad A, Chavoshi T. Acupuncture and botulinum toxin A injection in the treatment of chronic migraine: a randomized controlled study. Caspian Journal of Internal Medicine. 2017;8(3):196. [89]	Small sample size of chronic migraine
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93. Omranifard M, Abdali H, Ardakani MR, Talebianfar M. A comparison of outcome of medical and surgical treatment of migraine headache: In 1 year follow-up. Advanced Biomedical Research. 2016;5. [93]	Small sample size of chronic migraine

94. Ondo WG, Vuong KD, Derman HS. Botulinum toxin A for chronic daily headache: a randomized, placebo-controlled, parallel design study. Cephalalgia. 2004 Jan;24(1):60-5. [94]	Mixed of chronic tension type and chronic migraine headaches.
95. Ozyalcin SN, Talu GK, Kiziltan E, Yucel B, Ertas M, Disci R. The efficacy and safety of venlafaxine in the prophylaxis of migraine. Headache: The Journal of Head and Face Pain. 2005 Feb;45(2):144-52. [95]	Small sample size of migraine
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100. Pradalier A, Serratrice G, Collard M, Hirsch E, Feve J, Masson M, Masson C, Dry J, Koulikovsky G, Nguyen G, Schbath J. Long-acting propranolol in migraine prophylaxis: results of a double-blind, placebo-controlled study. Cephalalgia. 1989 Dec;9(4):247-53. [100]	Small sample size of episodic or chronic migraine
101. Pradalier A, Lantéri-Minet M, Géraud G, Attain H, Lucas C, Delgado A. The PROMISE study: PROphylaxis of migraine with SEglor®(dihydroergotamine mesilate) in French primary care. CNS drugs. 2004 Dec;18(15):1149-63. [101]	No report of Adverse Events
102. Rahimdel A, Zeinali A, Yazdian-Anari P, Hajizadeh R, Arefnia E. Effectiveness of vitamin B2 versus sodium valproate in migraine prophylaxis: a randomized clinical trial. Electronic Physician. 2015 Oct;7(6):1344. [102]	Small sample size of migraine
103. Rapoport A, Mauskop A, Diener HC, Schwalen S, Pfeil J. Long-term migraine prevention with topiramate: open-label extension of pivotal trials. Headache: The Journal of Head and Face Pain. 2006 Jul;46(7):1151-60. [103]	Mixed population of adults and adolescence
104. Rasmussen MJ, Holt Larsen B, Borg L, Soelberg Sørensen P, Hansen PE. Tolfenamic acid versus propranolol in the prophylactic treatment of migraine. Acta neurologica scandinavica. 1994 Jun;89(6):446-50. [104]	Small sample size of episodic or chronic migraine
105. Kaushik R, Kaushik RM, Mahajan SK, Rajesh V. Biofeedback assisted diaphragmatic breathing and systematic relaxation versus propranolol in long term prophylaxis of migraine. Complementary therapies in medicine. 2005 Sep 1;13(3):165-74. [105]	Small sample size of episodic or chronic migraine
106. Lipton RB, Silberstein S, Dodick D, Cady R, Freitag F, Mathew N, Biondi DM, Ascher S, Olson WH, Hulihan J. Topiramate intervention to prevent transformation of episodic migraine: the topiramate INTREPID study. Cephalalgia. 2011 Jan;31(1):18-30. [106]	Mixed population of adults and adolescence
107. Ryan Sr RE. Comparative study of nadolol and propranolol in prophylactic treatment of migraine. American Heart Journal. 1984 Oct 1;108(4):1156-9. [107]	Small sample size of episodic or chronic migraine
108. Ryan RE, Diamond S, Ryan RE. Double blind study of clonidine and placebo for the prophylactic treatment of migraine. Headache: The Journal of Head and Face Pain. 1975 Oct;15(3):202-6. [108]	Small sample size of migraine

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110. Weber RB, Reinmuth OM. The treatment of migraine with propranolol. Neurology. 1972 Apr 1;22(4):366-9. [110]	Small sample size of migraine
111. Ruff DD, Ford JH, Tockhorn-Heidenreich A, Stauffer VL, Govindan S, Aurora SK, Terwindt GM, Goadsby PJ. Efficacy of galcanezumab in patients with episodic migraine and a history of preventive treatment failure: results from two global randomized clinical trials. European journal of neurology. 2020 Apr;27(4):609-18. [111]	No report of Adverse Events
112. Evers S, Vollmer-Haase J, Schwaag S, Rahmann A, Husstedt IW, Frese A. Botulinum toxin A in the prophylactic treatment of migraine–a randomized, double-blind, placebo-controlled study. Cephalalgia. 2004 Oct;24(10):838-43. [112]	Small sample size of migraine
113. Ghobadi SH, Jivad N. The prophylactic activity of propranol and nimodipineon migraine headache. World J Med Sci. 2013;8(2):144-6. [113]	Small sample size of migraine
114. Sadeghian H, Motiei-Langroudi R. Comparison of Levetiracetam and sodium Valproate in migraine prophylaxis: A randomized placebo-controlled study. Annals of Indian Academy of Neurology. 2015 Jan;18(1):45. [114]	Mixed population of adolescent and adult
115. Sakai F, Takeshima T, Tatsuoka Y, Hirata K, Lenz R, Wang Y, Cheng S, Hirama T, Mikol DD. A randomized phase 2 study of erenumab for the prevention of episodic migraine in Japanese adults. Headache: The Journal of Head and Face Pain. 2019 Nov;59(10):1731-42. [115]	Small sample size of episodic migraine
116. Sakai F, Takeshima T, Tatsuoka Y, Hirata K, Cheng S, Numachi Y, Peng C, Xue F, Mikol DD. Long-term efficacy and safety during open-label erenumab treatment in Japanese patients with episodic migraine. Headache: The Journal of Head and Face Pain. 2021 Apr;61(4):653-61. [116]	Small sample size of episodic migraine
117. Santiago MD, Carvalho DD, Gabbai AA, Pinto MM, Moutran AR, Villa TR. Amitriptyline and aerobic exercise or amitriptyline alone in the treatment of chronic migraine: a randomized comparative study. Arquivos de neuro-psiquiatria. 2014;72:851-5. [117]	Small sample size of chronic migraine
118. Saper JR, Lake III AE, Cantrell DT, Winner PK, White JR. Chronic daily headache prophylaxis with tizanidine: a double-blind, placebo-controlled, multicenter outcome study. Headache: The Journal of Head and Face Pain. 2002 Jun;42(6):470-82. [118]	Small sample size of chronic daily headache
119. Schellenberg R, Lichtenthal A, Wöhling H, Graf C, Brixius K. Nebivolol and Metoprolol for Treating Migraine: An Advance on β-Blocker Treatment?. Headache: The Journal of Head and Face Pain. 2008 Jan;48(1):118-25. [119]	Small sample size of episodic or chronic migraine
120. Seng EK, Holroyd KA. Behavioral migraine management modifies behavioral and cognitive coping in people with migraine. Headache: The Journal of Head and Face Pain. 2014 Oct;54(9):1470-83. [120]	Not drug trial
121. Bulut S, Berilgen MS, Baran A, Tekatas A, Atmaca M, Mungen B. Venlafaxine versus amitriptyline in the prophylactic treatment of migraine: randomized, double-blind, crossover study. Clinical neurology and neurosurgery. 2004 Dec 1;107(1):44-8. [121]	Small sample size of episodic migraine
122. Sonbolestan SA, Heshmat K, Javanmard SH, Saadatnia M. Efficacy of enalapril in migraine prophylaxis: a randomized, double-blind, placebo-controlled trial. International Journal of Preventive Medicine. 2013 Jan;4(1):72. [122]	Small sample size of episodic migraine

123. Rafie S, Karimian F, Ghomifar A, Karimian A. Effect of Pramipexole on Headache Relief in Patients with Concomitant Migraine and Restless Legs Syndrome; A Randomized, Controlled, Clinical Trial. Jundishapur Journal of Natural Pharmaceutical Products. 2019 Aug 31;14(3). [123]	Small sample size of episodic or chronic migraine
124. Shehata HS, Esmail EH, Abdelalim A, El-Jaafary S, Elmazny A, Sabbah A, Shalaby NM. Repetitive transcranial magnetic stimulation versus botulinum toxin injection in chronic migraine prophylaxis: a pilot randomized trial. Journal of pain research. 2016;9:771. [124]	Small sample size of chronic migraine
125. Silberstein SD, Collins SD, Long-term Safety of Depakote in Headache Prophylaxis Study Group. Safety of divalproex sodium in migraine prophylaxis: An open-label, long-term study. Headache: The Journal of Head and Face Pain. 1999 Oct;39(9):633-43. [125]	Not a RCT
126. Silberstein SD, Neto W, Schmitt J, Jacobs D, MIGR-001 Study Group. Topiramate in migraine prevention: results of a large controlled trial. Archives of Neurology. 2004 Apr 1;61(4):490-5. [126]	Mixed population of adults and adolescence
127. Silberstein SD, Dodick DW, Lindblad AS, Holroyd K, Harrington M, Mathew NT, Hirtz D. Randomized, placebo-controlled trial of propranolol added to topiramate in chronic migraine. Neurology. 2012 Mar 27;78(13):976-84. [127]	Small sample size of chronic migraine
128. Silvestrini M, Bartolini M, Coccia M, Baruffaldi R, Taffi R, Provinciali L. Topiramate in the treatment of chronic migraine. Cephalalgia. 2003 Oct;23(8):820-4. [128]	Small sample size of chronic migraine
129. Skljarevski V, Oakes TM, Zhang QI, Ferguson MB, Martinez J, Camporeale A, Johnson KW, Shan Q, Carter J, Schacht A, Goadsby PJ. Effect of different doses of galcanezumab vs placebo for episodic migraine prevention: a randomized clinical trial. JAMA neurology. 2018 Feb 1;75(2):187-93. [129]	Small sample size of episodic migraine
130. Sørensen PS, Hansen K, Olesen J. A placebo-controlled, double-blind, cross-over trial of flunarizine in common migraine. Cephalalgia. 1986 Mar;6(1):7-14. [130]	Small sample size of migraine
131. Silberstein SD, Loder E, Forde G, Papadopoulos G, Fairclough D, Greenberg S. The impact of migraine on daily activities: effect of topiramate compared with placebo. Current medical research and opinion. 2006 Jun 1;22(6):1021-9. [131]	No report of Adverse Events
132. Silberstein S, Goode-Sellers S, Twomey C, Saiers J, Ascher J. Randomized, double-blind, placebo-controlled, phase II trial of gabapentin enacarbil for migraine prophylaxis. Cephalalgia. 2013 Jan;33(2):101-11. [132]	Small sample size of episodic migraine
133. Stovner LJ, Linde M, Gravdahl GB, Tronvik E, Aamodt AH, Sand T, Hagen K. A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study. Cephalalgia. 2014 Jun;34(7):523-32. [133]	Small sample size of episodic or chronic migraine
134. Sujan MU, Rao MR, Kisan R, Abhishekh HA, Nalini A, Raju TR, Sathyaprabha TN. Influence of hydrotherapy on clinical and cardiac autonomic function in migraine patients. Journal of neurosciences in rural practice. 2016 Jan;7(01):109-13. [134]	Not drug trial
135. Zain S, Khan M, Alam R, Zafar I, Ahmed S. Comparison of efficacy and safety of topiramate with gabapentin in migraine prophylaxis: randomized open label control trial. J Pak Med Assoc. 2013 Jan 1;63(1):3-7. [135]	Small sample size of episodic migraine
136. Tatsuoka Y, Takeshima T, Ozeki A, Matsumura T. Treatment Satisfaction of Galcanezumab in Japanese Patients with Episodic Migraine: A Phase 2 Randomized Controlled Study. Neurology and therapy. 2021 Jun;10(1):265-78. [136]	No report of Adverse Events

137. Oakes TM, Skljarevski V, Zhang Q, Kielbasa W, Hodsdon ME, Detke HC, Camporeale A, Saper JR. Safety of galcanezumab in patients with episodic migraine: a randomized placebo-controlled dose-ranging phase 2b study. Cephalalgia. 2018 May;38(6):1015-25. [137]	Small sample size of episodic migraine
138. Titus F, Dávalos A, Alom J, Codina A. 5-hydroxytryptophan versus methysergide in the prophylaxis of migraine. European neurology. 1986;25(5):327-9. [138]	Small sample size of migraine
139. Steiner TJ, Ahmed F, Findley LJ, MacGregor EA, Wilkinson M. S-fluoxetine in the prophylaxis of migraine: a phase II double-blind randomized placebo-controlled study. Cephalalgia. 1998 Jun;18(5):283-6. [139]	Small sample size of migraine
140. Vahedi K, Taupin P, Djomby RF, El-Amrani M, Lutz G, Filipetti V, Landais P, Massiou H, Bousser MG. Efficacy and tolerability of acetazolamide in migraine prophylaxis: a randomised placebo-controlled trial. Journal of neurology. 2002 Feb;249(2):206-11. [140]	Small sample size of episodic migraine
141. Todorov V, Bogdanova D, Tonchev P, Milanov I. Repetitive transcranial magnetic stimulation over two target areas, sham stimulation and topiramate in the treatment of chronic migraine. Comptes rendus de l'Académie bulgare des Sciences. 2020 Jan 1;73(9). [141]	Small sample size of chronic migraine
142. Villani V, Prosperini L, Palombini F, Orzi F, Sette G. Single-blind, randomized, pilot study combining shiatsu and amitriptyline in refractory primary headaches. Neurological Sciences. 2017 Jun;38(6):999-1007. [142]	Small sample size of episodic migraine
143. Wammes-van der EA, Smidt MH, Tijssen CC, Van 't Hoff AR, Lenderink, PharmD AW, Egberts, PharmD AC. Effect of low-intensity acenocoumarol on frequency and severity of migraine attacks. Headache: The Journal of Head and Face Pain. 2005 Feb;45(2):137-43. [143]	Small sample size of episodic or chronic migraine
144. Xu JH, Mi HY. A randomized controlled trial of acupressure as an adjunctive therapy to sodium valproate on the prevention of chronic migraine with aura. Medicine. 2017 Jul;96(27). [144]	Not a drug trial
145. Yurekli VA, Akhan G, Kutluhan S, Uzar E, Koyuncuoglu HR, Gultekin F. The effect of sodium valproate on chronic daily headache and its subgroups. The journal of headache and pain. 2008 Feb;9(1):37-41. [145]	Small sample size on chronic daily headache
146. Zidan A, Hussaini S, Gibson S, Brooks G, Mejico L. Onabotulinumtoxin Type A reconstitution with preserved versus preservative-free saline in chronic migraine (B-RECON). A randomised, double-blind trial. International Journal of Clinical Practice. 2020 Sep;74(9):e13522. [146]	Trial of Botox preservative on injection site pain
147. Silberstein SD, Hulihan J, Karim MR, Wu SC, Jordan D, Karvois D, Kamin M. Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults: a randomized, placebo-controlled, double-blind, 12-week pilot study. Clinical therapeutics. 2006 Jul 1;28(7):1002-11. [147]	Small sample size of episodic migraine
148. Askari G, Nasiri M, Mozaffari-Khosravi H, Rezaie M, Bagheri-Bidakhavidi M, Sadeghi O. The effects of folic acid and pyridoxine supplementation on characteristics of migraine attacks in migraine patients with aura: A double-blind, randomized placebo-controlled, clinical trial. Nutrition. 2017 Jun 1;38:74-9. [148]	Acute migraine
149. Hajihashemi P, Askari G, Khorvash F, Reza Maracy M, Nourian M. The effects of concurrent Coenzyme Q10, L-carnitine supplementation in migraine prophylaxis: A randomized, placebo-	Small sample size of episodic migraine

controlled, double-blind trial. Cephalalgia. 2019 Apr;39(5):648-54. [149]	
150. Bredfeldt RC, Sutherland JE, Kruse JE. Efficacy of transdermal clonidine for headache prophylaxis and reduction of narcotic use in migraine patients. J Fam Pract. 1989;29(2):153-6. [150]	Small sample size of episodic migraine Small episodic migraine
151. Centonze V, Macinagrossa G, Attolini E, Magrone D, Trizio T, Tesauro P, Campanozzi F, Altomare E, Albano O. Terapia preventiva dell'emicrania: flunarizina versus verapamil [Preventive therapy of migraine: flunarizine versus verapamil]. Clin Ter. 1985 Dec 15;115(5):333-9. Italian. PMID: 3830537. [151]	Small sample size of episodic migraine
152. Maizels M, Blumenfeld A, Burchette R. A combination of riboflavin, magnesium, and feverfew for migraine prophylaxis: a randomized trial. Headache: The Journal of Head and Face Pain. 2004 Oct;44(9):885-90. [152]	Small sample size of episodic migraine
153. Chitsaz A, Ghorbani A, Hoseinzadeh H, Nazari F, Norouzi R, Tajic S. Comparison of botulinum toxin type-A and divalproex sodium for prevention of chronic and episodic migraine. Neurology Asia. 2012 Jun 1;17(2). [153]	Small sample size of episodic or chronic migraine
154. Matin H, Taghian F, Chitsaz A. Artificial intelligence analysis to explore synchronize exercise, cobalamin, and magnesium as new actors to therapeutic of migraine symptoms: a randomized, placebo-controlled trial. Neurological Sciences. 2022 Feb 3:1-2. [154]	Small sample size of episodic migraine
155. Croop R, Lipton RB, Kudrow D, Stock DA, Kamen L, Conway CM, Stock EG, Coric V, Goadsby PJ. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. The Lancet. 2021 Jan 2;397(10268):51-60. [155]	Small sample size of episodic or chronic migraine
156. Diamond S, Kudrow L, Stevens J, Shapiro DB. Long-term study of propranolol in the treatment of migraine. Headache: The Journal of Head and Face Pain. 1982 Nov;22(6):268-71. [156]	No outcome of interests
157. Mottaghi T, Askari G, Khorvash F, Maracy MR. Effect of Vitamin D supplementation on symptoms and C-reactive protein in migraine patients. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2015 May;20(5):477. [157]	Mixed population of adults and adolescence
158. Nattagh-Eshtivani E, Dahri M, Hashemilar M, Tarighat-Esfanjani A. The effect of coenzyme Q10 supplementation on serum levels of lactate, pyruvate, matrix metalloproteinase 9 and nitric oxide in women with migraine. A double blind, placebo, controlled randomized clinical trial. European Journal of Integrative Medicine. 2018 Aug 1;21:70-6. [158]	Small sample size of episodic migraine
159. Shoeibi A, Olfati N, Soltani Sabi M, Salehi M, Mali S, Akbari Oryani M. Effectiveness of coenzyme Q10 in prophylactic treatment of migraine headache: an open-label, add-on, controlled trial. Acta Neurologica Belgica. 2017 Mar;117(1):103-9. [159]	Small sample size of episodic migraine
160. Tarighat Esfanjani A, Mahdavi R, Ebrahimi Mameghani M, Talebi M, Nikniaz Z, Safaiyan A. The effects of magnesium, l-carnitine, and concurrent magnesium–l-carnitine supplementation in migraine prophylaxis. Biological trace element research. 2012 Dec;150(1):42-8. [160]	Small sample size of episodic migraine
161. Hsieh LL, Liou HH, Lee LH, Chen TH, Yen AM. Effect of acupressure and trigger points in treating headache: a randomized controlled trial. The American Journal of Chinese Medicine. 2010;38(01):1-4. [161]	Small sample size of episodic migraine
162. Langohr HD, Gerber WD, Koletzki E, Mayer K, Schroth G. Clomipramine and Metoprolol in Migraine Prophylaxis—A Double-	Small sample size of episodic migraine

blind Crossover Study. Headache: The Journal of Head and Face Pain. 1985 Mar;25(2):107-12. [162]	
163. Sândor PS, Di Clemente L, Coppola G, Saenger U, Fumal A, Magis D, Seidel L, Agosti RM, Schoenen J. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. Neurology. 2005 Feb 22;64(4):713-5. [163]	Small sample size of episodic migraine
164. Mathew NT. Prophylaxis of migraine and mixed headache. A randomized controlled study. Headache: The Journal of Head and Face Pain. 1981 May;21(3):105-9. [164]	Small sample size of migraine
165. Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis A randomized controlled trial. Neurology. 1998 Feb 1;50(2):466-70. [165]	Small sample size of episodic migraine
166. Cao K, Yu L, Gao Y, Fan Y, Zhao J, Zhang X, Xie W, Yang W, Dong M, Li T, Qiao X. Efficacy of zhengtian pill for migraine prophylaxis: a randomized, multicenter, double-blind, placebo-controlled, parallel-group study. European Journal of Integrative Medicine. 2014 Jun 1;6(3):259-67. [166]	Episodic, is large enough for Safety, but unless Zhengtian is in main analysis no need to collect SAEs
167. Nelson CF, Bronfort G, Evans R, Boline P, Goldsmith C, Anderson AV. The efficacy of spinal manipulation, amitriptyline and the combination of both therapies for the prophylaxis of migraine headache. Journal of manipulative and physiological therapeutics. 1998 Oct 1;21(8):511-9. [167]	Small sample size of episodic migraine
168. Diener HC, Kronfeld K, Boewing G, Lungenhausen M, Maier C, Molsberger A, Tegenthoff M, Trampisch HJ, Zenz M, Meinert R, GERAC Migraine Study Group. Efficacy of acupuncture for the prophylaxis of migraine: a multicentre randomised controlled clinical trial. The Lancet Neurology. 2006 Apr 1;5(4):310-6. [168]	Episodic, Control treatment not standardized
169. Shukla R, Garg RK, Nag D, Ahuja RC. Nifedipine in migraine and tension headache: a randomised double blind crossover study. The Journal of the Association of Physicians of India. 1995 Nov 1;43(11):770-2. [169]	Small sample size of episodic migraine
170. Silberstein SD, Stark SR, Lucas SM, Christie SN, Degryse RE, Turkel CC, BoNTA-039 Study Group. Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. InMayo Clinic Proceedings 2005 Sep 1 (Vol. 80, No. 9, pp. 1126-1137). Elsevier. [170]	Paper has included mixed patients (77% chronic migraine, 18% chronic tension type headache, 3% new daily persistent headache and 1% other headaches). Hence, not all patients were chronic migraineurs.
171. Ford JH, Stauffer VL, McAllister P, Akkala S, Sexson M, Ayer DW, Wang S. Functional impairment and disability among patients with migraine: evaluation of galcanezumab in a long-term, open-label study. Quality of Life Research. 2021 Feb;30(2):455-64. [171]	Small sample size of episodic migraine
172. Anthony M. Interesting uses of beta blockers. 1. Beta blockers in migraine prevention. Australian family physician. 1981 Apr;10(4):258-62. [172]	Not RCT
173. Arthur GP, Hornabrook RW. The treatment of migraine with BC 105 (pizotifen): a double blind trial. The New Zealand Medical Journal. 1971 Jan 1;73(464):5-9. [173]	Small sample size of episodic migraine
174. Ashkenazi A, Silberstein S. Botulinum toxin type A for the treatment of headache: why we say yes. Archives of neurology. 2008 Jan 1;65(1):146-9. [174]	Not an RCT
175. Bademosi O, Osuntokun BO. Pizotifen in the management of migraine. The Practitioner. 1978 Feb 1;220(1316):325-7. [175]	Small sample size of episodic migraine

176. Behan PO, Reid M. Propranolol in the treatment of migraine. The Practitioner. 1980 Feb;224(1340):201-3. [176]	Small sample size of episodic migraine
177. Chen SP, Fuh JL, Wang SJ. OnabotulinumtoxinA: preventive treatment for chronic migraine. Current pain and headache reports. 2011 Feb;15(1):4-7. [177]	Not an RCT
178. Diamond S, Freitag FG. A double-blind trial of flunarizine in migraine prophylaxis. Headache Quarterly-Current Treatment and Research. 1993 Jan 1;4(2):169-72. [178]	Small sample size of episodic migraine
179. Feuerstein T, Quebe-Fehling E. A double-blind, placebo-controlled, parallel-group, multicenter study of the safety and efficacy of gabapentin (CI-945) as a prophylactic interval therapy in patients with common migraine (Protocols 879-201,-205,-206,-207,-209). Research Report No. RR 4301-00066. Freiburg: Goedecke AG Research and Development. Available at: http://dida. library. ucsf. edu/pdf/brr13j10 1990. Accessed May 26; 2015. [179]	Small sample size of episodic migraine
180. Hübbe P. Controlled clinical trials of drugs for use in the prophylaxis of migraine. Danish Medical Bulletin. 1975 Mar 1;22(3):92-6. [180]	Not an RCT
181. Lance JW, Curran DA, Anthony M. Investigations into the mechanism and treatment of chronic headache. Medical journal of Australia. 1965 Nov;2(22):909-14. [181]	Not an RCT
182. Magnus-Miller L, Bernstein P, Caswell K. Double-blind, randomized, placebo-controlled, multicenter trial to determine the efficacy and safety of Neurontin®(gabapentin) in migraine prophylaxis administered in doses divided three times a day (TID)(protocol 945-220). Research Report No. RR 995-00074. [182]	Small sample size of episodic migraine
183. Morris Plains, NJ: Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company Medical and Scientific Affairs Department; August 24, 1999. Available at: http://dida. library. ucsf. edu/pdf/arr13j10. 1999 Aug 24. [183]	Small sample size of episodic migraine
184. Linde K, Rossnagel K. WITHDRAWN: Propranolol for migraine prophylaxis. Cochrane Database Syst Rev. 2017;2(2):CD003225. Published 2017 Feb 17. doi:10.1002/14651858.CD003225.pub3 [184]	Not an RCT
185. Nair KG. A pilot study of the value of propranolol in migraine. Journal of postgraduate medicine. 1975 Jul;21(3):111-3. [185]	Small sample size of episodic migraine
186. Pita E, Higueras A, Bolanos J, Perez N, Mundo A. Propranolol and migraine. A clinical trial. Archivos de Farmacologia y Toxicologia. 1977 Dec 1;3(3):273-8. [186]	Small sample size of episodic migraine
187. Verstraete M, Verhaeghe R. 20 Drugs acting on the cerebral and peripheral. Side Effects of Drugs Annual. 1977;10:172. [187]	Small sample size of episodic migraine
188. Rothrock JF. Topiramate for migraine prevention: an update. Headache: The Journal of Head and Face Pain. 2012 May;52(5):859-60. [188]	Not an RCT
189. Ryan Sr RE, Ryan Jr RE, Sudilovsky A. Nadolol and placebo comparison study in the prophylactic treatment of migraine. Panminerva medica. 1982;24(2):89-94. [189]	Small sample size of episodic migraine
190. Saper JR, Good DC, Michalek J, Kaplan RJ, Xiao Y, Nadler S. Efficacy and tolerability of tizanidine as adjunctive therapy in the prophylaxis of chronic daily headache. Round Table Series-Royal Society of Medicine. 2002 Jan 1(75):13-22. [190]	Small sample size of episodic migraine
191. Yuan C, Wang JX, Yu JP, Yan F, Su SH. A double-blind trial of 5 calcium channel blockers in prophylaxis of migraine. CHINESE JOURNAL OF CLINICAL PHARMACOLOGY. 1998;14:14-7. [191]	Small sample size of episodic migraine
192. Mattimoe D, Newton W. High-dose riboflavin for migraine prophylaxis. The Journal of Family Practice. 1998 Jul 1;47(1):11-. [192]	Small sample size of episodic migraine

193. Gonçalves DA, Camparis CC, Speciali JG, et al.Treatment of comorbid migraine and temporo-mandibular disorders: A factorial, double-blind, ran-domized, placebo-controlled study.J Orofac Pain.2013;27:325-335. [193]	Small sample size of episodic migraine
194. Schoenen J, Jacquy J, Lenaerts M. High-dose riboflavin is effective in migraine prophylaxis: Results from a double blind, randomized, placebo controlled trial. InNeurology 1997 Mar 1 (Vol. 48, No. 3, pp. 8005-8005). 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106: LIPPINCOTT-RAVEN PUBL. [194]	Small sample size of episodic migraine
195. Hübbe P. The prophylactic treatment of migraine with an antiserotonin pizotifen (BC 105). Acta Neurologica Scandinavica. 1973 Mar;49(1):108-14. [195]	Small sample size of episodic migraine
196. Schoenen J, Jacquy J, Lenaerts ME, Loder E. High-dose riboflavin reduced the frequency of migraine headaches. Evidence-Based Medicine. 1998 Sep;3(5):151. [196]	Small sample size of episodic migraine
197. Rezaeiashtiani A, Jadidi A, Khanmohammadi-Hezaveh A, Aghaeipour SM, Pourandish Y, Malekhosseini S, Ghassami K, Mohammadbeigi A. Is the treatment of constipation can relieve the migraine symptoms? A randomized clinical trial study. Journal of Pediatric Neurosciences. 2019 Oct;14(4):186. [197]	Small sample size of episodic migraine
198. Shimell CJ, Fritz VU, Levien SL. A comparative trial of flunarizine and propranolol in the prevention of migraine. South African Medical Journal, 1990 Jan 1;77(2):75-7. [198]	Small sample size of episodic migraine
199. Wang LP, Zhang XZ, Guo J, Liu HL, Zhang Y, Liu CZ, Yi JH, Wang LP, Zhao JP, Li SS. Efficacy of acupuncture for migraine prophylaxis: a single-blinded, double-dummy, randomized controlled trial. PAIN®. 2011 Aug 1;152(8):1864-71. [199]	Small sample size of episodic migraine
200. Yang CP, Chang MH, Li TC, Hsieh CL, Hwang KL, Chang HH. Predicting prognostic factors in a randomized controlled trial of acupuncture versus topiramate treatment in patients with chronic migraine. The Clinical Journal of Pain. 2013 Nov 1;29(11):982-7. [200]	Small sample size of chronic migraine
201. Manzoni, GC, et all., Multicentric, double-blind, randomized study on the efficacy and tolerance of dothiepin and amitriptyline for the prophylaxis of chronic migraine. Giornale di neuropsicofarmacologia. 1990; 12(5):179-184. [201]	Small sample size of chronic migraine
202. Lipton RB, Croop R, Stock EG, Stock DA, Morris BA, Frost M, Dubowchik GM, Conway CM, Coric V, Goadsby PJ. Rimegepant, an oral calcitonin gene–related peptide receptor antagonist, for migraine. New England Journal of Medicine. 2019 Jul 11;381(2):142-9. [202]	Acute migraine
203. Diener HC, Tfelt-Hansen P, Dahlöf C, et al. Topiramate in migraine prophylaxis. J Neurol 251, 943– 950 (2004). https://doi.org/10.1007/s00415-004-0464-6. [203]	Mixed population of adult and adolescents
204. Ailani J, Andrews JS, Tockhorn-Heidenreich A, Wenzel R, Rettiganti M. Effect of Galcanezumab on Total Pain Burden in Patients Who Had Previously Not Benefited from Migraine Preventive Medication (CONQUER Trial): A Post Hoc Analysis. Advances in Therapy. 2022 Oct;39(10):4544-55. [204]	No safety data for adverse events review and a small sample size of chronic migraine
205. Igarashi H, Shibata M, Ozeki A, Matsumura T. Galcanezumab Effects on Migraine Severity and Symptoms in Japanese Patients with Episodic Migraine: Secondary Analysis of a Phase 2 Randomized Trial. Neurology and Therapy. 2022 Oct 20:1-5. [205]	No safety data for adverse events review
206. Chowdhury D, Chaudhuri JR, Ghosh P, Kulkarni R, Singh S, Thakur S, Thorat AV. Efficacy and tolerability of erenumab for	Small sample of episodic migraine

prevention of episodic migraine in India. Annals of Indian Academy of Neurology. 2022 May;25(3):433. [206]	
207. Igarashi H, Shibata M, Ozeki A, Day KA, Matsumura T. Early Onset and Maintenance Effect of Galcanezumab in Japanese Patients with Episodic Migraine. Journal of Pain Research. 2021;14:3555. [207]	No safety data for adverse events review
208. Sakai F, Takeshima T, Tatsuoka Y, Hirata K, Cheng S, Numachi Y, Peng C, Xue F, Mikol DD. Long-term efficacy and safety during open-label erenumab treatment in Japanese patients with episodic migraine. Headache: The Journal of Head and Face Pain. 2021 Apr;61(4):653-61. [208]	Small sample of episodic migraine
209. Okonkwo R, Tockhorn-Heidenreich A, Stroud C, Paget MA, Matharu MS, Tassorelli C. Efficacy of galcanezumab in patients with migraine and history of failure to 3–4 preventive medication categories: subgroup analysis from CONQUER study. The journal of headache and pain. 2021 Dec;22(1):1-1. [209]	No safety data for adverse events review
210. Okonkwo R, Tockhorn-Heidenreich A, Stroud C, Paget MA, Matharu MS, Tassorelli C. Efficacy of galcanezumab in patients with migraine and history of failure to 3–4 preventive medication categories: subgroup analysis from CONQUER study. The journal of headache and pain. 2021 Dec;22(1):1-1. [210]	No safety data for adverse events review
211. Couch JR, Amitriptyline Versus Placebo Study Group. Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. Headache: The Journal of Head and Face Pain. 2011 Jan;51(1):33-51. [211]	Definition for AEs and SAEs
212. Diener HC, Matias-Guiu J, Hartung E, Pfaffenrath V, Ludin HP, Nappi G, De Beukelaar F, Study Group. Efficacy and tolerability in migraine prophylaxis of flunarizine in reduced doses: a comparison with propranolol 160 mg daily. Cephalalgia. 2002 Apr;22(3):209-21. [212]	Definition for AEs and SAEs
213. Kalita J, Bhoi SK, Misra UK. Amitriptyline vs divalproate in migraine prophylaxis: a randomized controlled trial. Acta Neurologica Scandinavica. 2013 Jul;128(1):65-72. [213]	Definition for AEs and SAEs
214. Yang CP, Chang MH, Li TC, Hsieh CL, Hwang KL, Chang HH. Predicting prognostic factors in a randomized controlled trial of acupuncture versus topiramate treatment in patients with chronic migraine. The Clinical Journal of Pain. 2013 Nov 1;29(11):982-7. [214]	Not pharmacological intervention
215. Lucking CH, Oestreich W, Schmidt R, Soyka D. Flunarizine vs. propranolol in the prophylaxis of migraine: two double-blind comparative studies in more than 400 patients. Cephalalgia. 1988 Sep;8(8_suppl):21-6. [215]	Definition for AEs and SAEs
216. Relja M, Poole AC, Schoenen J, Pascual J, Lei X, Thompson C. A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A (BoNTA) for the prophylaxis of episodic migraine headaches. Cephalalgia. 2007 Jun;27(6):492-503. [216]	Definition for AEs and SAEs
217. Rapoport A, Mauskop A, Diener HC, Schwalen S, Pfeil J. Long-term migraine prevention with topiramate: open-label extension of pivotal trials. Headache: The Journal of Head and Face Pain. 2006 Jul;46(7):1151-60. [217]	The mixed population of adults and adolescence
218. Lipton RB, Silberstein S, Dodick D, Cady R, Freitag F, Mathew N, Biondi DM, Ascher S, Olson WH, Hulihan J. Topiramate intervention to prevent transformation of episodic migraine: the topiramate INTREPID study. Cephalalgia. 2011 Jan;31(1):18-30. [218]	Definition for AEs and SAEs
219. Ruff DD, Ford JH, Tockhorn-Heidenreich A, Stauffer VL, Govindan S, Aurora SK, Terwindt GM, Goadsby PJ. Efficacy of galcanezumab in patients with episodic migraine and a history of preventive treatment	No report of Adverse Events

failure: results from two global randomized clinical trials. European Journal of Neurology. 2020 Apr;27(4):609-18. [219]	
220. Sakai F, Takeshima T, Tatsuoka Y, Hirata K, Cheng S, Numachi Y, Peng C, Xue F, Mikol DD. Long-term efficacy and safety during open-label erenumab treatment in Japanese patients with episodic migraine. Headache: The Journal of Head and Face Pain. 2021 Apr;61(4):653-61. [220]	Small sample size of episodic migraine
221. Silberstein SD, Loder E, Forde G, Papadopoulos G, Fairclough D, Greenberg S. The impact of migraine on daily activities: effect of topiramate compared with placebo. Current medical research and opinion. 2006 Jun 1;22(6):1021-9. [221]	No adverse events reported
222. Silberstein S, Goode-Sellers S, Twomey C, Saiers J, Ascher J. Randomized, double-blind, placebo-controlled, phase II trial of gabapentin enacarbil for migraine prophylaxis. Cephalalgia. 2013 Jan;33(2):101-11. [222]	Small sample size of episodic migraine
223. Tatsuoka Y, Takeshima T, Ozeki A, Matsumura T. Treatment satisfaction of galcanezumab in Japanese patients with episodic migraine: a phase 2 randomized controlled study. Neurology and Therapy. 2021 Jun;10:265-78. [223]	No adverse events reported
224. Oakes TM, Skljarevski V, Zhang Q, Kielbasa W, Hodsdon ME, Detke HC, Camporeale A, Saper JR. Safety of galcanezumab in patients with episodic migraine: a randomized placebo-controlled dose-ranging phase 2b study. Cephalalgia. 2018 May;38(6):1015-25. [224]	Small sample size of episodic migraine
225. Fazlalizadeh H, Khamseh F, Soleimani B, Tajik A. Comparative study of topiramate versus sodium valproate in the prevention of migraine headaches. Medical Sciences Journal of Islamic Azad University. 2009;19(2). [225]	Definition for AEs and SAEs
226. Diener HC, Agosti R, Allais G, Bergmans P, Bussone G, Davies B, Ertas M, Lanteri-Minet M, Reuter U, Del Río MS, Schoenen J. Cessation versus continuation of 6-month migraine preventive therapy with topiramate (PROMPT): a randomised, double-blind, placebo-controlled trial. The Lancet Neurology. 2007 Dec 1;6(12):1054-62. [226]	Definition for AEs and SAEs
227. Elkind AH, O'Carroll P, Blumenfeld A, DeGryse R, Dimitrova R. A series of three sequential, randomized, controlled studies of repeated treatments with botulinum toxin type A for migraine prophylaxis. The Journal of Pain. 2006 Oct 1;7(10):688-96. [227]	Included for SAEs but not for AEs due to not provide a standard definition of adverse event.
228. Ho TW, Connor KM, Zhang Y, Pearlman E, Koppenhaver J, Fan X, Lines C, Edvinsson L, Goadsby PJ, Michelson D. Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. Neurology. 2014 Sep 9;83(11):958-66. [228]	Not recommended by NICE or SIGN
229. Ailani J, Andrews JS, Rettiganti M, Nicholson RA. Impact of galcanezumab on total pain burden: findings from phase 3 randomized, double-blind, placebo-controlled studies in patients with episodic or chronic migraine (EVOLVE-1, EVOLVE-2, and REGAIN trials). The Journal of Headache and Pain. 2020 Dec;21:1-9. [229]	Small sample size of migraine
230. Ament M, Day K, Stauffer VL, Skljarevski V, Rettiganti M, Pearlman E, Aurora SK. Effect of galcanezumab on severity and symptoms of migraine in phase 3 trials in patients with episodic or chronic migraine. The journal of headache and pain. 2021 Dec;22(1):1-0. [230]	No adverse events reported
231. Blumenfeld AM, Patel AT, Turner IM, Mullin KB, Manack Adams A, Rothrock JF. Patient-reported outcomes from a 1-year, real-world, head-to-head comparison of onabotulinumtoxinA and topiramate for headache prevention in adults with chronic migraine. Journal of	No adverse events reported

primary care & community health. 2020 Sep;11:2150132720959936. [231]	
232. Brandes JL, Diener HC, Dolezil D, Freeman MC, McAllister PJ, Winner P, Klatt J, Cheng S, Zhang F, Wen S, Ritter S. The spectrum of response to erenumab in patients with chronic migraine and subgroup analysis of patients achieving≥ 50%,≥ 75%, and 100% response. Cephalalgia. 2020 Jan;40(1):28-38. [232]	No adverse events reported
233. Dodick DW, Silberstein SD, Lipton RB, DeGryse RE, Adams AM, Diener HC. Early onset of effect of onabotulinumtoxinA for chronic migraine treatment: analysis of PREEMPT data. Cephalalgia. 2019 Jul;39(8):945-56. [233]	No adverse events reported
234. Dodick DW, Silberstein S, Saper J, Freitag FG, Cady RK, Rapoport AM, Mathew NT, Hulihan J, Crivera C, Rupnow MF, Mao L. The impact of topiramate on health-related quality of life indicators in chronic migraine. Headache: The Journal of Head and Face Pain. 2007 Nov;47(10):1398-408. [234]	No adverse events reported
235. Ford J, Tassorelli C, Leroux E, Wang S, Ayer D, Nichols R, Detke H. Changes in patient functioning and disability: results from a phase 3, double-blind, randomized, placebo-controlled clinical trial evaluating galcanezumab for chronic migraine prevention (REGAIN). Quality of Life Research. 2021 Jan;30:105-15. [235]	No adverse events reported
236. Lipton RB, Rosen NL, Ailani J, DeGryse RE, Gillard PJ, Varon SF. OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine over one year of treatment: pooled results from the PREEMPT randomized clinical trial program. Cephalalgia. 2016 Aug;36(9):899-908. [236]	No adverse events reported
237. Lipton RB, Tepper SJ, Reuter U, Silberstein S, Stewart WF, Nilsen J, Leonardi DK, Desai P, Cheng S, Mikol DD, Lenz R. Erenumab in chronic migraine: patient-reported outcomes in a randomized double-blind study. Neurology. 2019 May 7;92(19):e2250-60. [237]	No adverse events reported
238. Lipton RB, Cohen JM, Gandhi SK, Yang R, Yeung PP, Buse DC. Effect of fremanezumab on quality of life and productivity in patients with chronic migraine. Neurology. 2020 Aug 18;95(7):e878-88. [238]	No adverse events reported
239. Ruff DD, Ford JH, Tockhorn-Heidenreich A, Sexson M, Govindan S, Pearlman EM, Wang SJ, Khan A, Aurora SK. Efficacy of galcanezumab in patients with chronic migraine and a history of preventive treatment failure. Cephalalgia. 2019 Jul;39(8):931-44. [239]	No adverse events reported
240. Silberstein SD, Cohen JM, Seminerio MJ, Yang R, Ashina S, Katsarava Z. The impact of fremanezumab on medication overuse in patients with chronic migraine: subgroup analysis of the HALO CM study. The Journal of Headache and Pain. 2020 Dec;21:1-0. [240]	No adverse events reported
241. Winner PK, Spierings EL, Yeung PP, Aycardi E, Blankenbiller T, Grozinski-Wolff M, Yang R, Ma Y. Early onset of efficacy with fremanezumab for the preventive treatment of chronic migraine. Headache: The Journal of Head and Face Pain. 2019 Nov;59(10):1743-52. [241]	No adverse events reported
242. Brandes JL, Kudrow DB, Rothrock JF, Rupnow MF, Fairclough DL, Greenberg SJ. Assessing the ability of topiramate to improve the daily activities of patients with migraine. InMayo Clinic Proceedings 2006 Oct 1 (Vol. 81, No. 10, pp. 1311-1319). Elsevier. [242]	No adverse events reported
243. Diamond S, Kudrow L, Stevens J, Shapiro DB. Long-term study of propranolol in the treatment of migraine. Headache: The Journal of Head and Face Pain. 1982 Nov;22(6):268-71. [243]	Small sample size of migraine
244. Silberstein SD, Lipton RB, Dodick DW, Freitag FG, Ramadan N, Mathew N, Brandes JL, Bigal M, Saper J, Ascher S, Jordan DM. Efficacy and safety of topiramate for the treatment of chronic migraine: A	Definition for AEs and SAEs

randomized, double-blind, placebo-controlled trial. Headache: The Journal of Head and Face Pain. 2007 Feb;47(2):170-80. [244]	
245. Silberstein S, Lipton R, Dodick D, Freitag F, Mathew N, Brandes J, Bigal M, Ascher S, Morein J, Wright P, Greenberg S. Topiramate treatment of chronic migraine: A randomized, placebo-controlled trial of quality of life and other efficacy measures. Headache: The Journal of Head and Face Pain. 2009 Sep;49(8):1153-62. [245]	Definition for AEs and SAEs
246. Aurora SK, Gawel M, Brandes JL, Pokta S, VanDenburgh AM, BOTOX North American Episodic Migraine Study Group. Botulinum toxin type a prophylactic treatment of episodic migraine: A randomized, double-blind, placebo-controlled exploratory study. Headache: The Journal of Head and Face Pain. 2007 Apr;47(4):486-99. [246]	Definition for AEs and SAEs
247. Camporeale A, Kudrow D, Sides R, Wang S, Van Dycke A, Selzler KJ, Stauffer VL. A phase 3, long-term, open-label safety study of Galcanezumab in patients with migraine. BMC neurology. 2018 Dec;18(1):1-2. [247]	Comparing two dose of a drug
248. Ashina M, Lanteri-Minet M, Ettrup A, Christoffersen CL, Josiassen MK, Phul R, Sperling B, Pozo-Rosich P. Efficacy and safety of eptinezumab for migraine prevention in patients with prior preventive treatment failures: subgroup analysis of the randomized, placebo-controlled DELIVER study. Cephalalgia. 2023 May;43(5):03331024231170807. [248]	No adverse events reported
249. Ashina S, Campos VR, Cohen J, Janka L, Krasenbaum L, Blume L. 085 Medication overuse reversion following fremanezumab treatment in migraine patients with inadequate response to prior preventives. [249]	No adverse events reported
250. Barbanti P, Goadsby PJ, Lambru G, Ettrup A, Christoffersen CL, Josiassen MK, Phul R, Sperling B. Effects of eptinezumab on self-reported work productivity in adults with migraine and prior preventive treatment failure in the randomized, double-blind, placebo-controlled DELIVER study. The Journal of Headache and Pain. 2022 Dec;23(1):153. [250]	No adverse events reported
251. Hirata K, Takeshima T, Sakai F, Imai N, Matsumori Y, Tatsuoka Y, Numachi Y, Yoshida R, Peng C, Mikol DD, Lima GP. Early onset of efficacy with erenumab for migraine prevention in Japanese patients: Analysis of two randomized, double-blind, placebo-controlled studies. Brain and Behavior. 2022 Mar;12(3):e2526. [251]	No adverse events reported
252. Ehrlich M, Hentschke C, Sieder C, Maier-Peuschel M, Reuter U. Erenumab versus topiramate: post hoc efficacy analysis from the HER-MES study. The Journal of Headache and Pain. 2022 Dec;23(1):1-8. [252]	No adverse events reported
253. Goadsby PJ, Barbanti P, Lambru G, Ettrup A, Christoffersen CL, Josiassen MK, Phul R, Sperling B. Eptinezumab improved patient-reported outcomes and quality of life in patients with migraine and prior preventive treatment failures. European Journal of Neurology. 2023 Apr;30(4):1089-98. [253]	No adverse events reported
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Appendix 3: More details on baseline characteristics of the included studies

First author, year/ Country	Study design and Date	Key inclusion criteria	Key exclusion criteria
Author, year: Rothrock, 2019 [1] **Country:** USA	**Study design:** multicenter, randomised, parallel-group, post-authorisation, open-label prospective study. After 12 weeks, patients initially randomised to topiramate could cross over to BTA treatment **Date:** August 2014 to September 2017	• Adults (18-65) had to record ≥20 diary days during 28 days baseline screening • Reported ≥15 headache days. • Patients taking other preventive treatments were eligible for enrolment if the dose had been stable and well tolerated for ≥12 weeks before screening and the patient was willing to maintain a stable dose. • Patients were permitted to take prescription or over the counter acute headache pain medication, recording use in their daily diary	• Taking opioid-containing products for acute headache treatment more than 8 days during a 28-day period • Previous treatment with botulinum toxin of any serotype for any reason • Previous treatment with topiramate • On a ketogenic diet (high in fat, low in carbohydrates) • History of acute myopia or increased intraocular pressure • Diagnosis of myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis or any other significant disease that might interfere with neuromuscular function • Acupuncture, transcutaneous electrical stimulation (TENS), cranial traction, dental splints for headache, or injection of anesthetics/steroids in the 4 weeks prior to screening.
Author, year: Tepper, 2017 [2] **Country:** North America (Canada and the USA) and Europe (Czech Republic, Denmark, Finland, Germany, Norway, Poland, Sweden, and the UK	**Study design:** phase 2, randomised, double-blind, placebo-controlled, multicentre **Date:** April 2014, to Dec 2016	• History of at least 5 attacks of migraine without aura and/or migraine with visual sensory, speech and/or language, retinal or brainstem aura. • History of ≥ 15 headache days per month of which ≥ 8 headache days were assessed by the subject as migraine day. • ≥ 4 distinct headache episodes, each lasting ≥ 4 hours OR if shorter, associated with use of a triptan or ergot-derivative on the same calendar day based on the eDiary calculations.	• History of cluster headache or hemiplegic migraine headache • Unable to differentiate migraine from other headaches • Failed > 3 medication categories due to lack of efficacy for prophylactic treatment of migraine. • Received botulinum toxin in head or neck region within 4 months prior to screening. • Used a prohibited migraine prophylactic medication, device or procedure within 2 months prior to the start of the baseline phase

		• Demonstrated at least 80% compliance with the eDiary.	
Author, year: Dodick, 2019 [3] **Country:** 82 in the United States, four in Australia, and three each in New Zealand and the Republic of Georgia	**Study design:** phase 2b, parallel-group, double-blind, randomised, placebo-controlled, dose-ranging clinical trial. **Date:** December 2014 to December 2016	• Adults 18–55 years with CM according ICHD-3b • Established at age >=35 years and history of CM of >=1 year. • >=15 headache days, of which>=8 were assessed as migraine days during baseline priod. • Use of hormonal therapy and preventive medications for headache except botulinum toxin, was allowed if the dosing has been stable for >3 months before screening, and was maintained at the same dosing level throughout the trial • The use of barbiturates or opioids for the acute treatment of CM was allowed if the dosing had been stable for 3 months before screening, and dosing did not exceed 4 days/month. • Patients with CM who were diagnosed with medication overuse headache	• Confounding pain syndromes (e.g. fibromyalgia, chronic low back pain, complex regional pain syndrome) or any pain syndrome that requires regular analgesia • Psychiatric conditions that are uncontrolled and untreated, including conditions that are not controlled for a minimum of 6 months prior to screening. • History or diagnosis of complicated migraine (ICHD-III beta version, 2013), chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, migraine with brainstem aura, sporadic and familial hemiplegic migraine • Unable to differentiate migraine from other headaches • Subject has received botulinum toxin for migraine or for any other medical/cosmetic reasons requiring injections in the head, face, or neck within 4 months prior to screening. • Have any clinically significant concurrent medical condition
Author, year: Detke, 2018 [4] **Country:** Argentina, Canada, Czech Republic, Germany, Israel, Italy, Mexico, the Netherlands, Spain, Taiwan, the United Kingdom, and the United States	**Study design:** phase 3, randomised, double-blind, placebo-controlled study **Date:** January 2016 to March 2017	• Adults 18 to 65 years with CM as defined by ICHD-3 beta with at least 15 headache days • Migraine onset before 50 years of age. • Patients could take acute headache medication as needed throughout the trial but could take opioid or barbiturate containing medications no more than 3 days per month, could not take oral corticosteroids, and could receive no more than 1 steroid	• Are currently enrolled in or have participated within the last 30 days or within 5 half-lives (whichever is longer) in a clinical trial involving an investigational product. • Current use or prior exposure to galcanezumab or another calcitonin gene-related peptide (CGRP) antibody. • Known hypersensitivity to multiple drugs, monoclonal antibodies or other therapeutic proteins, or to galcanezumab.

		injection during the study and only if in an emergency setting. • Patients had to wash out all migraine preventive medications except topiramate or propranolol • Patients also needed at least 1 headache-free day per month within 3 months before screening period.	• History of persistent daily headache, cluster headache or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, and migraine with brainstem aura (basilar-type migraine) defined by IHS ICHD-3 beta
Author, year: Dodick 2010 [5]; [pooled Aurora 2010 [6], Diener 2010 [7]] **Country:** 56 North American sites	**Study design:** phase 3 study, with a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week, open-label phase **Date:** 23 January 2006 to 16 July 2008 and 7 February 2006 to 11 August 2008	• Adults (18 to 65 years) with a history of migraine according ICHD-II • Randomised patients provided diary data on >20 of 28 days during baseline. • Having >15 headache days with each day consisting of >4 hours of continuous headache and with >50% of days being migraine or probable migraine days and >4 distinct headache episodes, each lasting >4 hours.	• Previous use of botulinum toxin of any serotype or immunisation to any botulinum toxin serotype • Any medical condition that puts the patient at increased risk with exposure to BTA • Diagnosis of complicated migraine, chronic tension-type headache, hypnic headache, hemicrania continua, new daily persistent headache • Use of prophylactic headache medication within 28 days prior to week -4 • Unremitting headache lasting continuously throughout the 4-week baseline period • Known or suspected Temporomandibular Disorders (TMD) • Diagnosis of fibromyalgia • Beck depression inventory score >24 at week-4 • Psychiatric problems that may have interfered with study participation
Author, year: Ferrari, 2019 [8] **Country:** Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, UK, and the USA.	**Study design:** Phase 3 FOCUS trial, randomised, double-blind, placebo-controlled, parallel-group **Date:** October 2017 to May 2019	• Adults (18–70 years), had a diagnosis of migraine with onset at or before age 50 years. • Chronic migraine history at least 12 months before screening. • > 15 headache days per month, with at least 8 migraine days	• At the time of screening visit, participant is receiving any preventive migraine medications, regardless of the medical indication for more than 5 days and expects to continue with these medications. • Participant has received onabotulinumtoxinA for migraine or for any medical or cosmetic reasons requiring injections in the head, face,

		• Participants with and without overuse of acute headache medication • With failure to two to four classes of migraine preventive medications in the past 10 years.	or neck during the 3 months before screening visit. • Participant has used an intervention/device (for example; scheduled nerve blocks and transcranial magnetic stimulation) for migraine during the 2 months prior to screening. • Participant uses triptans/ergots as preventive therapies for migraine. • Participant uses non-steroidal anti-inflammatory drugs (NSAIDs) as preventive therapy for migraine on nearly daily basis for other indications. Note: Low dose aspirin (for example; 81 mg) used for cardiovascular disease prevention is allowed.
Author, year: Sakai F, 2021 [9] **Country:** Japan and Korea	**Study design:** multicenter, randomised, double-blind, placebo-controlled, parallel-group **Date:** November 2017 and November 2019	• Patient with migraine onset at ≤50 years of age • Headache occurring on ≥15 days and fulfilling any of the following on ≥8 days: (ICHD-3 beta diagnostic criteria C and D for 1.1 Migraine without aura, criteria B and C for 1.2 Migraine with aura, Probable migraine. • Not using preventive migraine medications for migraine or other medical conditions or using no more than 1 preventive migraine medication for migraine or other medical conditions if the dose and regimen have been stable for at least 2 months prior to giving informed consent.	• The lack of efficacy of at least two of four clusters of preventive medications despite an ade-quate treatment • Unremitting headaches with duration more than 80% of waking hours and with less than 4 days without headache per month • Clinically significant major organ disease • Patient has received onabotulinumtoxin A for migraine or for any medical or cosmetic reason requiring injection in the head, face, or neck during the 4 months prior to giving informed consent • Patient is using medications containing opioids or barbiturates on more than 4 days per month for the treatment of migraine or for any other reason • Patient has used an intervention or device for migraine during the 2 months prior to giving informed consent.
Author, year: Silberstein SD, 2017 [10]	**Study design:**	• Adults (18 to 70 years), a history of migraine according to ICHD-3 beta for at least 12 months.	• The use of BTA during the 4 months before screening

Country: 132 sites in nine countries	randomised, double-blind, placebo-controlled, parallel-group trial **Date:** March 2016 through January 2017	• ≥15 headache days with ≥8 migraine days. • The protocol allowed inclusion of up to 30% of patients using a stable dose of one migraine-preventive medication (hereafter referred to as preventive medication) for at least 2 months before the beginning of the pre-intervention period to continue these medications	• The use of interventions or devices for migraine, such as nerve blocks and transcranial magnetic stimulation, during the 2 months before screening • The use of opioid or barbiturate medications on more than 4 days during the pre-intervention period and a lack of efficacy, after an adequate therapeutic trial, of at least two of four clusters of preventive medications
Author, year: Lipton, 2020 [11] **Country:** 13 countries (United States, Spain, Ukraine, Russian Federation, United Kingdom, Republic of Georgia, Hungary, Italy, Slovakia, Germany, Czech Republic, Denmark, and Belgium)	**Study design:** phase 3, double-blind, randomised, placebo-controlled, parallel-group **Date:** November 2016 to April 2018.	• Adults (18 to 65 years) of age (inclusive) with a diagnosis of migraine at or before 50 years of age if they had a history of CM for ≥12 months before screening, • Completed the headache electronic diary (eDiary) on ≥24 of the 28 days and experienced ≥15 to ≤26 headache days and ≥8 migraine days during the 28-day screening period. • Migraine preventive medication use had to be stable for ≥3 months before screening. Hormonal therapy was also permitted if it was stable and ongoing ≥3 months before screening. • Patients using barbiturates or prescription opioids ≤4 d/mo were eligible for participation if use was stable for ≥2 months before screening. • Patients with CM and medication-overuse headache with the exception of the overuse of barbiturates or opioids	• Patients using opioids or barbiturates ≥5 d/mo • With a confounding pain disorder or clinically significant pain syndromes; uncontrolled or untreated psychiatric conditions; acute or active temporomandibular disorders; history or diagnosis of a headache or migraine disorders that did not meet the ICHD-3 criteria • Present or previous malignancies, any active, progressive, or unstable cardiovascular, neurologic, or autoimmune disorder; newly diagnosed or uncontrolled hypertension. • Women who were pregnant, breastfeeding, or planning to become pregnant during the study • positive for HIV, hepatitis B surface antigen, or hepatitis C • A concurrent medical condition or laboratory abnormality during the screening period or before dosing on day 0; • Body mass index ≥39 kg/m2 • Or recent or planned surgery requiring general anaesthesia within 8 weeks before screening or during the duration of the study

			• Botulinum toxin (any type) for migraine or for any other medical cosmetic reasons requiring injections within 4 months before screening or during the screening period • Any monoclonal antibody treatment within 6 months of screening; or Eptinezumab or any monoclonal antibody targeting the CGRP pathway.
Author, year: Ailani, 2021 [12] **Country:** United States	**Study design:** multicentre, double-blind, parallel group, randomised, placebo-controlled trial **Date:** December 2018 to June 2020	• Adults 18 to 80 years of age with 4 to 14 migraine days per month in the 3 months before visit 1 and 4 to 14 migraine days during the 28- day baseline period according to an electronic diary • Participants had to have at least a 1-year history of migraine with or without aura, diagnosed as specified in the International Classification of Headache Disorders, 3rd edition (ICHD-3), and with migraine onset before 50 years of age.	• Diagnosis of chronic migraine, new daily persistent headache, trigeminal autonomic cephalalgia, or painful cranial neuropathy as defined by the ICHD-3 or if they averaged 15 or more headache days per month across the 3 months before visit 1 or during the 28-day baseline period. • An inadequate response to more than four oral medications prescribed for the preventive treatment of migraine, two of which needed to have different mechanisms of action. • Participants who used opioids or barbiturates on more than 2 days per month, triptans or ergots on 10 or more days per month, or simple analgesic agents on 15 or more days per month in the 3 months before visit 1 or during the 28-day baseline period. • Use of barbiturates 30 days before screening • Pregnant, planning to become pregnant, or lactating.
Author, year: Sun, 2016 [13] **Country:** North America (Canada, USA) and Europe (Denmark, Finland, Germany, Norway, Sweden, and Portugal)	**Study design:** multicentre, randomised, double-blind, placebo-controlled trial **Date:**	• Adults, 18 to 60 years • History of migraine for more than 12 months prior to screening • Migraine frequency: ≥ 4 and ≤ 14 migraine days per month in each of the 3 months prior to screening and during baseline phase	• Older than 50 years of age at migraine onset • History of cluster headache or basilar or hemiplegic migraine headache • Unable to differentiate migraine from other headaches • No therapeutic response with > 2 of the following eight medication categories for

	August 2013 to November 2019	• Headache frequency: < 15 headache days per month (with > 50% of the headache days being migraine days) in each of the 3 months prior to screening and during baseline phase • Demonstrated at least 80% compliance with the eDiary during baseline phase	prophylactic treatment of migraine after an adequate therapeutic trial. Medication categories are: (Category 1: Divalproex sodium, sodium valproate, Category 2: Topiramate, Category 3: Beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol), Category 4: Tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline), Category 5: Venlafaxine, desvenlafaxine, duloxetine, milnacipran, Category 6: Flunarizine, verapamil, Category 7: Lisinopril, candesartan, Category 8: Butterbur, feverfew, magnesium (≥ 600 mg/day), riboflavin (≥ 100 mg/day) • Overuse of acute migraine medications in any month during the 3 months prior to screening or during screening
Author, year: Ashina, 2020 [14] **Country:** USA and the Republic of Georgia	**Study design:** multicenter, randomised, double-blind, placebo-controlled, parallel-group study **Date:** September 2015 to December 2017	• Adults, 18 to 75 years • Diagnosis of migraine at ≤ 50 years of age • History of migraine ≥ 12 months with ○ ≤ 14 headache days of which at least 4 have to be migraine days (migraine days count as headache days) in each 28-day period in the 3 months prior to screening ○ During the 28 days following the screening visit, the subject experiences ≤ 14 headache days of which at least 4 have to be migraine days (migraine days count as headache days) as recorded in the eDiary • No use of any botulinum toxin for migraine or for any other medical/cosmetic reasons requiring	• Confounding pain syndromes, e.g. fibromyalgia, complex regional pain syndrome or any pain syndrome that requires regular analgesia • Psychiatric conditions that are uncontrolled and untreated, including conditions that are not controlled for a minimum of 6 months prior to screening • History or diagnosis of complicated migraine (ICHD- II, 2004 Section 1), chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, migraine with brainstem aura, sporadic and familial hemiplegic migraine • Unable to differentiate migraine from other headaches

		injections in the head, face, or neck 4 months prior to screening and during the 28-day period prior to randomisation • Headache eDiary was completed on at least 25 of the 28 days prior to randomisation	• Have any clinically significant concurrent medical condition • Receipt of any monoclonal antibody treatment within 6 months of screening (within or outside a clinical trial) • Previously dosed with ALD403 or any monoclonal antibody targeting the CGRP pathway
Author, year: Dodick, 2014 [15] **Country:** USA	**Study design:** randomised, double-blind, placebo-controlled, phase 2 proof-of-concept study, parallel assignment. **Date:** July 2012 to September 2013	• Adults 18–65 years with four to 14 migraine headache days per month • Have a history of migraine as defined by ICHD-II, of at least 1 year prior to enrolment, migraine onset prior to age 50, and a moderate frequency of migraine headaches • Women of child-bearing potential (not surgically sterile or at least 1-year post-menopause) must test negative for pregnancy at the time of screening based on a serum pregnancy test and must agree to use a reliable method of birth control during the study and for 3 months following completion of participation in the study • Have clinical laboratory test results within normal reference ranges or, if outside the normal range, judged not clinically significant by the Investigator • Must not be on any migraine prevention therapy, including botulinum toxin • Agree not to post any personal medical data related to the study or information related to the study on any website or social media site.	• Current enrolment in, or discontinuation within the last 30 days from, a clinical trial involving any investigational drug or device, or concurrent enrolment in any other type of medical research judged not to be scientifically or medically compatible with this study • Previous completion or withdrawal from this study or any other study investigating LY2951742 or other therapeutic antibodies that target calcitonin gene-related peptide • History of chronic migraine or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, and basilar-type migraine • Evidence of significant active psychiatric disease including, but not limited to, manic depressive illness, schizophrenia, generalized anxiety disorder, obsessive compulsive disorder, personality disorders, or other serious mood, anxiety, depression, or substance use disorders • Have a history or presence of any other medical illness • Women who are pregnant or nursing • Confirmed corrected QT (QTc) interval >470 milliseconds (msec) for women and >450 for men

Author, year: Dodick, 2018 [16] **Country:** 69 sites across North America and Europe (including Russia)	**Study design:** multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial **Date:** July 2015 to March 2017	• Adults 18–65 years • Migraine onset prior to age 50 • History of migraines (with or without aura) for ≥ 12 months • Migraine frequency: ≥ 4 and < 15 migraine days per month on average across the 3 months prior to screening • Headache (i.e., migraine and non-migraine headache) frequency: < 15 headache days per month on average across the 3 months prior to screening • Demonstrated compliance with the eDiary	• History of cluster headache or hemiplegic migraine headache. • No therapeutic response with > 2 categories for prophylactic treatment of migraine after an adequate therapeutic trial. • Concomitant use of 2 or more medications with possible migraine prophylactic effects within 2 months prior to the start of the baseline phase or during the baseline phase. • Used a prohibited medication, device, or procedure within 2 months prior to the start of the baseline phase or during the baseline phase. • Received botulinum toxin • Active chronic pain syndromes (such as fibromyalgia and chronic pelvic pain). • History of major psychiatric disorder, seizure, HIV • Myocardial infarction (MI), stroke, transient ischemic attack (TIA), unstable angina, or coronary artery bypass surgery or other revascularization procedure within 12 months prior to screening.
Author, year: Dodick, 2009 [17] **Country:** United States	**Study design:** multicentre, randomised, double-blind, double-dummy, parallel-group noninferiority study **Date:** February 2004 to October 2005	• Adults (age ≥18 years) with a history of migraine without or with aura (International Headache Society class 1.1 and 1.2, respectively) for at least 6 months before the screening • Washout period, along with ~3 to 12 migraines per month in the 3 months before the screening • Washout period, from 3 to 12 migraine episodes during the 28-day prospective baseline period, and no	• With previously failed >2 adequate trials of migraine-preventive medications or had failed an adequate trial of topiramate or amitriptyline because of lack of efficacy or AEs. • Acute abortive medication uses on >15 treatment days per month • Migraine aura only (without headache) • History of cluster headache, a progressive neurologic disorder other than migraine, or a condition more painful than headache

		more than 15 headache days (migraine and nonmigraine) during the prospective baseline period, based on headache records. • Onset of migraine prior the age of 50 years	• History of a medical condition in which use of amitriptyline is contraindicated • History of an unstable medical condition within the past 2 years or of a major psychiatric disorder within the past 6 months that could impair reliable participation in the study or necessitate the use of medications not permitted in the study • History of drug or alcohol abuse within the past 2 years • History of nephrolithiasis, active liver disease, or liver function tests ≥2 times the upper limit of normal • Pregnant or nursing women and those who were not practicing a medically accepted method of birth control
Author, year: Dodick, 2018 [18] **Country:** Canada, Czech Republic, Finland, Israel, Japan, Poland, Russia, Spain, United States	**Study design:** randomised, double-blind, placebo-controlled, parallel group. **Date:** March 2016 to April 2017	• Males or females aged 18 to 70 years, inclusive, with migraine onset at ≤50 years of age (ICHD-3 beta) • Patient signs and dates the informed consent document • Patient has history of migraine according to International Classification of Headache Disorders, or clinical judgment suggests a migraine diagnosis • 85% e-diary compliance • Total body weight between 99 and 265 lbs, inclusive • A subset of patients was allowed to use 1 concomitant preventive migraine medication if the dosing was stable for at least 2 months prior to the beginning of the pre-treatment period and without any change in dose during the study.	• Clinically significant haematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease, at the discretion of the investigator • History of clinically significant psychiatric issues • History of cardiovascular disease or vascular ischemia or thromboembolic events, such as cerebrovascular accident, deep vein thrombosis, or pulmonary embolism • History of human immunodeficiency virus, tuberculosis, or chronic hepatitis B or C infection • Pregnant or nursing females • Using onabotulinumtoxinA during the 4 months before screening, • Using opioids or barbiturates on more than 4 days during the pre-treatment baseline period

		• Acute headache medications were permitted	• Having previous failure of 2 or more of the following medication clusters after at least 3 months of treatment for episodic or chronic migraine: divalproex sodium and sodium valproate; flunarizine and pizotifen; amitriptyline, nortriptyline, venlafaxine, and duloxetine; and atenolol, nadolol, metoprolol, propranolol, and timolol
Author, year: Goadsby, 2017 [19] **Country:** 121 sites across North America, Europe, and Turkey	**Study design:** Multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial **Date:** July 2015 to September 2016	• Adults 18 to 65 years • History of migraine (with or without aura) for ≥ 12 months prior to screening according to the International Headache Society (IHS) International Classification of Headache Disorders (ICHD-3) classification • Migraine frequency: ≥ 4 and < 15 migraine days per month on average across the 3 months prior to screening and during baseline • Headache frequency: < 15 headache days per month on average across the 3 months prior to screening and baseline • Demonstrated at least 80% compliance with the eDiary.	• Older than 50 years of age at migraine onset • History of cluster headache or hemiplegic migraine headache • Unable to differentiate migraine from other headache • No therapeutic response with > 2 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial • Used a prohibited medication, device, or procedure within 2 months prior to the start of the baseline phase or during the baseline phase • Concomitant use of 2 or more medications with possible migraine prophylactic effects within 2 months prior to the start of the baseline phase or during the baseline phase. If only 1 prophylactic medication is used, the dose must be stable within 2 months prior to the start of the baseline phase and throughout the study
Author, year: Sakai 2020 [20] **Country:** Japan from 40 sites	**Study design:** Phase 2, randomised, double-blind, placebo-controlled parallel-design study **Date:**	• Adults 18 to 65 years • Have a diagnosis of migraine as defined by International Headache Society (IHS) International Classification of Headache Disorders (ICHD)-3 beta guidelines (1.1 or 1.2) (ICHD-3 2013)	• Are currently enrolled in or have participated within the last 30 days or within 5 half-lives (whichever is longer) in a clinical trial involving an investigational product. • Current use or prior exposure to Galcanezumab or other antibodies to CGRP or its receptor.

	December 2016 to January 2019	• History of migraine headaches of at least 1 year prior to screening, and migraine onset prior to age 50 • Patients had to demonstrate ≥80% compliance (completion of daily entries) with the ePRO diary, and all patients agreed to use reliable methods of contraception during the study and for 5 months after the last dose	• Known hypersensitivity to multiple drugs, monoclonal antibodies or other therapeutic proteins, or to Galcanezumab and the excipients in the investigational product. • History of persistent daily headache, cluster headache or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, and migraine with brainstem aura (basilar-type migraine) defined by IHS ICHD-3 beta.
Author, year: Sakai, 2021 [21] **Country:** Japan and Korea	**Study design:** multicentred, randomised, double-blind, placebo-controlled, parallel-group Phase 2b/3 trial **Date:** November 2017 and November 2019	• Adults 18 to 70 years • Patient with migraine onset at ≤50 years of age • Patient has a history of migraine, based on [ICHD-3 beta] criteria or clinical judgment suggests a migraine diagnosis for ≥ 12 months prior to giving informed consent • Patient fulfils the criteria for Episodic migraine in baseline information collected during the 28-day screening period • Not using preventive migraine medications for migraine or other medical conditions or using no more than 1 preventive migraine medication for migraine or other medical conditions (e.g., propranolol used for hypertension) if the dose and regimen have been stable for at least 2 months prior to giving informed consent.	• Patients who have previously failed (lack of efficacy) 2 or more of the clusters of the medications for treatment of migraine after use for at least 3 months at accepted migraine therapeutic doses • Haematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease considered clinically significant in the judgment of the investigator • Female patient who is nursing at the time informed consent is obtained or who tests positive in pregnancy test at screening or baseline. • History of hypersensitivity reactions to injected proteins, including monoclonal antibodies.
Author, year: Stauffer, 2018 [22] **Country:** 90 sites in North America	**Study design:** phase 3, randomised, double-blind, placebo-controlled study, parallel design	• Adults 18 to 65 years • Have a diagnosis of episodic migraine as defined by International Headache Society (IHS) International	• Are currently enrolled in or have participated within the last 30 days or within 5 half-lives (whichever is longer) in a clinical trial involving an investigational product.

	Date: November 2015 to August 2018	Classification of Headache Disorders (ICHD)-3 beta guidelines (1.1 or 1.2) • History of migraine headaches of at least 1 year prior to screening, • Migraine onset prior to age 50 • Monthly frequency of 4-14 Migraine Headache Days (MHD).	• Current use or prior exposure to Galcanezumab or another CGRP antibody. • Known hypersensitivity to multiple drugs, monoclonal antibodies or other therapeutic proteins, or to Galcanezumab. • History of persistent daily headache, cluster headache or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, and migraine with brainstem aura (basilar-type migraine) defined by IHS ICHD-3 beta.
Author, year: Skljarevski, 2018 [23] **Country:** 109 study sites in the United States, United Kingdom, Netherlands, Spain, Czech Republic, Germany, Argentina, Israel, Korea, Taiwan, and Mexico	**Study design:** Phase 3, multicentre, placebo-controlled, double-blind, randomised **Date:** January 2016 and March 2017	• Adults 18 to 65 years • Have a diagnosis of episodic migraine as defined by International Headache Society (IHS) International Classification of Headache Disorders (ICHD)-3 beta guidelines (1.1 or 1.2) • History of migraine headaches of at least 1 year prior to screening, • Migraine onset prior to age 50 • Monthly frequency of 4-14 Migraine Headache Days (MHD). • 80% compliance rate in using the electronic diary • patients had to agree to use an acceptable method of birth control during the study and for at least 5 months afterwards	• Having failed treatment with three or more migraine prevention drugs from different classes (level A or B evidence per American Academy of Neurology guidelines for episodic migraine prevention) • Using opioids or barbiturates more than twice per month. • If participation were in another clinical trial within the past 30 days, prior exposure to galcanezumab or any another CGRP antibody, taking any therapeutic antibody in the past 12 months, known hypersensitivity to multiple drugs • Presence of any medical or psychiatric illness that would preclude study participation
Author, year: Reuter, 2018 [24] **Country:** 59 sites in 16 countries across Europe and Australia	**Study design:** randomised, double-blind, placebo-controlled, phase 3b study **Date:** March 2017 to January 2021	• Adults 18 – 65 years • Documented history of migraine in the 12 months prior to screen • 4-14 days per month of migraine symptoms • >=80% diary compliance during the Baseline period	• >50 years old at migraine onset • Pregnant or nursing • History of cluster or hemiplegic headache • Evidence of seizure or psychiatric disorder • Score of over 19 on Beck Depression Inventory-2 • Active chronic pain syndrome

		• Failure of previous migraine prophylactic treatments	• Cardiac or hepatic disease
Author, year: Reuter, 2022 [25] **Country:** 82 study sites in Germany	**Study design:** randomised, double-blind, double dummy, active-controlled, parallel-group phase 4 **Date:** February 2019 to July 2020	• Adults • Documented history of migraine in the 12 months prior to screen according ICHD-3 episodic and chronic migraine • at least 4 days per month of migraine symptoms • >=80% diary compliance during the Baseline period • If patients had not received prior prophylactic migraine treatment (naıve) or, due to lack of efficacy or tolerability, had failed or had not been suitable for up to three previous prophylactic treatments from the following: Metoprolol/propranolol, amitriptyline, and flunarizine	• Older than 50 years of age at migraine onset • Pregnant or nursing • History of cluster or hemiplegic headache, or if they were unable to differentiate migraine from other headaches • History or evidence of major psychiatric disorder • Score of 19 or higher on Beck Depression Inventory (BDI) • Having previously received valproate or, in the event of chronic migraine, onabotulinumtoxin A, in line with recommendations of the German HTA bod
Author, year: Wang, 2021 [26] **Country:** 83 sites across 11 countries in Asia, the Middle East, and Latin America	**Study design:** multicentre, randomised, double-blind, placebo controlled, parallel-group, phase 3 study **Date:** February 2018 to January 2020	• Adults 16- 65 years old with migraine diagnosis according with ICHD-3 beta • ≥4 and <15 migraine days per month and <15 headache days in the 12 months prior to screening • 4-14 days per month of migraine symptoms • >=80% diary compliance during the Baseline period	• >50 years old at migraine onset • Pregnant or nursing • History of cluster or hemiplegic headache • Evidence of seizure or major psychiatric disorder • Score of 19 or higher on the BDI • Active chronic pain syndrome • Cardiac or hepatic disease • No therapeutic response to >2 of the seven categories of migraine-preventive treatments after an adequate therapeutic trial • Use of a prohibited medication, device, or procedure prior to the start of the study • Use of botulinum toxin within 4 months, ergotamines or triptans on ≥10 days per month, simple analgesics on ≥15 days per

			month, or opioid or butalbital-containing analgesics on ≥4 days per month.
Author, year: Elkind, 2006 [27] **Country:** -	**Study design:** A series of 3 sequential, randomised, controlled studies **Date:** -	• Adults 18 to 65 years, with International Headache Society–defined migraines with or without aura. • Having an average of 4 to 8 moderate to severe migraines per month that occurred with a stable frequency and severity and had begun at least 1 year prior to the study. • Patients were first diagnosed with migraine before age 50 years and could distinguish between migraine and nonmigraine headaches. • Eligible patients were in stable medical condition and, if taking chronic medications (including prophylactic migraine medications), were on stable doses and regimens for at least 3 months prior to enrolment, which they agreed to continue throughout the study.	• Patients with more than 15 headache days per month. • History of complicated migraine or typical migraine pain localized predominantly to the occipital or suboccipital region. • Patients were ineligible if they were consistently refractory to multiple acute therapies or had never tried any acute therapies. • Patients who overused symptomatic medications, as were those who used caffeine excessively or abused alcohol/drugs. • Any medical condition or use of any agent that might have put the patient at increased risk with exposure to BTA or interfered with study participation or the results • Women who were pregnant, breastfeeding, or planning a pregnancy • Those with infection or skin problems at the injection site.
Author, year: Mulleners, 2020 [28] **Country:** 64 sites (hospitals, clinics, or research centres) in 12 countries (Belgium, Canada, Czech Republic, France, Germany, Hungary, Japan, the Netherlands, South Korea, Spain, the UK, and the USA)	**Study design:** multicentre, randomised, double-blind, placebo-controlled, phase 3b trial **Date:** Sept 2018 to March 21, 2019	• Adults 18–75 years with a diagnosis of migraine with aura or without aura, or chronic migraine defined ICHD-3, with a history of migraine headaches of at least 1 year before screening, and migraine onset before the age of 50 years. • History of at least four migraine headache days and at least one headache-free day per month on average within the past 3 months. • History of documented treatment failure of two to four standard-of-care	• History of cluster headache or migraine subtypes including hemiplegic migraine, ophthalmoplegic migraine, and migraine with brainstem aura, history of head or neck injury within 6 months before the screening visit, or history of traumatic head injury associated with significant change in the quality or frequency of headaches • Current use or prior exposure to galcanezumab or another calcitonin gene-related peptide (CGRP) antibody. • Pregnant or nursing.

		migraine preventive medication categories in the past 10 years owing to inadequate efficacy, or safety or tolerability reasons, or both, were eligible. • Treatment failure did not include contraindications; patients had to have taken the medications. • The medication categories were: propranolol or metoprolol, topiramate, valproate or divalproex, amitriptyline, flunarizine, candesartan, botulinum toxin A or B, and medications locally approved for prevention of migraine.	• Having acute cardiovascular events or a serious cardiovascular risk, or both, based on electrocardiogram (ECG) results during the screening visit, myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft or stroke within 6 months before screening, hepatic disease based on liver tests, or serious or unstable medical or psychiatric condition.
Author, year: Croop, 2021 [29] **Country:** 92 sites in the USA	**Study design:** multicentre, randomised, double-blind, placebo-controlled trial **Date:** November 2018 to August 2019	• Adults 18 years and older • Subject has at least 1 year history of migraine (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition, including the following: o Age of onset of migraines prior to 50 years of age o Migraine attacks, on average, lasting 4 - 72 hours if untreated o Per subject report, 4 - 18 migraine attacks of moderate to severe intensity per month within the last 3 months prior to the Screening Visit o 6 or more migraine days during the Observation Period o Not more than 18 headache days during the Observation Period o Ability to distinguish migraine attacks from tension/cluster headaches	• History of HIV disease • Subject history with current evidence of uncontrolled, unstable or recently diagnosed cardiovascular disease, such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia. Subjects with Myocardial Infarction (MI), Acute Coronary Syndrome (ACS), Percutaneous Coronary Intervention (PCI), cardiac surgery, stroke or transient ischemic attack (TIA) during the 6 months prior to screening • Uncontrolled hypertension (high blood pressure), or uncontrolled diabetes (however subjects can be included who have stable hypertension and/or diabetes for at least 3 months prior to screening). • Subjects with major depressive episode within the last 12 months, major depressive disorder or any anxiety disorder requiring more than 1 medication for each disorder. Medications to treat major depressive disorder or an anxiety disorder must have

		○ Subjects on prophylactic migraine medication are permitted to remain on 1 medication with possible migraine-prophylactic effects if the dose has been stable for at least 3 months prior to the Screening Visit, and the dose is not expected to change during the course of the study.	been at a stable dose for at least 3 months prior to the Screening visit. • Subjects with other pain syndromes, psychiatric conditions, dementia, or significant neurological disorders (other than migraine) that, in the Investigator's opinion, might interfere with study assessments • Subject has a history of gastric, or small intestinal surgery (including Gastric Bypass, Gastric Banding, Gastric Sleeve, Gastric Balloon, etc.), or has disease that causes malabsorption • Subject has current diagnosis of major depressive disorder requiring treatment with atypical antipsychotics, schizophrenia, bipolar disorder, or borderline personality disorder • History of gallstones or cholecystectomy. • The subject has a history or current evidence of any unstable medical conditions (e.g., history of congenital heart disease or arrhythmia, known or suspected infection, hepatitis B or C, or cancer) that, in the investigator's opinion, would expose them to undue risk of a significant adverse event (AE) or interfere with assessments of safety or efficacy during the course of the trial
Author, year: Winner, 2021 [30] **Country:** 47 sites in the United States and the country of Georgia	**Study design:** Phase 3, multicentre, parallel-group, double-blind, randomised, placebo-controlled trial **Date:** November 2019 to July 2020	• Greater than 1-year history of migraine, with or without aura, with onset of first migraine before age 50. • Migraine on 4 to 15 days per month in the 3 months prior to screening. • Headache free for at least 24 hours prior to onset of a qualifying migraine. • Adults 18 Years to 75 Years	• Use of the following medication, for any indication, within the 24-hour period prior to dosing with study drug: ○ triptans, ergotamines and ergot-derivatives, analgesics and other acute migraine medication(s), antiemetic medications, antihistamines, devices, neuromodulation, neurostimulation, or injectable therapy

		• Diagnosis of migraine based on ICHD-3 criteria1 for migraine with or without aura	• Use of the following medication, for any indication, in each of the 3 months prior to screening: o opioids/narcotics or butalbital containing products (including combinations) on more than 4 days per month o triptans, ergotamines, or combination analgesics for 10 or more days per month o acetaminophen, aspirin or NSAIDs for 15 or more days per month (except if participant is taking 81 mg dose of aspirin for cardiac prophylaxis) • History or diagnosis of chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, or unusual migraine subtypes that are not typical of migraine aura. • Any use of approved devices, neuromodulation, neurostimulation, or injectable therapy within the 24-hour period prior to treatment with study drug (Day 0). • Any use of botulinum toxin for migraine or for any other medical/cosmetic reasons requiring injections within 7 days prior to treatment with study drug (Day 0). • Any use of systemic corticosteroid for migraine or any other reason within 3 months prior to treatment with study drug (Day 0). • History of clinically significant psychiatric diseases • Receipt of any monoclonal antibody treatment, for migraine or any other indication within 6 months prior to screening.
Author, year: Bo Hu, 2022 [31]	**Study design:**	• Participants must have a diagnosis of migraine as defined by International	• Are currently enrolled in any other clinical trial involving an investigational product or

Country: 40 centres in China (n=26), India (n=10), and Russia (n=4)	Phase 3, randomised, double-blind, placebo-controlled study **Date:** July 2019 to March 2022	Headache Society (IHS) International Classification of Headache Disorders (ICHD)-3 (1.1 or 1.2) (ICHD-3 2018) with a history of migraine of at least 1 year prior to screening and migraine onset prior to age 50 • Prior to screening, participants must have a history of 4-14 migraine headache days and at least 2 migraine attacks per month on average within the past 3 months • Adults 18 to 65 years	any other type of medical research judged not to be scientifically or medically compatible with this study • Current use or prior exposure to galcanezumab or another calcitonin gene-related peptide antibody, including those who have previously completed or withdrawn from this study or any other study investigating a CGRP antibody • Participants who are taking, or are expected to take, therapeutic antibodies during the course of the study (for example, adalimumab, infliximab, trastuzumab, bevacizumab, etc.) • Known hypersensitivity to multiple drugs, monoclonal antibodies or other therapeutic proteins, or to galcanezumab • Women who are pregnant or nursing • History of chronic migraine, daily persistent headache, cluster headache, medication overuse headache, migraine with brainstem aura, or hemiplegic migraine.
Author, year: Ashina, 2022 [32] **Country:** 96 study locations across Europe (n=93) and the USA (n=3)	**Study design:** multicentre, multi-arm, double-blind, placebo-controlled **Date:** June 2020 to Oct 2021	• Diagnosis of migraine, with a history of chronic or episodic migraines of at least 12 months prior to the screening visit • History of migraine onset of ≤50 years of age. • The participant has ≥4 migraine days per month for each month within the past 3 months prior to the screening visit. • The participant has demonstrated compliance with the Headache eDiary by entry of data for at least 24 of the 28 days following the Screening Visit.	• History of failure on a previous treatment targeting the CGRP pathway. • Participant has a treatment failure on valproate/divalproex or botulinum toxin A/B and the treatment is not the latest preventive medication prior to study inclusion. The medication is regarded as the latest if the medication start date is after the start date of the other preventive medications and the medication stop date is after the stop date of the other preventive medications. • Participant has confounding and clinically significant pain syndromes

		• The participant fulfils the following criteria for CM or EM in prospectively collected information in the eDiary during the screening period: • For CM participants: Migraine occurring on ≥8 days and headache occurring on >14 days • For EM participants: Migraine occurring on ≥4 days and headache occurring on ≤14 days • Participant has documented evidence of treatment failure (must be supported by medical record or by physician's confirmation specific to each treatment) in the past 10 years of 2-4 different migraine preventive medications. • Participant has a history of either previous or active use of triptans for migraine.	• History of acute or active temporomandibular disorder. • History or diagnosis of chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, or unusual migraine subtypes such as hemiplegic migraine, ophthalmoplegic migraine, and migraine with neurological accompaniments that are not typical of migraine aura. • Participant has a psychiatric condition • Participants with a lifetime history of psychosis and/or mania in the last 5 years prior to the screening visit are excluded. • History of clinically significant cardiovascular disease or vascular ischaemia or thromboembolic events.
Author, year: Ashina 2023 [33] **Country:** United state	**Study design:** A 52-week, multicenter, randomized, open-label trial **Date:** September 2016 to April 2018	• Has at least a 1-year history of migraine with or without aura • Age of the patient at the time of migraine onset < 50 years • History of 4 to 14 migraine days (migraine/probable migraine headache days) per month on average in the 3 months prior to Visit 1 in the Investigator's judgment • Demonstrated compliance with e-diary •	• Has a history of migraine accompanied by diplopia or decreased level of consciousness and retinal migraine • Has a current diagnosis of chronic migraine, new persistent daily headache, trigeminal autonomic cephalgia (eg, cluster headache), or painful cranial neuropathy • Difficulty distinguishing migraine headache from other headaches • Has a history of malignancy in the prior 5 years, except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer • Has a history of gastric or small intestinal surgery, or has a disease that causes malabsorption

			• Has a history of hepatitis within previous 6 months • Usage of opioids or barbiturates > 2 days/month, triptans or ergots ≥ 10 days/month, or simple analgesics (eg, aspirin, non-steroidal anti-inflammatory drugs [NSAIDs], acetaminophen) ≥ 15 days/month in the 3 months prior to Visit 1 • Pregnant or nursing females
Author, year: Takeshima 2021 [34] **Country:** Japan	**Study design:** Phase 3, randomized, double-blind, placebo-controlled **Date:** April 2019 to November 2020	• Japanese patients ≥20 to ≤65 years of age • History of migraine (with or without aura) for ≥12 months before screening, according to International Classification of Headache Disorders, 3rd edition (ICHD-3). • During the 4-week baseline phase, patients had to have the same migraine type as assessed by their handheld electronic diary (eDiary) during screening and had to have demonstrated ≥80% compliance with their eDiary	• Subjects greater than 50 years of age at migraine onset. • History of cluster headache or hemiplegic migraine headache. • Unable to differentiate migraine from other headaches. • Migraine with continuous pain, in which the subject does not experience any pain-free periods (of any duration) during the 1 month before the screening period. • Malignancy, except non-melanoma skin cancers, cervical or breast ductal carcinoma in situ within the last 5 years.
Author, year: Shengyuan Yu 2022 [35] **Country:** Mainland China, India, the Republic of Korea, Malaysia, the Philippines, Singapore, Taiwan, Tailand, and Vietnam	**Study design:** phase 3, randomised, double-blind, placebo-controlled **Date:** August 2019 and August 2021	• Adults aged 18–65 years with a history of CM with or without aura for at least 12 months before screening as defned by the International Classifcation of Headache Disorders, 3rd edition (ICHD-3). • Patients with a history of≥15 headache days/month, of which≥8 headache days met criteria as migraine days during the baseline period, and who had demonstrated at least 80% compliance with the eDiary during the baseline period.	• Participants older than 50 years at migraine onset. • History of cluster or hemiplegic migraine headache; CM with continuous pain; unable to diferentiate migraine from other headaches; opioid and/or opioid-containing analgesic (for>4 days per month) or butalbital-containing analgesic (for>2 days per month) for any indication within one month before the start of or during the baseline period; • prior migraine preventive treatment failure in>3 medication categories (categories provided in Supplementary Table 2);

		• Concomitant therapies with possible migraine prophylactic efects taken for indications other than migraine must have been administered at a stable dose within the 3 months prior to the start of the baseline period and throughout the study.	• prior botulinum toxin A treatment in the head/ neck region within 4 months before the start of or during the baseline period, active chronic pain syndromes (such as fibromyalgia and chronic pelvic pain), or other medical conditions. • Pregnant or nursing (lactating) women, and women of childbearing potential

Appendix 4: Further results for adverse events (AEs)

Table 1: Arm level data on adverse events and treatment-related AEs (%)

Author	Year	Intervention	Participants	Any AEs	Treatment-related AEs
Ashina [33]	2023	Atogepant 60 mg	543	67	18
Ashina [33]	2023	Standard care	196	78.6	36.2
Shengyuan Yu [35]	2022	Erenumab 70mg	279	45.5	12.9
Shengyuan Yu [35]	2022	Placebo	278	47.5	13.3
HO [31]	2022	Galcanezumab 120 mg	261	49.8	
HO [31]	2022	Placebo	259	43.2	
Ashina [32]	2022	Eptinezumab 100 mg	299	42	3
Ashina [32]	2022	Eptinezumab 300 mg	294	41	1
Ashina [32]	2022	Placebo	298	40	3
Takeshima [34]	2021	Erenumab 70mg	130	65.4	
Takeshima [34]	2021	Placebo	131	58.8	
Sakai [9]	2021	Fremanezumab-M	188	61.7	29.3
Sakai [9]	2021	Fremanezumab-Q	190	61.1	32.1
Sakai [9]	2021	Placebo	191	61.8	28.3
Ailani [12]	2021	Atogepant 10 mg	221	52.9	23.1
Ailani [12]	2021	Atogepant 30 mg	228	52.2	14.9
Ailani [12]	2021	Atogepant 60 mg	231	53.7	19.5
Ailani [12]	2021	Placebo	222	56.8	9
Sakai [21]	2021	Fremanezumab-M	121	57	26.4
Sakai [21]	2021	Fremanezumab-Q	118	62.7	31.4
Sakai [21]	2021	Placebo	117	65.8	23.9
Reuter [25]	2021	Erenumab 140 mg	388		55.4
Reuter [25]	2021	Topiramate 100 mg	388		81.2
Wang [26]	2021	Erenumab 70 mg	335	34.9	11.3
Wang [26]	2021	Erenumab 140 mg	224	34.4	10.7
Wang [26]	2021	Placebo	335	36.7	9.6
Winner [30]	2021	Eptinezumab 100 mg	238	10.9	
Winner [30]	2021	Placebo	242	10.3	
Lipton [11]	2020	Eptinezumab 100 mg	356	43.5	
Lipton [11]	2020	Eptinezumab 300 mg	350	52	
Lipton [11]	2020	Placebo	366	46.7	
Ashina [14]	2020	Eptinezumab 100 mg	223	63.2	
Ashina [14]	2020	Eptinezumab 300 mg	224	57.6	
Ashina [14]	2020	Placebo	222	59.5	
Sakai [20]	2020	Galcanezumab 120 mg	115	85.2	
Sakai [20]	2020	Galcanezumab 240 mg	114	81.6	
Sakai [20]	2020	Placebo	230	64.8	
Mulleners [28]	2020	Galcanezumab 120 mg	232	51	15

Mulleners [28]	2020	Placebo	230	53	16
Croop [29]	2020	Rimegepant 75 mg	370	36	11
Croop [29]	2020	Placebo	371	36	9
Dodick [3]	2019	Eptinezumab 100 mg	122	57.5	19.8
Dodick [3]	2019	Eptinezumab 300 mg	121	63.6	17.4
Dodick [3]	2019	Placebo	121	56.2	14
Ferrari [8]	2019	Fremanezumab-Q	276	55	21
Ferrari [8]	2019	Fremanezumab-M	285	45	19
Ferrari [8]	2019	Placebo	277	48	20
Rothrock [1]	2019	BTA 150 U	220	48	17
Rothrock [1]	2019	Topiramate 100 mg	142	79	70
Detke [4]	2018	Galcanezumab 120 mg	273	58	
Detke [4]	2018	Galcanezumab 240 mg	282	57	
Detke [4]	2018	Placebo	558	50	
Dodick [16]	2018	Erenumab 70 mg	283	48.1	
Dodick [16]	2018	Placebo	289	54.7	
Dodick [18]	2018	Fremanezumab-M	290	66.2	47.6
Dodick [18]	2018	Fremanezumab-Q	291	66.3	47.1
Dodick [18]	2018	Placebo	293	58.4	37.2
Stauffer [22]	2018	Galcanezumab 120 mg	206	65.5	
Stauffer [22]	2018	Galcanezumab 240 mg	220	67.7	
Stauffer [22]	2018	Placebo	432	60.4	
Vladimir [23]	2018	Galcanezumab 120 mg	226	65	
Vladimir [23]	2018	Galcanezumab 240 mg	228	71.5	
Vladimir [23]	2018	Placebo	461	62.3	
Reuter [24]	2018	Erenumab 140 mg	119	55	
Reuter [24]	2018	Placebo	124	54	
Silberstein [10]	2017	Fremanezumab-Q	376	70	49
Silberstein [10]	2017	Fremanezumab-M	379	71	51
Silberstein [10]	2017	Placebo	375	64	42
Tepper [2]	2017	Erenumab 70 mg	190	44	
Tepper [2]	2017	Erenumab 140 mg	188	47	
Tepper [2]	2017	Placebo	282	39	
Goadsby [19]	2017	Erenumab 70 mg	314	57.3	
Goadsby [19]	2017	Erenumab 140 mg	319	55.5	
Goadsby [19]	2017	Placebo	319	63	
Hong Sun [13]	2016	Erenumab 7 mg	108	50	
Hong Sun [13]	2016	Erenumab 21 mg	105	51	
Hong Sun [13]	2016	Erenumab 70 mg	106	54	
Hong Sun [13]	2016	Placebo	153	54	
Dodick [15]	2014	Galcanezumab 150 mg	107	72	
Dodick [15]	2014	Placebo	110	67	

Dodick [5]	2010	BTA 150 U	687	62.4	29.4
Dodick [5]	2010	Placebo	692	51.7	12.7
Dodick [17]	2009	Topiramate 100 mg	177	85.9	68.4
Dodick [17]	2009	Amitriptyline 100 mg	169	88.8	75.7

Table 2: Details for investigations of system organ class (SOC) (%)

Author(s)	Year of Publication	Intervention	Participants	Weight increase	Weight decrease	Increased blood creatine kinase	Blood creatinine phosphokinase	INR increased	Alanine aminotransferase ≥3x ULN	Aspartate aminotransferase ≥3x ULN	Total bilirubin ≥2x ULN
Ashina [33]	2023	Atogepant 60 mg	543		2.6				2	2.4	
Ashina [33]	2023	Oral standard care	196	5.6							
HO [31]	2022	Galcanezumab 120 mg	261				1.5			1.9	
HO [31]	2022	Placebo	259				0			0	
Ashina [32]	2022	Eptinezumab 100 mg	299				1.5				
Ashina [32]	2022	Eptinezumab 300 mg	294				0				
Ashina [32]	2022	Placebo	298								
Ailani [12]	2021	Atogepant 10 mg	221			2.3			1.4		
Ailani [12]	2021	Atogepant 30 mg	228			0.9			0.9		
Ailani [12]	2021	Atogepant 60 mg	231			3			0.9		
Ailani [12]	2021	Placebo	222			0.9			2.7		
Reuter [25]	2021	Erenumab	388		0.8						
Reuter [25]	2021	Topiramate	388		5.7						
Ferrari [8]	2019	Fremanezumab-Q	276					1			
Ferrari [8]	2019	Fremanezumab-M	285					0.5			
Ferrari [8]	2019	Placebo	277					0.5			
Stauffer [22]	2018	Galcanezumab 120 mg	206	1.9							
Stauffer [22]	2018	Galcanezumab 240 mg	220	0.9							
Stauffer [22]	2018	Placebo	432	1.4							
Silberstein [10]	2017	Fremanezumab-Q	376						0.26	0.26	0.6
Silberstein [10]	2017	Fremanezumab-M	379						0.26	0.26	0
Silberstein [10]	2017	Placebo	375						0	0	0

Table 1: Details for injury, poisoning and procedural complications of system organ class (SOC) (%)

First Author	Year of Publication	Intervention	Participants	Ecchymosis	Injury	Contusion
Stauffer [22]	2018	Galcanezumab 120mg	206			2.4
Ashina [33]	2023	Oral standard care	196			3.1
Stauffer [22]	2018	Placebo	432			1.2

Table 4: Details for metabolism and nutrition disorders of system organ class (SOC) (%)

Author	Year of Publication	Intervention	Participants	Anorexia	Decreased appetite
Reuter [25]	2021	Erenumab 140 mg	388		2.1
Reuter [25]	2021	Topiramate 100 mg	388		9

Rothrock [1]	2019	BTA 150 U	220		0
Rothrock [1]	2019	Topiramate 100 mg	142		11

Table 5: Details for reproductive system and breast disorders of system organ class (SOC) (%)

Author(s)	Year of Publication	Intervention	Participants	Menstrual irregularity	Dysmenorrhea
Stauffer [22]	2018	Galcanezumab 120 mg	206		0.6
Stauffer [22]	2018	Galcanezumab 240 mg	220		2.2
Stauffer [22]	2018	Placebo	432		0.6

Table 6: Details for skin and subcutaneous of system organ class (SOC) (%)

Author(s)	Year of Publication	Intervention	Participants	Eczema	Urticaria	Pruritus	Hair fall	Skin tightness	Rash	Alopecia	Sweat discoloration
HO [31]	2022	Galcanezumab 120 mg	261			1.5					
HO [31]	2022	Placebo	259			0.8					
Sakai [21]	2021	Fremanezumab-M	121	2.5							
Sakai [21]	2021	Fremanezumab-Q	118	0.8							
Sakai [21]	2021	Placebo	117	0							
Saka i [20]	2020	Galcanezumab 120 mg	115		1.7						
Sakai [20]	2020	Galcanezumab 240 mg	114		6.1						
Sakai [20]	2020	Placebo	230		0						
Ferrari [8]	2019	Fremanezumab-Q	276						0.5	0.5	
Ferrari [8]	2019	Fremanezumab-M	285						1	0.5	
Ferrari [8]	2019	Placebo	277						0.5	0.5	
Stauffer [22]	2018	Galcanezumab 120 mg	206			1					
Stauffer [22]	2018	Galcanezumab 240 mg	220			2.7					
Stauffer [22]	2018	Placebo	432			0.2					
Dodick [15]	2014	Galcanezumab 150 mg	107						5		
Dodick [15]	2014	Placebo	110						0		

Fremanezumab-Q, Fremanezumab quarterly; Fremanezumab-M, Fremanezumab monthly

Table 7: Details for eye disorders of system organ class (SOC) (%)

Author	Year of Publication	Intervention	Participants	Belpharotosis	Abnormal vision	Visual disturbance	Vision blurred	Eyelid edema
Rothrock [1]	2019	BTA 150U	220				3	
Rothrock [1]	2019	Topiramate 100 mg	142				8	
Dodick [15]	2014	Galcanezumab 150 mg	107			3		
Dodick [15]	2014	Placebo	110			2		

Table 8: Details for renal and urinary disorders of system organ class (SOC) (%)

Author	Year of Publication	Intervention	Participants	Urinary retention	Protein urine present
HO [31]	2022	Galcanezumab 120 mg	261		2.3
HO [31]	2022	Placebo	259		1.5

Table 9: Details for vascular disorders and Cardiac Disorders of system organ class (SOC) (%)

Author	Year	Intervention	Vascular disorders			Cardiac Disorders
			Participants	Hypotension	Hypertension	Tachycardia
Ashina [33]	2023	Atogepant 60 mg	543		2.6	
Ferrari [8]	2019	Fremanezumab quarterly	276		1	
Ferrari [8]	2019	Fremanezumab monthly	285		0.5	
Ferrari [8]	2019	Placebo	277		0.5	
Goadsby [19]	2017	Erenumab 70 mg	314		1.6	
Goadsby [19]	2017	Erenumab 140 mg	319		0	
Goadsby [19]	2017	Placebo	319		2.5	
Dodick [15]	2014	Galcanezumab 150 mg	107		5	
Dodick [15]	2014	Placebo	110		0	

Table 10: Details for respiratory, thoracic and mediastinal disorders of system organ class (SOC)(%)

Author	Year of Publication	Intervention	Participants	Nasal congestion	Bronchitis	Rhinitis	Sinus congestion	Cough	Asthma
Sakai [9]	2021	Fremanezumab-M	188						1.1
Sakai [9]	2021	Fremanezumab-Q	190						2.1
Sakai [9]	2021	Placebo	191						0
Ailani [12]	2021	Atogepant 10 mg	221				0.5		
Ailani [12]	2021	Atogepant 30 mg	228				0.9		
Ailani [12]	2021	Atogepant 60 mg	231				1.7		
Ailani [12]	2021	placebo	222				2.3		
Ashina [14]	2020	Eptinezumab 100 mg	223		2.7			3.6	
Ashina [14]	2020	Eptinezumab 300 mg	224		3.1			2.7	
Ashina [14]	2020	Placebo	222		3.6			3.2	
Mulleners [28]	2020	Galcanezumab 120 mg	232		1				
Mulleners [28]	2020	Placebo	230		2				
Dodick [3]	2019	Eptinezumab 100 mg	122		3.3				
Dodick [3]	2019	Eptinezumab 300 mg	121		3.3				
Dodick [3]	2019	Placebo	121		7.4				
Dodick [18]	2018	Fremanezumab-M	290		21				
Dodick [18]	2018	Fremanezumab-Q	291		1.4				
Dodick [18]	2018	Placebo	293		1				
Stauffer [22]	2018	Galcanezumab 120 mg	206	0.5	1.5			1.9	
Stauffer [22]	2018	Galcanezumab 240 mg	220	2.3	3.2			2.7	
Stauffer [22]	2018	Placebo	432	0.9	1.4			1.6	
Hong Sun [13]	2016	Erenumab 7 mg	108					2	
Hong Sun [13]	2016	Erenumab 21 mg	105					1	
Hong Sun [13]	2016	Erenumab 70 mg	106					0	
Hong Sun [13]	2016	Placebo	153					2	
Dodick [17]	2009	Topiramate 100 mg	177					5.1	
Dodick [17]	2009	Amitriptyline 100 mg	169					4.1	

Fremanezumab-Q, Fremanezumab quarterly; Fremanezumab-M, Fremanezumab monthly

Table 11: Details for gastrointestinal disorders of system organ class (SOC) (%)

Author	Year of Publication	Intervention	Participants	Abdominal pain	Oropharyngeal pain	Abdominal discomfort	Diarrhoea	Flatulence	Dry mouth	Oropharyngeal pain	Toothache	Upper abdominal pain	Dyspepsia	Nausea	Dry mucous membrane	Constipation	Vomiting	Gastrointestinal symptoms	Vertigo	Giddiness
Ashina [33]	2023	Oral standard care	196				3.1		4.1				6.1			3.1				
HO [31]	2022	Galcanezumab 120 mg	261			1.9	1.5													
HO [31]	2022	Placebo	259			0.8	2.3													
Ashina [32]	2022	Eptinezumab 100	299				0					2		1						
Ashina [32]	2022	Eptinezumab 300 mg	294				2					1		2						
Ashina [32]	2022	Placebo	298				2					1		1						
Takeshima [34]	2021	Erenumab 70 mg	130				3.8									4.6				
Takeshima [34]	2021	Placebo	131				0.8									0.8				
Shengyuan Yu [35]	2022	Erenumab 70 mg	279													8.6				
Shengyuan Yu [35]	2022	Placebo	278													3.2				
Sakai [9]	2021	Fremanezumab-M	188				1.6							1.1						
Sakai [9]	2021	Fremanezumab-Q	190				2.1							2.6						
Sakai [9]	2021	Placebo	191				0							1						
Ailani [12]	2021	Atogepant 10 mg	221											5		7.7				
Ailani [12]	2021	Atogepant 30 mg	228											4.4		7				
Ailani [12]	2021	Atogepant 60 mg	231											6.1		6.9				
Ailani [12]	2021	Placebo	222											1.8		0.5				
Sakai [21]	2021	Fremanezumab-M	121				0					0.8		0.8						
Sakai [21]	2021	Fremanezumab-Q	118				2.5					2.5		0						
Sakai [21]	2021	Placebo	117				0					0		2.6						
Reuter [25]	2021	Erenumab 140mg	388				1.8		2.1			2.8	1.5	6.7		11.3			4.4	
Reuter [25]	2021	Topiramate	388				4.1		4.6			2.6	2.3	6.7		3.1			5.9	
Wang [26]	2021	Erenumab 70 mg	335													5.7				

Wang [26]	2021	Erenumab 140 mg	224													5.4				
Wang [26]	2021	Placebo	335													1.5				
Winner [30]	2021	Eptinezumab 100mg	238											0						
Winner [30]	2021	Placebo	242											0.8						
Lipton [11]	2020	Eptinezumab 100 mg	356											1.7						
Lipton [11]	2020	Eptinezumab 300 mg	350											3.4						
Lipton [11]	2020	Placebo	366											1.9						
Ashina [14]	2020	Eptinezumab 100 mg	223				1.3							2.2						
Ashina [14]	2020	Eptinezumab 300 mg	224				3.6							2.2						
Ashina [14]	2020	Placebo	222				1.4							3.6						
Mulleners [28]	2020	Galcanezumab 120 mg	232		1					1				2		2			2	
Mulleners [28]	2020	Placebo	230		2					2				2		2			0.004	
Croop [29]	2020	Rimegepant	370											3						
Croop [29]	2020	Placebo	371											1						
Dodick [3]	2019	Eptinezumab 100 mg	122											7.4						
Dodick [3]	2019	Eptinezumab 300 mg	121											6.6						
Dodick [3]	2019	Placebo	121											7.4						
Ferrari [8]	2019	Fremanezumab-Q	276				3					1		1		3				
Ferrari [8]	2019	Fremanezumab-M	285				0.5					0.5		0.5		0.5				
Ferrari [8]	2019	Placebo	277				1					0		2		0.5				
Rothrock [1]	2019	BTA	220											0.5						
Rothrock [1]	2019	Topiramate	142											13						
Detke [4]	2018	Galcanezumab 120 mg	273	2	1		1			1										
Detke [4]	2018	Galcanezumab 240 mg	282	1	2		2			2										
Detke [4]	2018	Placebo	558	2	1		1			1										
Dodick [16]	2018	Erenumab 70 mg	283											2.5		1.4				
Dodick [16]	2018	Placebo	289											4.5		2.1				
Dodick [18]	2018	Fremanezumab-M	290											1.4						
Dodick [18]	2018	Fremanezumab-Q	291											2.4						
Dodick [18]	2018	Placebo	293											1.7						
Stauffer [22]	2018	Galcanezumab 120 mg	206		1.9					1.9				2.4					1	

Stauffer [22]	2018	Galcanezumab 240 mg	220		1.4					1.4				3.6					1.8	
Stauffer [22]	2018	Placebo	432		0.7					0.7				3.5					0.5	
Vladimir [23]	2018	Galcanezumab 120 mg	226				3.1													
Vladimir [23]	2018	Galcanezumab 240 mg	228				1.3													
Vladimir [23]	2018	Placebo	461				2.4													
Silberstein [10]	2017	Fremanezumab-Q	376											1						
Silberstein [10]	2017	Fremanezumab-M	379											2						
Silberstein [10]	2017	Placebo	375											3						
Tepper [2]	2017	Erenumab 70 mg	190											2		0				
Tepper [2]	2017	Erenumab 140 mg	188											3		4				
Tepper [2]	2017	Placebo	282											2		0.5				
Goadsby [19]	2017	Erenumab 70 mg	314											2.2		1.6				
Goadsby [19]	2017	Erenumab 140 mg	319											1.9		3.4				
Goadsby [19]	2017	Placebo	319											1.9		1.3				
Hong Sun [13]	2016	Erenumab 7 mg	108				0							3						
Hong Sun [13]	2016	Erenumab 21 mg	105				1							1						
Hong Sun [13]	2016	Erenumab 70 mg	106				1							3						
Hong Sun [13]	2016	Placebo	153				3							1						
Dodick [15]	2014	Galcanezumab 150 mg	107	6							4			4						
Dodick [15]	2014	Placebo	110	3							1			9						
Dodick [17]	2009	Topiramate 100mg	177						6.8				5.1	10.2		3.4				

Dodick [17]	2009	Amitriptyline 100mg	169						35.5				8.3	7.1		8.3				

Table 12: Details for psychiatric disorders of system organ class (SOC) (%)

Author	Year of Publication	Intervention	Participants	Anxiety	Agitation	Sleep disorder	Nervousness	Insomnia	Mood swings	Irritability	Confusion	Depressed mood	Depression
Ashina [33]	2023	Atogepant 60 mg	543	2.9									
Ashina [33]	2023	Oral standard care	196	5.6				3.6					
Reuter [25]	2021	Erenumab 140 mg	388			4.1		1.5	2.1	1.3		0.3	1.5
Reuter [25]	2021	Topiramate 100 mg	388			1.5		2.6	4.1	4.6		3.6	4.1
Mulleners [28]	2020	Galcanezumab 120 mg	232					2					
Mulleners [28]	2020	Placebo	230					0					
Ferrari [8]	2019	Fremanezumab-quarterly	276	1				2					
Ferrari [8]	2019	Fremanezumab-monthly	285	0.5				2					
Ferrari [8]	2019	Placebo	277	0				0.5					
Rothrock [1]	2019	BTA 155U	220										2
Rothrock [1]	2019	Topiramate 100 mg	142										6
Lipton [11]	2011	Topiramate 100mg	176								5.7		
Lipton [11]	2011	Placebo	185								1.6		

Table 13: Details for musculoskeletal and connective tissue disorders of system organ class (SOC) (%)

Author	Year of Publication	Intervention	Participants	Muscular weakness	Muscle spasms	Muscle tightness	Myalgia	Musculoskel etal stiffness	Back pain	Musculoskel etal pain	Arthralgia	Neck pain	Arm pain
Ashina [33]	2023	Atogepant 60 mg	543			2			2.4		2		
Ashina [33]	2023	Oral standard care	196						2.6				
Ashina [32]	2022	Eptinezumab 100	299						2		2		
Ashina [32]	2022	Eptinezumab 300 mg	294						1		1		
Ashina [32]	2022	Placebo	298						1		0		
Takeshima [34]	2021	Erenumab 70 mg	130					3.8	5.4				
Takeshima [34]	2021	Placebo	131					0.8	4,6				
Sakai [9]	2021	Fremanezumab-M	188						2.7				
Sakai [9]	2021	Fremanezumab-Q	190						0.5				
Sakai [9]	2021	Placebo	191						0.5				
Sakai [21]	2021	Fremanezumab-M	121							0			
Sakai [21]	2021	Fremanezumab-Q	118							2.5			
Sakai [21]	2021	Placebo	117							0			
Winner [30]	2021	Eptinezumab 100 mg	238						0				
Winner [30]	2021	Placebo	242						0.8				
Ashina [14]	2020	Eptinezumab 100 mg	223						3.1				
Ashina [14]	2020	Eptinezumab 300 mg	224						1.3				
Ashina [14]	2020	Placebo	222						3.2				

Mulleners [28]	2020	Galcanezumab 120 mg	232						3				
Mulleners [28]	2020	Placebo	230						2				
Ferrari [8]	2019	Fremanezumab-Q	276						2		0.5	0.5	
Ferrari [8]	2019	Fremanezumab-M	285						0.5		0.5	1	
Ferrari [8]	2019	Placebo	277						2		1	0	
Rothrock [1]	2019	BTA 155 U	220									4	
Rothrock [1]	2019	Topiramate 100 mg	142									2	
Dodick [5]	2010	BTA 155U	687	5.5			2.6	2.3		2.2		6.7	
Dodick [5]	2010	Placebo	692	0.3			0.3	0.7		0.7		2.2	
Detke [4]	2018	Galcanezumab 120 mg	273						3		0	3	
Detke [4]	2018	Galcanezumab 240 mg	282						1		2	0	
Detke [4]	2018	Placebo	558						3		1	1	
Stauffer [22]	2018	Galcanezumab 120 mg	206						2.4			1.5	
Stauffer [22]	2018	Galcanezumab 240 mg	220						3.2			1.8	
Stauffer [22]	2018	Placebo	432						1.4			0.9	
Reuter [24]	2018	Erenumab 140 mg	119						4			3	
Reuter [24]	2018	Placebo	124						2			0	
Tepper [2]	2017	Erenumab 70 mg	190		<1								
Tepper [2]	2017	Erenumab 140 mg	188		4								
Tepper [2]	2017	Placebo	282		1								
Goadsby [19]	2017	Erenumab 70 mg	314						1.9		2.2		
Goadsby [19]	2017	Erenumab 140 mg	319						1.9		2.2		
Goadsby [19]	2017	Placebo	319						2.2		1.9		
Hong Sun [13]	2016	Erenumab 70 mg	108			0			3		1		

Hong Sun [13]	2016	Erenumab 21 mg	105			0					0		
Hong Sun [13]	2016	Erenumab 70 mg	106			0					1		
Hong Sun [13]	2016	Placebo	153			2					3		
Dodick [15]	2014	Galcanezumab 150 mg	107						7		6	4	
Dodick [15]	2014	Placebo	110						7		6	2	

Fremanezumab-Q, Fremanezumab quarterly; Fremanezumab-M, Fremanezumab monthly

Table 14: Details for nervous system disorders of system organ class (SOC) (%)

Author	Year	Intervention	Participants	Neck rigidity	Dysesthesia	Paraesthesia	Hypertonia	Hypoesthesia	Difficulty with memory	Difficulty with concentration	Taste perversion	Migraine	Dizziness	Aphasia	Dysgeusia	Cognitive disorder	Headache	Somnolence	Drowsiness	Facial paralysis
Ashina [33]	2023	Atogepant 60 mg	543										3.1							
Ashina [33]	2023	Oral standard care	196									3.1	11.2					4.1		
HO [31]	2022	Galcanezumab 120 mg	261										3.4							
HO [31]	2022	Placebo	259										2.3							
Ashina [32]	2022	Eptinezumab 100	299										1							
Ashina [32]	2022	Eptinezumab 300 mg	294										1							
Ashina [32]	2022	Placebo	298										2							
Shengyuan Yu [35]	2022	Erenumab 70 mg	298										1.8							
Shengyuan Yu [35]	2022	Placebo	297										4.3							
Ailani [12]	2021	Atogepant 10 mg	221															3.2		
Ailani [12]	2021	Atogepant 30 mg	228															1.8		
Ailani [12]	2021	Atogepant 60 mg	231															1.7		
Ailani [12]	2021	Placebo	222															0.9		
Sakai [21]	2021	Fremanezumab-M	121									0	0				1.7			
Sakai [21]	2021	Fremanezumab-Q	118									0	0.8				1.7			

Sakai [21]	2021	Placebo	117									2.6	2.6				3.4			
Reuter [25]	2021	Erenumab 140 mg	388		0.5	4.4		0.5	0.3	4.6	0		5.2	0.5	0.8		0.5			
Reuter [25]	2021	Topiramate 100 mg	388		2.1	39.9		3.4	2.6	16.2	6.2		13.1	2.8	5.7		2.1			
Wang [26]	2021	Erenumab 70 mg	335										0.9							
Wang [26]	2021	Erenumab 140 mg	224										3.1							
Wang [26]	2021	Placebo	335										1.8							
Lipton [11]	2020	Eptinezumab 100 mg	356									1.7								
Lipton [11]	2020	Eptinezumab 300 mg	350									2.3								
Lipton [11]	2020	Placebo	366									4.4								
na [14]	2020	Eptinezumab 100 mg	223										4.5							
Ashina [14]	2020	Eptinezumab 300 mg	224										1.8							
Ashina [14]	2020	Placebo	222										3.6							
Mulleners [28]	2020	Galcanezumab 120 mg	232									2								
Mulleners [28]	2020	Placebo	230									0								
Dodick [3]	2019	Eptinezumab 100 mg	122									5.7	9.8							
Dodick [3]	2019	Eptinezumab 300 mg	121									0.8	1.7							
Dodick [3]	2019	Placebo	121									1.7	7.4							
Ferrari [8]	2019	Fremanezumab-Q	276									0.5	2							
Ferrari [8]	2019	Fremanezumab-M	285									1	1							
Ferrari [8]	2019	Placebo	277									3	1							
Rothrock [1]	2019	BTA 155 U	220			0.5				0		3	3			5				
Rothrock [1]	2019	Topiramate 100 mg	142			31				8		2	13			13				
Dodick [5]	2010	BTA 155U	687														2.9			
Dodick [5]	2010	Placebo	692														1.6			
Detke [4]	2018	Galcanezumab 120 mg	273									2								
Detke [4]	2018	Galcanezumab 240 mg	282									1								
Detke [4]	2018	Placebo	558									1								
Dodick [16]	2018	Erenumab 70 mg	283									2.1								
Dodick [16]	2018	Placebo	289									2.8								
Stauffer [22]	2018	Galcanezumab 120 mg	206									1	2.6							
Stauffer [22]	2018	Galcanezumab 240 mg	220									2.3	2.3							
Stauffer [22]	2018	Placebo	432									0.9	2.6							

Vladimir [23]	2018	Galcanezumab 120 mg	226										3.5							
Vladimir [23]	2018	Galcanezumab 240 mg	228										3.1							
Vladimir [23]	2018	Placebo	461										2.2							
Reuter [24]	2018	Erenumab 140 mg	119										3							
Reuter [24]	2018	Placebo	124										2							
Silberstein [10]	2017	Fremanezumab-Q	376										2							
Silberstein [10]	2017	Fremanezumab-M	379										3							
Silberstein [10]	2017	Placebo	375										1							
Tepper [2]	2017	Erenumab 70 mg	190									2								
Tepper [2]	2017	Erenumab 140 mg	188									3								
Tepper [2]	2017	Placebo	282									1								
Goadsby [19]	2017	Erenumab 70 mg	314									1.3								
Goadsby [19]	2017	Erenumab 140 mg	319									0.9								
Goadsby [19]	2017	Placebo	319									3.1								
Hong Sun [13]	2016	Erenumab 7 mg	108									1					4			
Hong Sun [13]	2016	Erenumab 21 mg	105									3					1			
Hong Sun [13]	2016	Erenumab 70 mg	106									3					3			
Hong Sun [13]	2016	Placebo	153									1					1			
Dodick [15]	2014	Galcanezumab 150 mg	107										5							
Dodick [15]	2014	Placebo	110										3							
Dodick [17]	2009	Topiramate 100mg	177			29.9		10.7		6.8	5.6		8.5				5.1	11.9		
Dodick [17]	2009	Amitriptyline 100mg	169			4.7		3.6		3	3.6		10.7				0	17.8		

Fremanezumab-Q, Fremanezumab quarterly; Fremanezumab-M, Fremanezumab monthly

Table 15: Details for infection and infestation of system organ class (SOC) (%)

Author	Year of Publication	Intervention	Participants	Infection	Nasopharyngitis	Sinus infection	Pharyngitis	Sinusitis	Upper respiratory tract infection	Urinary tract infection	Cystitis	Influenza	Pyrexia	COVID-19	Viral infection	Viral gastroenteritis	Flu syndrome	Gastroenteritis
Ashina [33]	2023	Atogepant 60 mg	543		4.4			2.8				3.3						2.4

Ashina [33]	2023	Oral standard care	196		5.1			3.1	12.2	4.6		2.6						
HO [31]	2022	Galcanezumab 120 mg	261		2.7				5.4				2.3					
HO [31]	2022	Placebo	259		3.5				5				1.2					
Ashina [32]	2022	Eptinezumab 100	299		2					0.33				7				
Ashina [32]	2022	Eptinezumab 300 mg	294		3					2				6				
Ashina [32]	2022	Placebo	298		1					1				5				
Takeshima [34]	2021	Erenumab 70 mg	130		26.9		3.8											
Takeshima [34]	2021	Placebo	131		28.2		0.8											
Shengyuan Yu [35]	2022	Erenumab 70 mg	298		3.6				5.4									
Shengyuan Yu [35]	2022	Placebo	297		1.8				7.2									
Sakai [9]	2021	Fremanezumab-M	188		16.6						0	2.1						
Sakai [9]	2021	Fremanezumab-Q	190		21.1						2.5	1.1						
Sakai [9]	2021	Placebo	191		18.8						1	1.6						
Ailani [12]	2021	Atogepant 10 mg	221		1.8			1.8	4.1	1.4		1.4						0.9
Ailani [12]	2021	Atogepant 30 mg	228		3.5			1.3	5.7	3.9		0.9						2.2
Ailani [12]	2021	Atogepant 60 mg	231		3.5			2.2	3.9	3.9		2.2						1.3
Aliani [12]	2021	Placebo	222		3.6			1.4	4.5	3.6		0.9						1.8
Sakai [21]	2021	Fremanezumab-M	121		14							5						
Sakai [21]	2021	Fremanezumab-Q	118		12.7							1.7						
Sakai [21]	2021	Placebo	117		13.7							0.9						
Wang [26]	2021	Erenumab 70 mg	335		0.6				2.7				3					
Wang [26]	2021	Erenumab 140 mg	224		3.6				1.8				2.2					

Wang [26]	2021	Placebo	335		2.4				2.1				4.5					
Winner [30]	2021	Eptinezumab 100 mg	238						0.8			0.8						
Winner [30]	2021	Placebo	242						0.8			0.8						
Lipton [11]	2020	Eptinezumab 100 mg	356		5.3			2	4.2	2.2								
Lipton [11]	2020	Eptinezumab 300 mg	350		9.4			2.6	5.4	3.4								
Lipton [11]	2020	Placebo	366		6			4.1	5.5	1.6								
Ashina [14]	2020	Eptinezumab 100 mg	223		7.6			2.7	9.9			1.8						
Ashina [14]	2020	Eptinezumab 300 mg	224		6.3			4.9	10.3			3.6						
Ashina [14]	2020	Placebo	222		5.4			6.3	7.2			2.3						
Sakai [20]	2020	Galcanezumab 120 mg	115									7.8						
Sakai [20]	2020	Galcanezumab 240 mg	114									0.9						
Sakai [20]	2020	Placebo	230									1.3						
Mulleners [28]	2020	Galcanezumab 120 mg	232		9			2	2	2		3						1
Mulleners [28]	2020	Placebo	230		7			2	2	1		5						2
Croop [29]	2020	Rimegepant 75 mg	370		4				2	2								
Croop [29]	2020	Placebo	371		2				3	2								
Dodick [3]	2019	Eptinezumab 100 mg	122		6.6			2.5	6.6									
Dodick [3]	2019	Eptinezumab 300 mg	121		7.4			6.6	10.7									
Dodick [3]	2019	Placebo	121		5			5	5									
Ferrari [8]	2019	Fremanezumab-Q	276		5				1	1		0.5						1
Ferrari [8]	2019	Fremanezumab-M	285		2				3	1		2						1
Ferrari [8]	2019	Placebo	277		4				1	2		0.5						3

Rothrock [1]	2019	BTA 155 U	220					6									
Rothrock [1]	2019	Topiramate 100 mg	142					7									
Detke [4]	2018	Galcanezumab 120 mg	273		6			1	3	2		2	2				
Detke [4]	2018	Galcanezumab 240 mg	282		3			3	3	1		1	0				
Detke [4]	2018	Placebo	558		5			1	2	1		1	2				
Dodick [16]	2018	Erenumab 70 mg	283		5.3			2.1	6.4			3.9					
Dodick [16]	2018	Placebo	289		5.9			2.1	4.8			3.5					
Dodick [18]	2018	Fremanezumab-M	290		3.8			1.4	5.5	2.4							
Dodick [18]	2018	Fremanezumab-Q	291		3.8			0.7	3.8	3.4							
Dodick [18]	2018	Placebo	293		3.1			2.7	5.1	1.4							
Stauffer [22]	2018	Galcanezumab 120 mg	206		7.8			4.6		3.9		2.4					
Stauffer [22]	2018	Galcanezumab 240 mg	220		2.7			3.6		5.9		1.8					
Stauffer [22]	2018	Placebo	432		6.3			3		3.5		1.2					
Vladimir [23]	2018	Galcanezumab 120 mg	226		8.4				5.8			1.3					
Vladimir [23]	2018	Galcanezumab 240 mg	228		7				5.3			4.4					
Vladimir [23]	2018	Placebo	461		8.9				3.5			3					
Reuter [24]	2018	Erenumab 140 mg	119		4				3								
Reuter [24]	2018	Placebo	124		10				0								
Silberstein [10]	2017	Fremanezumab-Q	376		5			3	5								

Silberstein [10]	2017	Fremanezumab-M	379		4			1	4								
Silberstein [10]	2017	Placebo	375		5			3	4								
Tepper [2]	2017	Erenumab 70 mg	190		3				3								
Tepper [2]	2017	Erenumab 140 mg	188		2				3								
Tepper [2]	2017	Placebo	282		6				1								
Goadsby [19]	2017	Erenumab 70 mg	314		9.9			2.2	6.7	1.6		1.3					
Goadsby [19]	2017	Erenumab 140 mg	319		11			3.4	4.7	2.2		2.5					
Goadsby [19]	2017	Placebo	319		10			2.2	5.6	2.2		1.9					
Hong Sun [13]	2016	Erenumab 7 mg	108		9				1			1					
Hong Sun [13]	2016	Erenumab 21 mg	105		5				2			4					
Hong Sun [13]	2016	Erenumab 70 mg	106		6				3			1					
Hong Sun [13]	2016	Placebo	153		8				2			3					
Dodick [15]	2014	Galcanezumab 150 mg	107		4			3	17						2		
Dodick [15]	2014	Placebo	110		7			5	9						4		

Fremanezumab-Q, Fremanezumab quarterly; Fremanezumab-M, Fremanezumab monthly

Table 16: Details for general disorders and site injection administration of system organ class (SOC) (%)

Author	Year	Intervention	Participants	Influenza-like illness	I-S pain	I-S reaction	I-S haemorrhage	Pain	Pain in extremity	I-S rash	I-S paraesthesia	I-S bruising	Infusion-S extravasation	I-S Discolouration	I-S discomfort	I-S induration	I-S warmth	I-S pruritus	I-S Oedema	I-S erythema	I-S swelling	Asthenia	Fatigue	Non-cardiac chest pain	I-S Hypersensitivity	I-S Haematoma
Ashina [33]	2023	Atogepant 60 mg	543																				2.6			
Ashina [33]	2023	Oral standard care	196																				6.1			
HO [31]	2022	GAL 120	261		7.3	3.8									2.3			5		1.9						
HO [31]	2022	PBO	259		6.2	0.4									0			0		0						
Ashina [32]	2022	EPT 100	299																				1			
Ashina [32]	2022	EPT 300	294																				2			
Ashina [32]	2022	PBO	298																				1			
Yu [35]	2022	ERE 70	298						1																	
Yu [35]	2022	PBO	297						0.4																	
Sakai [9]	2021	FRE-M	188		7.4	29.3										17.6		5.3		15.4						
Sakai [9]	2021	FRE-Q	190		12.6	26.8										12.1		1.6		12.1						
Sakai [9]	2021	PBO	191		8.9	25.1										12.6		2.6		11						
Ailani [12]	2021	ATO 10	221																				1.4			
Ailani [12]	2021	ATO 30	228																				3.1			
Ailani [12]	2021	ATO 60	231																				3.9			
Ailani [12]	2021	PBO	222																				1.8			
Sakai [21]	2021	FRE-M	121		9.1	25.6	0.8									14.9		5.8		15.7	3.3					

Sakai [21]	2021	FRE-Q	118		13.6	29.7	3.4									11.9		1.7		11.9	1.7					
Sakai [21]	2021	PBO	117		6	21.4	0.9									10.3		0		12.8	0					
Reuter [25]	2021	ERE 140	388																				9.8			
Reuter [25]	2021	TOP 100	388																				17.3			
Wang [26]	2021	ERE 70	335																	1.2						
Wang [26]	2021	ERE 140	224																	0.4						
Wang [26]	2021	PBO	335																	2.4						
Winner [30]	2021	EPT 100	238										0.8												2.1	
Winner [30]	2021	PBO	242										0.8												0	
Lipton [11]	2020	EPT 100	356																				2.2			
Lipton [11]	2020	EPT 300	350																				1.7			
Lipton [11]	2020	PBO	366																				1.9			
Ashina [14]	2020	EPT 100	223																				3.6			
Ashina [14]	2020	EPT 300	224																				3.6			
Ashina [14]	2020	PBO	222																				<1			
Sakai [20]	2020	GAL 120	115		6.1													8.7		14.8	10.4					
Sakai [20]	2020	GAL 240	114		7													20.2		27.2	10.5					
Sakai [20]	2020	PBO	230		1.3													0		2.2	1.3					
Mulleners [28]	2020	GAL 120	232		6	3					1	2				2		0	0	3	0					
Mulleners [28]	2020	PBO	230		2	0						0						1	1	3			2			0
Ferrari [8]	2019	FRE-Q	276		4				0.5	1	1	0.5				4	0.5	1		7		0.5	3			

Ferrari [8]	2019	FRE-M	285		3				1	1	1	2				5	1	2		6		1	3			
Ferrari [8]	2019	PBO	277		3				1	0.5	1	0.5				4	0	1		5		1	1			
Rothrock [1]	2019	BTA 155 U	220																				0.5			
Rothrock [1]	2019	TOP 100	142																				13			
Detke [4]	2018	GAL 120	273		6	3												0		1			2			
Detke [4]	2018	GAL 240	282		7	5												2		5			2			
Detke [4]	2018	PBO	558		4	2												0		1			2			
Dodick [16]	2018	ERE 70	283		6																		3.5			
Dodick [16]	2018	PBO	289		4.2																		2.1			
Dodick [18]	2018	FRE-M	290		30		1									24				17.9			0.7			
Dodick [18]	2018	FRE-Q	291		29.6		3.1									19				18.9			2.1			
Dodick [18]	2018	PBO	293		25.9		2									15				14			1.4			
Stauffer [22]	2018	GAL 120	206		16	3.4						1						4.4		4.9						
Stauffer [22]	2018	GAL 240	220		20.5	5.5						1.8						4.6		4.1						
Stauffer [22]	2018	PBO	432		17.4	0.9						1.4						0.2		2.6						
Vladimir [23]	2018	GAL 120	226		9.3	3.1												2.7		2.7	2.2		2.7			
Vladimir [23]	2018	GAL 240	228		8.8	7.9												3.1		3.1	0.4		2.2			
Vladimir [23]	2018	PBO	461		8.5	0												0		0.9	0		2.6			
Reuter [24]	2018	ERE 140	119		6															3			3			
Reuter [24]	2018	PBO	124		6															3			2			
Silberstein [10]	2017	FRE-Q	376		30		2									20				21						

Silberstein [10]	2017	FRE-M	379		26		2									24				20						
Silberstein [10]	2017	PBO	375		28		3									18				16						
Tepper [2]	2017	ERE 70	190		4																					
Tepper [2]	2017	ERE 140	188		4																					
Tepper [2]	2017	PBO	282		1																					
Goadsby [19]	2017	ERE 70	314		3.2																		1.9			
Goadsby [19]	2017	ERE 140	319		0.3																		2.2			
Goadsby [19]	2017	PBO	319		0.3																		2.5			
Hong Sun [13]	2016	ERE 7	108																				5			
Hong Sun [13]	2016	ERE 21	105																				2			
Hong Sun [13]	2016	ERE 70	106																				4			
Hong Sun [13]	2016	PBO	153																				2			
Dodick [15]	2014	GAL 150	107		17				4											5						
Dodick [15]	2014	PBO	110		6				5											0						

I-S; Injection Site, GAL 120, Galcanezumab 120 mg; GAL 240, Galcanezumab 240 mg; GAL 150, Galcanezumab 150 mg; PBO, Placebo; EPT 100, Eptinezumab 100 mg; EPT 300, Eptinezumab 300 mg; FRE-M, Fremanezumab monthly; FRE-Q, Fremanezumab quarterly; ATO 10, Atogepant 10 mg; ATO 30, Atogepant 30 mg; ATO 60, Atogepant 60 mg; ERE 140, Erenumab 140 mg; ERE 70, Erenumab 70 mg; ERE 7, Erenumab 7 mg; ERE 21, Erenumab 21 mg; TOP 100, Topiramate 100 mg;; AMI 100, Amitriptyline 100 mg; BTA 150, BTA 150 U; BTA 260, BTA 105 to 260 U.

Table 17: Any adverse events reported from 32 trials

Intervention	Dose	Frequency	Total participants	Participants with AEs (%)*
Erenumab [2, 19, 24-26]	140 mg	Monthly	1238	408 (33)
Rimegepant [29]	75 mg,	Once daily	370	133 (36)
Topiramate [1, 17, 25]	100 mg	Twice daily	707	264 (37)
Eptinezumab [3, 11, 14, 30, 32]	100 mg	Single dose on day 0	1238	517 (42)
Erenumab [2, 13, 16, 19, 26, 34, 35]	70 mg	Monthly	1637	786 (48)
Erenumab [13]	7 mg	Monthly	108	54 (50)
Erenumab [13]	21 mg	Monthly	105	54 (51)
Eptinezumab [3, 11, 14, 30, 32]	300 mg	Single dose on day 0	989	509 (51)
Placebo [2-5, 8-16, 18-24, 26, 28-32, 34, 35]	-	Matched with active treatments	7977	4040 (52)
Atogepant [12]	30 mg	Once daily	228	119 (52)
Atogepant [12]	10 mg	Once daily	221	117 (53)
*OnabotulinumtoxinA (*BTA) [1, 5]	150 U	Every 12 weeks	907	534 (59)
Galcanezumab [4] [4, 20, 22, 23, 28, 31]	120 mg	Monthly	1313	786 (60)
Fremanezumab [8-10, 18, 21]	Monthly (225 mg)	Monthly	1263	774 (61)
Atogepant [12, 33]	60 mg	Once daily	774	488 (63)
Fremanezumab [8-10, 18, 21]	Quarterly (675 mg)	Single dose on day 0	1251	798 (64)
Galcanezumab [4, 20, 22, 23, 28]	240 mg	Monthly	844	566 (67)
Galcanezumab [15]	150 mg	Every 2 weeks	107	77 (72)
Amitriptyline [17]	25 to 100 mg	Twice daily	169	150 (89)

*The treatments are listed in order of increasing AEs percentage.; Abbreviations; mg: milligram.

Table 18: Classification of AEs by SOC

System Organ Class (SOC)	Adverse Events (AEs)
Cardiac disorders	Acute myocardial infarction, atrial fibrillation, syncope
Ear and labyrinth disorders	Labyrinthitis, **sudden hearing loss,** vertigo, **vestibular neuronitis**
Eye disorders	Angle closure glaucoma, diplopia, **optic neuritis,** retinal detachment, rhegmatogenous retinal detachment
Gastrointestinal disorders	Abdominal pain, alcoholic pancreatitis, appendicitis, **diverticulitis,** esophagitis, **gastric ulcer haemorrhage,** gastritis, haemorrhoids, **intestinal haemorrhage,** irritable bowel syndrome, mechanical ileus, obstructive defaecation, pancreatitis, pancreatitis acute, parotitis, small intestinal obstruction, vomiting
General disorders and administration site conditions	**Abdominal adhesions,** asthenia, chest pain, **edema peripheral,** malaise, **nasal septum deviation,** non-cardiac chest pain, tooth impacted, **vocal cord thickening**
Hepatobiliary disorders	Cholecystitis, cholecystitis acute, cholelithiasis, **common bile duct stone,**
Immune system disorders	Anaphylactic reaction, anaphylactic shock, hypersensitivity
Infections and infestations	**Acute pyelonephritis**, bacterial pharyngitis, bacteriuria, **clostridium difficile colitis,** COVID-19 pneumonia, gastroenteritis, gastrointestinal infection, **infected dermal cyst**, influenza, kidney infection, nasopharyngitis, papilloma viral infection, parasitic gastroenteritis, pyelonephritis, pyrexia, sepsis, **tonsillitis,** urinary tract infection, viral gastroenteritis, viral infection
Injury	Accident, ankle fracture, brain contusion, **cartilage injury,** clavicle fracture, concussion, contusion, fall, foot fracture, hand fracture, humerus fracture, injury, ligament rupture, limb injury, lower limb fracture, **meniscus injury**, radius fracture, respiratory fume inhalation, rib fracture, road traffic accident, skin laceration, sternal fracture, tendon injury, **thoracic vertebral fracture**, traumatic orbital fracture, ulna fracture, wrist fracture
Investigations	Alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, weight decreased
Metabolism and nutrition disorders	Decreased appetite, hypokalaemia, hyponatremia
Musculoskeletal and connective tissue disorders	Arthralgia, back pain, Behçet's syndrome, **costochondritis,** flank pain, intervertebral disc protrusion, **osteoarthritis,** periarthritis**, post-traumatic neck syndrome**
Neoplasms benign malignant and unspecified (incl cysts and polyps)	Adenocarcinoma of the cervix, brain neoplasm, breast cancer, colon cancer, **fibroma, gallbladder polyp, ovarian cyst, polycystic ovaries**, rectal polyp**, ruptured ovarian cyst**, **uterine leiomyoma**, **breast neoplasm**, fibroadenoma of breast, malignant melanoma, neoplasm malignant, vulval cancer
Nervous system disorders	Cerebellar syndrome, **cerebral venous thrombosis**, cervical radiculopathy, **hypoaesthesia**, lumbar spinal stenosis, migraine, **migraine aggravated**, migraine with aura, nervous system disorders, **neuropathy**, seizure, speech disorder, transient ischemic attack
Neurological	**Spinal pain**

Poisoning and procedural complications	Overdose, **intentional overdose**
Pregnancy, puerperium and perinatal conditions	Pregnancy
Psychiatric disorders	Confusional state, depression, disorientation, major depression, **psychogenic seizure**, suicidal ideation, suicide attempt
Psychiatry	**Panic attack**
Renal and urinary disorders	Bladder dysfunction, **calculus urinary, nephrolithiasis, renal calculus**, renal colic, urinary incontinence
Reproductive system and breast disorders	Cervical dysplasia, dysmenorrhoea, **endometriosis**, menorrhagia, **menstrual disorder and vaginal haemorrhage**, metrorrhagia, ovarian disorder, **spontaneous abortion, threatened abortion**
Respiratory, thoracic and mediastinal	Asthma, **chronic obstructive pulmonary disease, chronic obstructive pulmonary disease (COPD) and apnoea related to COPD**, dyspnoea, epistaxis, pneumonia, **postsurgical laryngospasm with hypoxic brain injury**
Skin and subcutaneous tissue disorders	**Erythema nodosum**
Vascular disorders	**Hypertensive crisis**, orthostatic hypotension, **peripheral vascular disease**, **pulmonary embolism**

AEs in bold font were not found in the CTCAE Version 5.0, thus the best respective categories were chosen by clinical consensus.

Appendix 5: Further results for serious adverse events (SAEs)

Table 19: Arm level data on any serious adverse events and treatment-related serious adverse events (%)

Author, year	Interventions	Participants	Any SAEs	Treatment-related SAEs	Death
Ailani, 2021 [12]	Atogepant 10 mg	221	0.9	0.5	0
Ailani, 2021 [12]	Atogepant 30 mg	228	0	0	0
Ailani, 2021 [12]	Atogepant 60 mg	231	0	0	0
Ailani, 2021 [12]	Placebo	222	0.9	0	0
Ashina, 2020 [14]	Eptinezumab 100 mg	223	1.79	0	0
Ashina, 2020 [14]	Eptinezumab 300 mg	224	1.34	0	0
Ashina, 2020 [14]	Placebo	222	2.8	0	0
Dodick, 2014 [15]	Galcanezumab 150 mg	107	0	-	0
Dodick, 2014 [15]	Placebo	110	0.91		0
Dodick, 2018 [16]	Erenumab 70 mg	283	1.1	-	0
Dodick, 2018 [16]	Placebo	289	1.7	-	0
Dodick, 2009 [17]	Amitriptyline 100 mg	169	4.7	0.5	0
Dodick, 2009 [17]	Topiramate 100 mg	177	2.3	0	0
Detke, 2018 [4]	Galcanezumab 120 mg	273	0.18	-	0
Detke, 2018 [4]	Galcanezumab 240 mg	282	1.8	-	0
Detke, 2018 [4]	Placebo	558	0.7	-	0
Dodick, 2010 [5]	BTA 150 U	687	4.8	0.1	0
Dodick, 2010 [5]	Placebo	692	2.3	0	0
Dodick, 2018 [18]	Fremanezumab-M	289	1	0	0
Dodick, 2018 [18]	Fremanezumab-Q	291	1	0	0.3
Dodick, 2018 [18]	Placebo	293	2.4	0	0
Dodick, 2019 [3]	Eptinezumab 100 mg	122	3.3	0	0
Dodick, 2019 [3]	Eptinezumab 300 mg	121	5.8	0	0
Dodick, 2019 [3]	Placebo	121	0.8	0	0
Goadsby, 2017 [19]	Erenumab 140 mg	319	2.51	-	0
Goadsby, 2017 [19]	Erenumab 70 mg	314	2.5	-	0
Goadsby, 2017 [19]	Placebo	319	2.2	-	0
Hong Sun, 2016 [13]	Erenumab 21mg	105	1	0	0
Hong Sun, 2016 [13]	Erenumab 7 mg	108	0	0	0
Hong Sun, 2016 [13]	Erenumab 70 mg	106	0	0	0
Hong Sun, 2016 [13]	Placebo	153	1	0	
Lipton, 2020 [11]	Eptinezumab 100 mg	356	0.84	-	0
Lipton, 2020 [11]	Eptinezumab 300 mg	350	1.1	-	0
Lipton, 2020 [11]	Placebo	366	0.81	-	0
Rothrock, 2019 [1]	BTA 150 U	220	2	0	0
Rothrock, 2019 [1]	Topiramate 100 mg	142	4	1	0
Sakai, 2020 [20]	Galcanezumab 120 mg	115	2.6	-	0
Sakai, 2020 [20]	Galcanezumab 240 mg	114	0.9	-	0

Sakai, 2020 [20]	Placebo	230	0	0	0
Sakai, 2021 [21]	Fremanezumab-M	121	0	0	0
Sakai, 2021 [21]	Fremanezumab-Q	118	0	0	0
Sakai, 2021 [21]	Placebo	117	0	0	0
Sakai, 2021 [9]	Fremanezumab-M	188	1.6	0	0
Sakai, 2021 [9]	Fremanezumab-Q	190	0.5	0	0
Sakai, 2021 [9]	Placebo	191	0.5	0	0
Silberstein, 2017 [10]	Fremanezumab-M	379	1.32	0	0
Silberstein, 2017 [10]	Fremanezumab-Q	376	0.8		0.26
Silberstein, 2017 [10]	Placebo	375	1.6	-	0
Stauffer, 2018 [22]	Galcanezumab 120 mg	206	2.91	0	0
Stauffer, 2018 [22]	Galcanezumab 240 mg	220	0	0	0
Stauffer, 2018 [22]	Placebo	432	1.16	0	0
Tepper, 2017 [2]	Erenumab 140 mg	188	1	-	0
Tepper, 2017 [2]	Erenumab 70 mg	190	3	-	0
Tepper, 2017 [2]	Placebo	282	2	-	-
Reuter, 2018 [24]	Erenumab 140 mg	119	1.68	0	0
Reuter, 2018 [24]	Placebo	124	0.8	0	0
Reuter, 2021 [25]	Erenumab 140 mg	388	2.58	0.3	0
Reuter, 2021 [25]	Topiramate 100 mg	388	4.9	0.5	0
Vladimir, 2018 [23]	Galcanezumab 120 mg	226	2.2	-	0
Vladimir, 2018 [23]	Galcanezumab 240 mg	228	3.1	-	0
Vladimir, 2018 [23]	Placebo	461	1.1	-	0
Wang, 2021 [26]	Erenumab 140 mg	224	0	0	0
Wang, 2021 [26]	Erenumab 70 mg	335	2.99	0.3	0
Wang, 2021 [26]	Placebo	335	1.94	0	0
Elkind, 2006 (study 1) [27]	BTA 25 U	101	-	0	0
Elkind, 2006 (study 2) [27]	BTA 25 U	173	-	0	0
Elkind, 2006 (study 3) [27]	BTA 25 U	50	-	0	0
Elkind, 2006 (study 1) [27]	BTA 50 U	106	-	0	0
Elkind, 2006 (study 2) [27]	BTA 50 U	180	-	0	0
Elkind, 2006 (study 3) [27]	BTA 50 U	51	-	0	0
Elkind, 2006 (study 1) [27]	BTA 7 U	105	-	0	0
Elkind, 2006 (study 1) [27]	Placebo	106	-	0	0
Elkind, 2006 (study 3) [27]	Placebo	100	-	0	0
Ferrari, 2019 [8]	Fremanezumab-M	285	3.86	0	0
Ferrari, 2019 [8]	Fremanezumab-Q	276	3.62	0	0
Ferrari, 2019 [8]	Placebo	277	1	0	0
Mulleners, 2020 [28]	Galcanezumab 120 mg	232	1	-	0

Mulleners, 2020 [28]	Placebo	230	1	-	0
Ashina, 2022 [32]	Eptinezumab 100 mg	299	1.67	0	0
Ashina, 2022 [32]	Eptinezumab 300 mg	294	2.38	0.68	
Ashina, 2022 [32]	Placebo	298	1.34	0	0
HO, 2022 [31]	Galcanezumab 120 mg	261	0.76	-	0
HO, 2022 [31]	Placebo	259	1.54	-	0
Winner, 2021 [30]	Eptinezumab 100 mg	238	0	0	0
Winner, 2021 [30]	Placebo	242	0	0	0
Croop, 2020 [29]	Placebo	371	1	0.26	0
Croop, 2020 [29]	Rimegepant 75 mg	370	0.81	0	0
Takeshima, 2021 [34]	Erenumab 70 mg	131	1.5	0	0
Takeshima, 2021 [34]	Placebo	130	1.5	0	0
Shengyuan Yu, 2022 [35]	Erenumab 70 mg	279	2.5	0.4	0
Shengyuan Yu, 2022 [35]	Placebo	278	2.5	0	0
Ashina, 2023 [33]	Atogepant 60 mg	543	4.4		0.4
Ashina, 2023 [33]	Oral standard care	197	3.6		0

Table 20: Details for neoplasms benign malignant and unspecified of system organ class (SOC) (%)

Author, year	Interventions	Participants	Breast cancer	Fibroadenoma of breast	breast neoplasm	polycystic ovaries	Thyroid adenoma	vulval cancer	Benign colonic neoplasm	Anal polyp	Uterine leiomyoma	Gallbladder polyp	Lentigo maligna	Neoplasm malignant	Malignant melanoma in situ	Malignant melanoma	Pelvic pain	Squamous cell carcinoma	Papillary thyroid cancer	ruptured ovarian cyst	Adenocarcinoma of the cervix	Ovarian cyst	Colon cancer	Rectal polyp	Brain neoplasm	Fibroma
Ashina, 2023 [33]	Oral Standard care	196	0.5																				0.5			
Hong Sun, 2016 [13]	Erenumab 70 mg	106																		0						
Hong Sun, 2016 [13]	Erenumab 7 mg	108																		0.1						
Hong Sun, 2016 [13]	Erenumab 21mg	105																		0						
Dodick, 2009 [17]	Amitriptyline 100 mg	169			0.6																				0.6	
Dodick, 2010 [5]	BTA 150 U	687	0.44						0.15		0.3				0.15	0.15		0.15							0.15	
Rothrock, 2019 [1]	BTA 150 U	220	0.45																							
Dodick, 2019 [3]	Eptinezumab 100 mg	122									0.82															
Ashina, 2020 [14]	Eptinezumab 300 mg	224	0.45		0.45																					
Dodick, 2019 [3]	Eptinezumab 300 mg	121									0.83						0.83									
Tepper, 2017 [2]	Erenumab 70 mg	190																								0.53
Goadsby, 2017 [19]	Erenumab 70 mg	314																				0.31				
Ferrari, 2019	Fremanezumab-Q	276						0		0.36	0															
Detke, 2018 [4]	Galcanezumab 120 mg	273																					0.36			

Vladimir, 2018 [23]	Galcanezumab 120 mg	226										0									0.44			0.44		
Croop, 2020 [29]	Rimegepant 75 mg	370														0.27										
Reuter, 2021 [25]	Topiramate 100 mg	388		0.26																						
Rothrock, 2019 [1]	Topiramate 100 mg	142	0.7																							
Sakai, 2021 [9]	Placebo	191	0.5																							
Silberstein, 2017 [10]	Placebo	375										0.26														
Dodick, 2010 [5]	Placebo	692																		0.28						
Ferrari, 2019	Placebo	277	0.36				0.36	0.36			0.36															
Ashina, 2020 [14]	Placebo	222	0.45																							
Dodick, 2018 [16]	Placebo	289									0.3															
Dodick, 2018 [18]	Placebo	293											0.34													
Vladimir, 2018 [23]	Placebo	461										0.2									0			0		

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 21: Details for nervous system disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Migraine with aura	Dizziness	Migraine aggravated	Neuropathy	Hypoesthesia	Intracranial aneurysm	Multiple sclerosis	Optic neuritis	Transient ischemic attack	Tonic-clonic seizure	Nervous system disorders	Cerebellar syndrome	Spinal pain	Speech disorder	Serotonin syndrome	Migraine	Headache	Convulsion	Seizure	Cervical radiculopathy

Hong Sun, 2016 [13]	Erenumab 70 mg	106																0.1				
Dodick, 2009 [17]	Amitriptyline 100 mg	169			0.6																	
Dodick, 2010 [5]	BTA 150 U	687																0.59		0.15		
Dodick, 2019 [3]	Eptinezumab 100 mg	122																	0.82			
Ashina, 2022 [32]	Eptinezumab 100 mg	299																0			0	0.33
Ashina, 2022 [32]	Eptinezumab 300 mg	294																0			0.34	0
Dodick, 2019 [3]	Eptinezumab 300 mg	121															0.83			0.83		
Goadsby, 2017 [19]	Erenumab 140 mg	319													0.26			0				
Reuter, 2018 [24]	Erenumab 140 mg	119																0.84				
Dodick, 2018 [16]	Erenumab 70 mg	283																0.4				
Goadsby, 2017 [19]	Erenumab 70 mg	314													0			0.31				
Dodick, 2018 [18]	Fremanezumab-M	289									0.35											
Ferrari, 2019 [8]	Fremanezumab-M	285					0		0.35	0.35												
Ferrari, 2019 [8]	Fremanezumab-Q	276					0	0.35														
Vladimir, 2018 [23]	Galcanezumab 240 mg	228									0.44							0				
Reuter, 2021 [25]	Topiramate 100 mg	388	0															0.26				
Silberstein, 2017 [10]	Placebo	375																0.26				
Dodick, 2010 [5]	Placebo	692																0.28				
Tepper, 2017 [2]	Placebo	282																0.35				

Ferrari, 2019	placebo	277					0.36											0.36				
Ashina, 2020 [14]	Placebo	222																0.45				
Dodick, 2018 [16]	Placebo	289																0.3				
Dodick, 2018 [18]	Placebo	293		0.34														0.34				
Vladimir, 2018 [23]	Placebo	461									0							0.2				
Wang, 2021 [26]	Placebo	335																0.3				
Ashina, 2022 [32]	Placebo	298																0.34			0	0

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 22: Details for injury, poisoning and procedural complications of system organ class (SOC) (%) – part 1

Author, year	Interventions	Participants	respiratory fume inhalation	Seroma	Incarcerated incisional hernia	Foot Fracture	Clavicle fracture	Accident	Cartilage injury	Wrist fracture	Ulna fracture	thoracic vertebral fracture	lower limb fracture	Injury	Hand fracture	Humours fracture	Ankle fracture	Traumatic orbital fracture	Meniscus injury	Radius fracture	Fall	Tendon injury	Ankle fracture
Rothrock, 2019 [1]	BTA 150 U	220						0.45															
Ashina, 2022 [32]	Eptinezumab 100 mg	299														0.33							
Tepper, 2017 [2]	Erenumab 140 mg	188							0.53														
Goadsby, 2017 [19]	Erenumab 140 mg	319																					0.26
Reuter, 2018 [24]	Erenumab 140 mg	119																0.84					
Reuter, 2021 [25]	Erenumab 140 mg	388																			0.26	0.26	
Silberstein, 2017 [10]	Fremanezumab-M	379									0.26									0.26	0.26		
Ferrari, 2019 [8]	Fremanezumab-M	285	0.35																				
Silberstein, 2017 [10]	Fremanezumab-Q	376								0.26													
Ferrari, 2019 [8]	Fremanezumab-Q	276				0.36	0.36																
Dodick, 2018 [18]	Fremanezumab-Q	291																				0.34	
Sakai, 2020 [20]	Galcanezumab 120 mg	115																	0.9				
Stauffer, 2018 [22]	Galcanezumab 120 mg	206		0.49	0.49																		

Vladimir, 2018 [23]	Galcanezumab 240 mg	228																	0.44				
Dodick, 2009 [17]	Topiramate 100 mg	177												0.5									
Reuter, 2021 [25]	Topiramate 100 mg	388															0.26						
Rothrock, 2019 [1]	Topiramate 100 mg	142						0.7															
Silberstein, 2017 [10]	Placebo	375					0.26	0.26															
Ferrari, 2019 [8]	Placebo	277										0.36						0.35					
Dodick, 2018 [18]	Placebo	293								0.34											0.34		
Goadsby, 2017 [19]	Placebo	319																			0.26		
Vladimir, 2018 [23]	Placebo	461				0.2																	
Mulleners, 2020 [28]	Placebo	230											0.43										
Ashina, 2022 [32]	Placebo	298													0.34	0							

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 23: Details for injury, poisoning and procedural complications of system organ class (SOC) (%) - part 2

Author, year	Interventions	Participants	Ligament rupture	Sternal fracture	Skin laceration	Limb injury	Stomal Hernia	Procedural Pain	Postprocedural Constipation	Postprocedural Complication	Abdominal Wound Dehiscence	Road traffic accident	Head injury	Concussion	Brain contusion	Contusion	Rib Fracture	Radius fracture	Overdose	Intentional overdose
Rothrock, 2019 [1]	BTA 150 U	220												0.45						

Ashina, 2020 [14]	Eptinezumab 100 mg	223						0.45	0.45											
Ashina, 2020 [14]	Eptinezumab 300 mg	224								0.45	0.45									
Dodick, 2019 [3]	Eptinezumab 300 mg	121											0.83	0.83						
Reuter, 2021 [25]	Erenumab 140 mg	388	0.26	0.26	0.26	0.26								0		0.26				
Tepper, 2017 [2]	Erenumab 70 mg	190																0.53		
Sakai, 2021 [9]	Fremanezumab-M	188													0.53					
Ferrari, 2019	Fremanezumab-M	285															0.36			
Silberstein, 2017 [10]	Fremanezumab-Q	376										0.26								
Ferrari, 2019	Fremanezumab-Q	276										0.36					0.35			
Reuter, 2021 [25]	Topiramate 100 mg	388												0.26						
Rothrock, 2019 [1]	Topiramate 100 mg	142												0.7						
Dodick, 2014 [15]	Placebo	110						0.91												
Dodick, 2018 [18]	Placebo	293										0.34								
Goadsby, 2017 [19]	Placebo	319																		0.26
Vladimir, 2018 [23]	Placebo	461										0.2					0.2	0.2		
Croop, 2020 [29]	Placebo	371																	0.27	
Ashina, 2022 [32]	Placebo	298										0.34		0.34						

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 24: Details for respiratory, thoracic and mediastinal disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Pneumonia	Postsurgical laryngospasm with hypoxic brain injury	Chronic obstructive pulmonary disease (COPD) and apnea related to COPD	Chronic obstructive pulmonary disease	Asthma	Respiratory distress	Dyspnoea	Vocal cord thickening	Pulmonary embolism	Pulmonary sarcoidosis	Sleep apnoea syndrome	Hypoxia	Epistaxis
Ailani, 2021 [12]	Atogepant 10 mg	221					0.45								
Dodick, 2010 [5]	BTA 150 U	687	0.44										0.15	0.15	
Rothrock, 2019 [1]	BTA 150 U	220	0.45		0.45										
Dodick, 2019 [3]	Eptinezumab 300 mg	121						0.83							
Sakai, 2021 [9]	Fremanezumab-M	188					0.53								
Ferrari, 2019 [8]	Fremanezumab-M	285								0.35					
Silberstein, 2017 [10]	Fremanezumab-Q	376	0.26			0.26	0		0						
Rothrock, 2019 [1]	Topiramate 100 mg	142	0.7		0.7										
Silberstein, 2017 [10]	Placebo	375	0			0	0.26		0.26						
Dodick, 2010 [5]	Placebo	692	0.28									0.28			
Detke, 2018 [4]	Placebo	558													0.18
Ailani, 2021 [12]	Placebo	222		0.45			0								
Ashina, 2020 [14]	Placebo	222				0.45							0.45		
Stauffer, 2018 [22]	Placebo	432									0.23				
Croop, 2020 [29]	Placebo	371	0.27												

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 25: Details for gastrointestinal disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Mechanical ileus	intestinal haemorrhage	Haemorrhoids	Irritable bowel syndrome	esophagitis	Pancreatitis acute	Pancreatitis acute	Colitis ischaemic	Colitis	Pancreatitis	Gastroesophageal reflux	Inguinal hernia	Parotitis	gastric ulcer haemorrhage	Vomiting	diverticulitis	Abdominal pain	gastritis	Small intestinal obstruction	Obstructive defaecation	alcoholic pancreatitis
Dodick, 2009 [17]	Amitriptyline 100 mg	169					0.6																
Dodick, 2010 [5]	BTA 150 U	687							0.15	0.15	0.15												
Tepper, 2017 [2]	Erenumab 140 mg	188																	0.53				
Reuter, 2021 [25]	Erenumab 140 mg	388	0.26																			0.26	
Sakai, 2021 [9]	Fremanezumab-M	188		0.53																			
Ferrari, 2019 [8]	Fremanezumab-Q	276											0.36	0.36									
Dodick, 2018 [18]	Fremanezumab-Q	291		0.34																			
Mulleners, 2020 [28]	Galcanezumab 120 mg	232			0.43																		
Stauffer, 2018 [22]	Galcanezumab 120 mg	206						0.5													0.5		
Vladimir, 2018 [23]	Galcanezumab 120 mg	226																		0.44			
Detke, 2018 [4]	Galcanezumab 240 mg	282										0.35											
Reuter, 2021 [25]	Topiramate 100 mg	388				0.26														0.26			
Detke, 2018 [4]	Placebo	558																		0.18			0.18
Tepper, 2017 [2]	Placebo	282										0.35			0.35		0.35		0				

Ailani, 2021 [12]	Placebo	222														0.45							
HO, 2022 [31]	Placebo	259			0.38																		

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 26: Details for renal and urinary disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Nephrolithiasis	Urinary incontinence	Kidney injury	Calculus urinary	Renal calculus	Renal colic	Bladder dysfunction
Dodick, 2009 [17]	Amitriptyline 100 mg	169					0.6		
Dodick, 2010 [5]	BTA 150 U	687				0.15			
Silberstein, 2017 [10]	Fremanezumab-M	379				0.26			
Ferrari, 2019 [8]	Fremanezumab-M	285	0.7						
Ferrari, 2019 [8]	Fremanezumab-Q	276						0.35	
Vladimir, 2018 [23]	Galcanezumab 120 mg	226							0.44
Vladimir, 2018 [23]	Galcanezumab 240 mg	228							
Detke, 2018 [4]	Galcanezumab 240 mg	282	0.35					0.35	
Rothrock, 2019 [1]	Topiramate 100 mg	142	0.7						
Silberstein, 2017 [10]	Placebo	375	0.26						

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 27: Details for infections and infestations of system organ class (SOC) (%) - part 1

Author, year	Interventions	Participants	Gastrointestinal infection	Viral infection	Nasopharyngitis	Tonsillitis	Upper respiratory tract infection bacterial	Sepsis	Pyelonephritis	Kidney infection	Vaginal abscess	Viral gastroenteritis	Gastroenteritis	Pharyngitis streptococcal	Infected dermal cyst	Sinusitis
Dodick, 2009 [17]	Amitriptyline 100 mg	169											0.6			
Dodick, 2010 [5]	BTA 150 U	687								0.5						
Dodick, 2019 [3]	Eptinezumab 300 mg	121									0.83	0.83				
Goadsby, 2017 [19]	Erenumab 140 mg	319						0.26	0.26	0.26		0.26				
Wang, 2021 [26]	Erenumab 70 mg	335											0.3			
Mulleners, 2020 [28]	Galcanezumab 120 mg	232				0.43										
HO, 2022 [31]	Galcanezumab 120 mg	261											0.38		0.38	
Croop, 2020 [29]	Rimegepant 75 mg	370											0.27			
Reuter, 2021 [25]	Topiramate 100 mg	388	0.26		0.26				0.26				0.26			
Dodick, 2010 [5]	Placebo	692					0.28	0.28					0.28	0.28		
Ferrari, 2019 [8]	placebo	277														0.35
Reuter, 2018 [24]	Placebo	124	0.8													
Wang, 2021 [26]	Placebo	335		0.3									0.3			

Croop, 2020 [29]	Placebo	371							0.27						

Table 28: Details for infections and infestations of system organ class (SOC) (%) - part 2

Author, year	Interventions	Participants	Peri tonsillitis	Diverticulitis	Dengue fever	Cellulitis	Labyrinthitis	Clostridium difficile colitis	Influenza	Papilloma viral infection	Appendicitis	Parasitic gastroenteritis	Bacteriuria	Pyrexia	Acute pyelonephritis	COVID-19 pneumonia	Urinary tract infection	Bacterial pharyngitis
Ashina, 2022 [32]	Eptinezumab 100 mg	299														0.33		
Ashina, 2022 [32]	Eptinezumab 300 mg	294														0.68		
Goadsby, 2017 [19]	Erenumab 140 mg	319						0.26										
Reuter, 2021 [25]	Erenumab 140 mg	388								0.26								
Tepper,2017 [2]	Erenumab 70 mg	190									0.53							
Dodick, 2018 [16]	Erenumab 70 mg	283															0.4	
Goadsby, 2017 [19]	Erenumab 70 mg	314													0.31			
Wang, 2021 [26]	Erenumab 70 mg	335					0.3											
Dodick, 2018 [18]	Fremanezumab-M	289									0.35							
Sakai, 2021 [9]	Fremanezumab-Q	190							0.5									
Ferrari, 2019 [8]	Fremanezumab-Q	276		0.35														
Vladimir, 2018 [23]	Galcanezumab 120 mg	226																0.44
Vladimir, 2018 [23]	Galcanezumab 240 mg	228							0.44					0.44				
Reuter, 2021 [25]	Topiramate 100 mg	388							0.26		0.26	0.26	0.26					

Tepper, 2017 [2]	Placebo	282															0.35	
Ferrari, 2019 [8]	Placebo	277	0.35		0.35													
Ashina, 2020 [14]	Placebo	222				0.45												
Wang, 2021 [26]	Placebo	335				0.3												
Croop, 2020 [29]	Placebo	371									0.27							

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 29: Details for cardiac disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Atrial fibrillation	Acute coronary syndrome	Tachycardia	Atrial fibrillation	Palpitations	Pericarditis	Syncope	Acute myocardial infarction
Dodick, 2010 [5]	BTA 150 U	687		0.15	0.15			0.15		0.15
Rothrock, 2019 [1]	BTA 150 U	220			0.45				0.45	
Ferrari, 2019 [8]	Fremanezumab-M	285				0.35				
Ferrari, 2019 [8]	Fremanezumab-Q	276	0.36							
Vladimir, 2018 [23]	Galcanezumab 240 mg	228								0.44
Reuter, 2021 [25]	Topiramate 100 mg	388							0.26	
Detke, 2018 [4]	Placebo	558								0.18
Ferrari, 2019 [8]	Placebo	277					0.36			
Ashina, 2020 [14]	Placebo	222							0.45	

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 30: Details for congenital, familial and genetic disorders and reproductive system and breast disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Congenital diaphragmatic hernia	Metrorrhagia	Menometrorrhagia	Ovarian disorder	Abortion threatened	Spontaneous abortion	Uterine Prolapse	Endometriosis	Menstrual disorder and vaginal hemorrhage	Dysmenorrhoea	Menorrhagia	Cervical dysplasia
Dodick, 2009 [17]	Amitriptyline 100 mg	169											0.6	
Dodick, 2010 [5]	BTA 150 U	687						0.15						
Lipton, 2020 [11]	Eptinezumab 300 mg	350					0.38							
Reuter, 2021 [25]	Erenumab 140 mg	388										0.26		0.26
Dodick, 2018 [18]	Fremanezumab-M	289											0.35	
Ferrari, 2019 [8]	Fremanezumab-M	285			0.35					0.35				
Ferrari, 2019 [8]	Fremanezumab-Q	276										0.35	0.35	
Dodick, 2009 [17]	Topiramate 100 mg	177				0.5					0.5		0.5	
Reuter, 2021 [25]	Topiramate 100 mg	388								0.26				
Dodick, 2010 [5]	Placebo	692								0.28				
Lipton, 2020 [11]	Placebo	366			0.27									
Ferrari, 2019 [8]	Placebo	277	0.36	0.36										
Ashina, 2020 [14]	Placebo	222							0.45					

Dodick, 2018 [18]	Placebo	293						0.34						
Goadsby, 2017 [19]	Placebo	319								0.26				
Wang, 2021 [26]	Placebo	335						0.5						

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 31: Details for hepatobiliary disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Cholelithiasis	Hepatic Cholestatic	Cerebral venous thrombosis	Common bile duct stone	Cholecystitis acute
Dodick, 2009 [17]	Amitriptyline 100 mg	169	0.6				
Dodick, 2019 [3]	Eptinezumab 100 mg	122	0.5				
Ashina, 2020 [14]	Eptinezumab 100 mg	223	0.45				
Ashina, 2022 [32]	Eptinezumab 100 mg	299	0.33				
Goadsby, 2017 [19]	Erenumab 140 mg	319	0.63		0.26		
Ferrari, 2019 [8]	Fremanezumab-Q	276	0.36				0.36
Vladimir, 2018 [23]	Galcanezumab 240 mg	228	0.44				
Reuter, 2021 [25]	Topiramate 100 mg	388	0.26				
Dodick, 2010 [5]	Placebo	692	0.28				
Tepper, 2017 [2]	Placebo	282	0.35				
Dodick, 2018 [16]	Placebo	289					0.3
Stauffer, 2018 [22]	Placebo	432	0.5				

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 32: Details for psychiatric disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Major depression	Depression	Stress	Conversion disorder	Suicidal ideation	Suicidal attempt	Confessional state	Disorientation	Substance-induced mood disorders	Panic attack	Menorrhagia	Suicide attempt	Psychogenic seizure
Ashina, 2023 [33]	Atogepant 60 mg	543					0.9	0.4							
Ashina, 2023 [33]	Oral standard care	196					0.5								
Dodick, 2010 [5]	BTA 150 U	687		0.3	0.15	0.15	6.8								
Dodick, 2019 [3]	Eptinezumab 100 mg	122									0.82		0.82		
Ashina, 2020 [14]	Eptinezumab 100 mg	223					0.45					0.45		0.45	
Ashina, 2022 [32]	Eptinezumab 300 mg	294													0.34
Reuter, 2021 [25]	Erenumab 140 mg	388	0.26												
Silberstein, 2017 [10]	Fremanezumab-M	379					0.26								
Vladimir, 2018 [23]	Galcanezumab 240 mg	228								0.44					
Croop, 2020 [29]	Rimegepant 75 mg	370												0.27	
Reuter, 2021 [25]	Topiramate 100 mg	388		0.26											
Vladimir, 2018 [23]	Placebo	461												0.2	
Ashina, 2022 [32]	Placebo	298					0.34								

Fremanezumab-M, Fremanezumab monthly

Table 33: Details for musculoskeletal and connective tissue disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Costochondritis	Tendonitis	Vertebral osteophyte	Rhabdomyolysis	Periarthritis	Post-traumatic neck syndrome	Back pain	Behcets syndrome	Intervertebral disc protrusion	Osteoarthritis	Lumbar spinal stenosis	Arthralgia	Flank pain
Dodick, 2010 [5]	BTA 150 U	687							0.15						
Ashina, 2022 [32]	Eptinezumab 300 mg	294									0.34				
Tepper, 2017 [2]	Erenumab 140 mg	188									0.52				
Reuter, 2021 [25]	Erenumab 140 mg	388									0.26				
Tepper, 2017 [2]	Erenumab 70 mg	190	0.53								0				
Dodick, 2018 [16]	Erenumab 70 mg	283									0.4				
Goadsby, 2017 [19]	Erenumab 70 mg	314						0.31	0.31						
Silberstein, 2017 [10]	Fremanezumab-M	379							0.26						
Ferrari, 2019 [8]	Fremanezumab-Q	276							0.35						
Stauffer, 2018 [22]	Galcanezumab 120 mg	206		0.46											
Reuter, 2021 [25]	Topiramate 100 mg	388											0.26		
Dodick, 2010 [5]	Placebo	692									0.28				
Tepper, 2017 [2]	Placebo	282									0.35				
Ashina, 2020 [14]	Placebo	222									0.45				
Dodick, 2018 [16]	Placebo	289													0.3
Goadsby, 2017 [19]	Placebo	319										0.26		0.26	
Stauffer, 2018 [22]	Placebo	432			0.23										
Mulleners, 2020 [28]	Placebo	230								0.43					
Ashina, 2022 [32]	Placebo	298					0.34								

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 34: Details for investigations of system organ class (SOC) (%)

Author, year	Interventions	Participants	Weight decreased	International normalised ratio abnormal	Blood pressure increased	Hepatic enzyme increased	Aspartate aminotransferase increased	Alanine aminotransferase increased
Ferrari, 2019 [8]	Fremanezumab-Q	276		0.35				
Reuter, 2021 [25]	Topiramate 100 mg	388	0.26					

Fremanezumab-Q, Fremanezumab quarterly

Table 35: Details for metabolism and nutrition disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Hypokalaemia	Hypoglycaemia	Dehydration	Hyponatremia	Decreased appetite	Erythema nodosum
Dodick, 2010 [5]	BTA 150 U	687	0.15					
Detke, 2018	Galcanezumab 240 mg	282	0.35					
Reuter, 2021 [25]	Topiramate 100 mg	388					0.26	
Rothrock, 2019 [1]	Topiramate 100 mg	142			0.7			
Dodick, 2018 [16]	Placebo	289				0.3		
Dodick, 2018 [18]	Placebo	293		0.34				

Table 36: Details for vascular disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Hypertensive crisis	Peripheral arterial occlusive disease	Deep vein thrombosis	Peripheral vascular disease	Pulmonary embolism	Orthostatic hypotension
Dodick, 2010 [5]	BTA 150 U	687	0.15					
Silberstein, 2017 [10]	Fremanezumab-M	379	0.26					
Detke, 2018 [4]	Galcanezumab 240 mg	282					0.35	
Rothrock, 2019 [1]	Topiramate 100 mg	142		0.7	0.7			
Stauffer, 2018 [22]	Placebo	432			0.23			

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 37: Details for general disorders and administration site conditions of system organ class (SOC) (%)

Author, year	Interventions	Participants	Non-cardiac chest pain	Malaise	Nasal septum deviation	Tooth impacted	Chest pain	Abdominal adhesions	Asthenia	Edema peripheral
Dodick, 2010 [5]	BTA 150 U	687	0.15							
Tepper, 2017 [2]	Erenumab 140 mg	188	0					0.53		
Goadsby, 2017 [19]	Erenumab 140 mg	319	0.31							
Tepper, 2017 [2]	Erenumab 70 mg	190	0.53							
Goadsby, 2017 [19]	Erenumab 70 mg	314	0.26							
Wang, 2021 [26]	Erenumab 70 mg	335							0.3	
Sakai, 2020 [20]	Galcanezumab 120 mg	115				0.9				
Sakai, 2020 [20]	Galcanezumab 240 mg	114			0.9					
Silberstein, 2017 [10]	Placebo	375								0.26
Goadsby, 2017 [19]	Placebo	319	0.26							

Table 38: Details for eye disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Diplopia	Retinal tear	Rhegmatogenous retinal detachment	Angle closure glaucoma	Retinal detachment	Optic neuritis
Ailani, 2021 [12]	Atogepant 10 mg	221						0.45
Ashina, 2022 [32]	Eptinezumab 100 mg	299					0.33	
Ferrari, 2019 [8]	Fremanezumab-M	285		0.35				
Reuter, 2021 [25]	Topiramate 100 mg	388			0.26	0.26	0.26	
Silberstein, 2017 [10]	Placebo	375	0.26					

Fremanezumab-M, Fremanezumab monthly

Table 39: Details for ear and labyrinth disorders, immune system disorders, and blood and lymphatic system disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Ear and labyrinth disorders			Immune system disorders			Blood and lymphatic system disorders
			Vestibular neuronitis	Sudden hearing loss	Vertigo	Hypersensitivity	Anaphylactic reaction	Anaphylactic shock	Thrombocytopenia
Hong Sun, 2016 [13]	Erenumab 70 mg	106			0.1				
Ashina, 2020 [14]	Eptinezumab 300 mg	224			0.45				
Ashina, 2022 [32]	Eptinezumab 300 mg	294					0.68		
Goadsby, 2017 [19]	Erenumab 140 mg	319	0.26						
Ferrari, 2019 [8]	Fremanezumab-M	285					0.35		
Sakai, 2020 [20]	Galcanezumab 120 mg	115		0.9					
Reuter, 2021 [25]	Topiramate 100 mg	388						0.26	
Silberstein, 2017 [10]	Placebo	375				0.26			
Dodick, 2010 [5]	Placebo	692							0.28
Dodick, 2018 [18]	Placebo	289				0.3			
Dodick, 2018 [18]	Placebo	293				0.3			

Goadsby, 2017 [19]	Placebo	319				0.26			

Fremanezumab-M, Fremanezumab monthly

Table 40: Any serious adverse events reported from 32 trials

Treatments	Doses	Frequency	Total participants (n)	Participants with any SAEs* (%)
Atogepant [12]	30 mg	Once daily	228	0
Erenumab [13]	21 mg	Monthly	105	0
Galcanezumab [15]	150 mg	Every two weeks	107	0
Rimegepant [29]	75 mg	Once daily	370	3 (0.81)
Atogepant [12]	10 mg	Once daily	221	2 (0.9)
Erenumab [13]	7 mg	Monthly	108	1 (0.93)
Fremanezumab [8-10, 18, 21]	Quarterly, 625 mg	Single dose on day 0	1251	15 (1.2)
Eptinezumab [3, 11, 14, 30, 32]	100 mg	Single dose on day 0	1238	16 (1.29)
Galcanezumab [4, 20, 22, 23]	240 mg	Monthly	844	12 (1.42)
Placebo [2-5, 8-12, 14-16, 18-24, 26, 28-32, 34-36]	-	Matched with active treatments	7979	120 (1.5)
Galcanezumab [4, 20, 22, 23, 28, 31]	120 mg	Monthly	1313	20 (1.52)
Fremanezumab [8-10, 18, 21]	Monthly, 225 mg	Monthly	1262	22 (1.74)
Erenumab [2, 19, 24-26]	140 mg	Monthly	1238	22 (1.78)
Eptinezumab [3, 11, 14, 32]	300 mg	Single dose on day 0	989	21 (2.12)
Erenumab [2, 16, 19, 26, 34, 35]	70 mg	Monthly	1555	39 (2.5)
Atogepant [12, 33]	60 mg	Once daily	774	30 (3.87)
BTA [1, 5]	150 U	Every 12 weeks	907	37 (4.08)
Topiramate [1, 17, 25]	100 mg	Twice daily	707	29 (4.1)
Amitriptyline [17]	25 to 100 mg	Twice daily	169	8 (4.73)

*Treatments are listed in order of increasing SAEs percentage.

Table 41: Classification of SAEs by SOC

System Organ Class (SOC)	Serious Adverse Events (SAEs)
Cardiac disorders	Acute myocardial infarction, atrial fibrillation, syncope
Ear and labyrinth disorders	Labyrinthitis, **sudden hearing loss,** vertigo, **vestibular neuronitis**
Eye disorders	Angle closure glaucoma, diplopia, **optic neuritis,** retinal detachment, rhegmatogenous retinal detachment
Gastrointestinal disorders	Abdominal pain, alcoholic pancreatitis, appendicitis, **diverticulitis,** esophagitis, **gastric ulcer haemorrhage,** gastritis, haemorrhoids, **intestinal haemorrhage,** irritable bowel syndrome, mechanical ileus, obstructive defaecation, pancreatitis, pancreatitis acute, parotitis, small intestinal obstruction, vomiting
General disorders and administration site conditions	**Abdominal adhesions,** asthenia, chest pain, **edema peripheral,** malaise, **nasal septum deviation,** non-cardiac chest pain, tooth impacted, **vocal cord thickening**
Hepatobiliary disorders	Cholecystitis, cholecystitis acute, cholelithiasis, **common bile duct stone,**
Immune system disorders	Anaphylactic reaction, anaphylactic shock, hypersensitivity
Infections and infestations	**Acute pyelonephritis**, bacterial pharyngitis, bacteriuria, **clostridium difficile colitis,** COVID-19 pneumonia, gastroenteritis, gastrointestinal infection, **infected dermal cyst**, influenza, kidney infection, nasopharyngitis, papilloma viral infection, parasitic gastroenteritis, pyelonephritis, pyrexia, sepsis, **tonsillitis,** urinary tract infection, viral gastroenteritis, viral infection
Injury	Accident, ankle fracture, brain contusion, **cartilage injury,** clavicle fracture, concussion, contusion, fall, foot fracture, hand fracture, humerus fracture, injury, ligament rupture, limb injury, lower limb fracture, **meniscus injury**, radius fracture, respiratory fume inhalation, rib fracture, road traffic accident, skin laceration, sternal fracture, tendon injury, **thoracic vertebral fracture**, traumatic orbital fracture, ulna fracture, wrist fracture
Investigations	Alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, weight decreased
Metabolism and nutrition disorders	Decreased appetite, hypokalaemia, hyponatremia
Musculoskeletal and connective tissue disorders	Arthralgia, back pain, Behçet's syndrome, **costochondritis,** flank pain, intervertebral disc protrusion, **osteoarthritis,** periarthritis**, post-traumatic neck syndrome**
Neoplasms benign malignant and unspecified (incl cysts and polyps)	Adenocarcinoma of the cervix, brain neoplasm, breast cancer, colon cancer, **fibroma, gallbladder polyp, ovarian cyst, polycystic ovaries**, rectal polyp**, ruptured ovarian cyst**, **uterine leiomyoma**, **breast neoplasm**, fibroadenoma of breast, malignant melanoma, neoplasm malignant, vulval cancer
Nervous system disorders	Cerebellar syndrome, **cerebral venous thrombosis**, cervical radiculopathy, **hypoaesthesia**, lumbar spinal stenosis, migraine, **migraine aggravated**, migraine with aura, nervous system disorders, **neuropathy**, seizure, speech disorder, transient ischemic attack

Neurological	**Spinal pain**
Poisoning and procedural complications	Overdose, **intentional overdose**
Pregnancy, puerperium and perinatal conditions	Pregnancy
Psychiatric disorders	Confusional state, depression, disorientation, major depression, **psychogenic seizure**, suicidal ideation, suicide attempt
Psychiatry	**Panic attack**
Renal and urinary disorders	Bladder dysfunction, **calculus urinary, nephrolithiasis, renal calculus**, renal colic, urinary incontinence
Reproductive system and breast disorders	Cervical dysplasia, dysmenorrhoea, **endometriosis**, menorrhagia, **menstrual disorder and vaginal haemorrhage**, metrorrhagia, ovarian disorder, **spontaneous abortion, threatened abortion**
Respiratory, thoracic and mediastinal	Asthma, **chronic obstructive pulmonary disease, chronic obstructive pulmonary disease (COPD) and apnoea related to COPD**, dyspnoea, epistaxis, pneumonia, **postsurgical laryngospasm with hypoxic brain injury**
Skin and subcutaneous tissue disorders	**Erythema nodosum**
Vascular disorders	**Hypertensive crisis**, orthostatic hypotension, **peripheral vascular disease**, **pulmonary embolism**

SAEs in bold font were not found in the CTCAE Version 5.0, and thus were categorised by our clinical team.

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Supplementary materials

Supplementary Table 1-3

Supplementary Table 1: Characteristics of included trials

Author, Year	Purpose	Country and setting	Chronic/ Episodic	Treatment duration (week) and study design	Treatment					Number of participants (ITT)	Female (%)	Mean Age	% Any AEs (% TAEs)	% Any SAEs (% TSAEs)	Conclusion	Risk of bias
					Name		Dose	Route of administration	Frequency							
Dodick 2009 [1]	To compare the efficacy and tolerability of Topiramate and Amitriptyline in the prophylaxis of EM	32 sites in the United States	Episodic	22 DB	Topiramate		100mg	Oral	Twice daily	177	86.6	39.7	85.9 (68.4)	2.3 (0)	Both appeared to be well tolerated in this EM population	Some concerns
					Amitriptyline		100mg	Oral	Twice daily	169	83	37.9	88.8 (75.7)	4.7 (0.5)		
Elkind[a] 2006 [2]	To examine the effects of multiple treatments with low doses of BTA versus placebo for prophylaxis of EM	-	Episodic	12 DB	Study I	Placebo	-	-	-	106	84.9	43.8	47.2 (6.6)	(0)	Adverse events were similar among the groups within each study. BTA was safe and well tolerated	Some concerns
						BTA	7 U	IM	each 4 months	105	84.3	44.3	49.5 (6.7)	(0)		
							25 U	IM	each 4 months	101	82.2	43.6	46.5 (21.8)	(0)		
							50 U	IM	each 4 months	106	86.8	44.6	56.6 (30.2)	(0)		

Author, Year	Purpose	Country and setting	Chronic/ Episodic	Treatment duration (week) and study design	Treatment					Number of participants (ITT)	Female (%)	Mean Age	% Any AEs (% TAEs)	% Any SAEs (% TSAEs)	Conclusion	Risk of bias
					Name		Dose	Route of administration	Frequency							
					Study II	BTA	25 U	IM	each 4 months	173	-	-	78 (24.9)	(0)		
							50 U	IM	each 4 months	180	-	-	77.2 (29.4)	(0)		
					Study III	Placebo	-	-	-	100	-	-	60	(0)		
						BTA	25 U	IM	each 4 months	50	-	-	70	(0)		
							50 U	IM	each 4 months	51	-	-	68.6	(0)		
Dodick 2010 [3]; [pooled Aurora 2010 **[4]**, **Diener 2010 [5]]**	To assess efficacy, safety and tolerability of BTA as headache prophylaxis in adults with CM.	56 sites in North America	Chronic	24 DB	Placebo		-	-	-	687	85.2	41.5	51.7 (13.7)	2.3 (0)	BTA treatments were safe and well tolerated	Low
					BTA		155 U +40 U	IM at 39 sites	Every 12 week	692	87.6	41.1	62.4 (33.4)	4.8 (0.3)		
Rothrock 2019 [6]	To compare the effectiveness of BTA and Topiramate for CM prevention	USA (number of sites is not reported)	Chronic	24 OL	BTA		155 U	IM	Every 12 week	140	84	40.2	48 (17)	2 (0)	BTA is safe; 51% of patients discontinued Topiramate due to AEs	High
					Topiramate		100mg	Oral	Twice daily	142	86	39.4	79 (70)	4 (1)		

Author, Year	Purpose	Country and setting	Chronic/ Episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean Age	% Any AEs (% TAEs)	% Any SAEs (% TSAEs)	Conclusion	Risk of bias
					Name	Dose	Route of administration	Frequency							
Ashina 2020 [7]	To evaluate the efficacy and safety of Eptinezumab in the preventive treatment of EM	84 sites in the USA and the Republic of Georgia	Episodic	24 DB	Placebo	-	-	-	222	83.8	39.9	59.5	0. 4	Eptinezumab was well tolerated, and had an acceptable safety profile	Some concerns
					Eptinezumab	100mg	IV	Every 12 weeks	223	80.3	40	63.2	1.79 (0)		
						300mg	IV	Every 12 weeks	224	88.8	40.2	57.6	1.34 (0)		
Ashina 2022 [8]	To investigate the safety and efficacy of Eptinezumab for migraine prevention in adults with migraine and two-to-four previous failures	96 study locations across Europe (n=93) and the USA (n=3)	Episodic & Chronic	24 DB	Placebo	-	-	-	298	88	43.8	40	1.3 (0)	The safety and tolerability of Eptinezumab were similar to placebo	Some concerns
					Eptinezumab	100mg	IV	Every 12 weeks	299	93	44.6	42	1.7 (0)		
						300mg	IV	Every 12 weeks	294	89	43.1	41	2.4 (0.7)		
Dodick 2019 [9]	To determine the safety, tolerability, and effectiveness	92 clinics/sites in the USA, Australia,	Chronic	12 DB	Placebo	-	-	-	121	90	37.2	56.2 (14)	0.8 (0)	Eptinezumab appeared effective and well-tolerated	Some concerns
					Eptinezumab	300mg	IV	Single dose	121	81	37.2	63.6 (17.4)	5.8 (0)		

Author, Year	Purpose	Country and setting	Chronic/ Episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean Age	% Any AEs (% TAEs)	% Any SAEs (% TSAEs)	Conclusion	Risk of bias
					Name	Dose	Route of administration	Frequency							
	of four dose levels of Eptinezumab	New Zealand, and the republic of Georgia.				100mg	IV	Single dose	122	85	36.7	57.5 (19.8)	3.3 (0)		
Lipton 2020 [10]	To evaluate the efficacy and safety of Eptinezumab, in the preventive treatment of CM.	128 sites in 13 countries across the USA and Europe	Chronic	24 DB	Placebo	-	-	-	366	88.8	39.6	46.7	0.81	Eptinezumab was well tolerated and demonstrated an acceptable safety profile.	Low
					Eptinezumab	300mg	IV	Single dose	350	89.7	41	52	1.1		
						100mg	IV	Single dose	356	86.2	41	43.5	0.84		
Winner 2021 [11]	To evaluate the efficacy and safety of Eptinezumab,	47 sites in the United States and Georgia	Episodic	4 DB	Placebo	-	-	-	242	83.1	44.1	10.3	0	No notable safety findings were identified.	Low
					Eptinezumab	100mg	IV	Single dose	238	84.9	44.9	10.9	0		
Dodick 2018 [12]	To evaluate the efficacy and safety of Erenumab in migraine prevention	69 sites in North America and Europe	Episodic	12 DB	Placebo	-	-	-	289	84.9	42	54.7	1.7	AEs was similar in both, and did not suggest any particular safety risk with Erenumab administration	Low
					AMG 334 (Erenumab)	70mg	SC	Once a month	283	85.7	42	48.1	1.1		

Author, Year	Purpose	Country and setting	Chronic/ Episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean Age	% Any AEs (% TAEs)	% Any SAEs (% TSAEs)	Conclusion	Risk of bias
					Name	Dose	Route of administration	Frequency							
Goadsby 2017 [13]	To compare the efficacy and safety of Erenumab for the preventive treatment of EM	121 sites across North America, Europe, and Turkey	Episodic	24 DB	Placebo	-	-	-	319	85.9	41.3	63	2.2	The overall safety profile of Erenumab was similar to that of placebo.	Low
					Erenumab	70mg	SC	Monthly	314	84.5	41.1	57.3	2.5		
						140mg	SC	Monthly	319	85.3	40.4	55.5	2.5		
Reuter 2018 [14]	To compare the efficacy and tolerability of Erenumab with placebo in a well-defined group of patients with EM	59 sites in 16 countries	Episodic	12 DB	Placebo	-	-	-	124	82	44.2	54	1	The tolerability and safety profiles of Erenumab and placebo were similar.	Some concerns
					Erenumab	140mg	SC	Monthly	119	80	44.6	55	2		
Reuter 2022 [15]	To compare the tolerability and efficacy of Erenumab to Topiramate for migraine in adults	82 sites in Germany	Episodic & chronic	24 DB	Erenumab	140mg	SC	Monthly	388	85.3	40.8	65.21 (55.4)	2.58 (0.3)	Erenumab demonstrated a favourable tolerability and efficacy profile compared to Topiramate	Some concerns
					Topiramate	100mg	Oral	Daily	388	86.3	40.7	85.31 (81.2)	4.9 (0.5)		
Sun 2016 [16]			Episodic	12 DB	Placebo	-	-	-	153	83	41.4	54	0		Low

Author, Year	Purpose	Country and setting	Chronic/ Episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean Age	% Any AEs (% TAEs)	% Any SAEs (% TSAEs)	Conclusion	Risk of bias
					Name	Dose	Route of administration	Frequency							
	To assess the safety and efficacy of Erenumab (AMG 334) for the prevention of migraine	59 headache and clinical research centres in North America and Europe			AMG 334 (Erenumab)	7mg	SC	Monthly	108	81	40.3	50	1 (0)	No apparent association was recorded between patients with positive anti-AMG 334 antibodies and adverse events	
						21mg	SC	Monthly	105	81	39.9	51	0		
						70mg	SC	Monthly	106	77	42.6	54	1 (0)		
Tepper 2017 [17]	To assess the safety and efficacy of Erenumab 70mg and 140mg in CM patients	69 headache and clinical research centers in Canada the USA, and Europe	Chronic	12 DB	Placebo	-	-	-	286	79	42.1	39	2	Erenumab 70 and 140mg have a safety profile similar to placebo	Low
					Erenumab	70mg	SC	Monthly	191	87	41.4	44	3		
						140mg	SC	Monthly	190	84	42.9	47	1		
Wang 2021 [18]	To evaluate the efficacy and safety of Erenumab in adults with EM	83 sites in Asia, the Middle East, and Latin America	Episodic	12 DB	Placebo	-	-	-	335	83.1	38	36.7 (9.6)	1.5 (0)	The safety profile of Erenumab was comparable with placebo; no new safety signals were observed.	Low
					Erenumab	70mg	SC	Monthly	335	80.5	37.3	34.9 (11.3)	2.9 (0.3)		
						140mg	SC	Monthly	224	82.1	37.1	34.4 (10.7)	0		

Author, Year	Purpose	Country and setting	Chronic/ Episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean Age	% Any AEs (% TAEs)	% Any SAEs (% TSAEs)	Conclusion	Risk of bias
					Name	Dose	Route of administration	Frequency							
Takeshima 2021 [19]	To investigate the efficacy and tolerability of Erenumab 70mg	41 centers across Japan	Chronic & Episodic	24 DB	Placebo	-	-	-	131	88.5	44.6	58.8	1.5 (0)	Erenumab 70mg shows favorable efficacy and safety profile in Japanese participants.	Low
					Erenumab	70mg	SC	Monthly	130	85.4	44.2	65.4	1.5 (0)		
Shengyuan Yu 2022 [20]	To evaluate the efficacy and safety of Erenumab 70mg in patients with CM	64 sites in 9 Asian countries including China	Chronic	12 DB	Placebo	-	-	-	278	85.3	41.9	47.5 (13.3)	2.5 (0)	No new safety signals or increased risks with known adverse drug reactions with Erenumab were observed.	Some concerns
					Erenumab	70mg	SC	Monthly	279	77.8	41.4	45.5 (12.9)	2.5 (0.4)		
Dodick 2018 [21]	To compare the efficacy and safety of Fremanezumab for the preventive treatment of EM	123 investigative sites in 9 countries	Episodic	12 DB	Placebo	-	-	-	293	84	41.3	58.4 (37.2)	2.4	The most common AE reported was injection site pain, greater incidence with Fremanezumab than with placebo	Low
					Fremanezumab	675mg	SC	Single dose	291	86.3	41.1	66.3 (47.1)	1		
						225/225/ 225mg	SC	Monthly	289	84.1	42.9	66.2 (47.6)	1		
Ferrari 2019 [22]	To evaluate the efficacy and tolerability of	104 sites in Europe and the USA	Chronic & Episodic	12 DB	Placebo	-	-	-	279	84	46.8	48 (20)	1 (0)	Fremanezumab was well tolerated in patients with difficult-to-treat migraine	Low
					Fremanezumab	675mg	SC	Single dose	276	83	45.8	55 (21)	0.7 (0)		

Author, Year	Purpose	Country and setting	Chronic/ Episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean Age	% Any AEs (% TAEs)	% Any SAEs (% TSAEs)	Conclusion	Risk of bias
					Name	Dose	Route of administration	Frequency							
	Fremanezumab in patients with difficult-to-treat episodic or chronic migraine.					225+225+ 225mg	SC	Monthly	283	84	45.9	45 (19)	1 (0)	who had previously not responded to up to four classes of migraine preventive medications.	
Sakai 2021 [23]	To determine the efficacy and safety of Fremanezumab administration in patients with CM	67 institutions in Japan and Korea	Chronic	12 DB	Placebo	-	-	-	191	85.3	42.1	61.8 (28.3)	0.5 (0)	Fremanezumab was well tolerated. No safety signals were detected.	Low
					Fremanezumab	675mg	SC	Single dose	191	86.4	43.5	61.1 (32.1)	0.5 (0)		
						225+225+ 225mg	SC	Monthly	189	86.2	42.7	61.7 (29.3)	1.6 (0)		
Sakai 2021 [24]	To evaluate the efficacy and safety Fremanezumab in patients with EM	57 institutions in Japan and 10 institutions in Korea	Episodic	12 DB	Placebo	-	-	-	117	85.5	44.2	65.8 (23.9)	0	No new safety concerns for Fremanezumab in patients with EM	Low
					Fremanezumab	675mg	SC	Single dose	118	84.9	41.9	62.7 (28.9)	0		
						225+225+ 225mg	SC	Monthly	121	83.5	44.4	57 (26.4)	0		
Silberstein			Chronic	12 DB	Placebo	-	-	-	375	88	41.4	64	1.7 (0)		

Author, Year	Purpose	Country and setting	Chronic/ Episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean Age	% Any AEs (% TAEs)	% Any SAEs (% TSAEs)	Conclusion	Risk of bias
					Name	Dose	Route of administration	Frequency							
2017 [25]	To compare two Fremanezumab dosing regimens with placebo for the prevention of CM.	132 sites in nine countries across the USA and Europe			Fremanezumab	675mg	SC	Single dose	376	88	42	70	0.8 (0)	Injection-site reactions to Fremanezumab were common. The long-term durability and safety of Fremanezumab requires further study.	Some concerns
						225+225+225mg	SC	Monthly	379	87	40.6	71	1.3 (0)		
Bo Hu 2022 [26]	To assess the efficacy and safety of Galcanezumab in patients with EM.	40 centres in China (n=26), India (n=10), and Russia (n=4)	Episodic	12 DB	Placebo	-	-	-	259	75.7	36.8	43.2	1.54	Galcanezumab 120mg once monthly was well tolerated in patients with episodic migraine.	Some concerns
					Galcanezumab	120mg (240mg in the first month followed by 120mg	SC	Monthly	261	72	37.2	49.8	0.76		
Detke 2018 [27]	To evaluate the efficacy and safety of Galcanezumab	116 centres in Argentina, Canada, Czech Republic,	Chronic	12 DB	Placebo	-	-	-	558	87	41.6	50	0.71	Galcanezumab appears safe, and well tolerated for the preventive treatment for CM	Some concerns
					Galcanezumab	120mg	SC	Monthly	278	85	39.7	58	0.18		

Author, Year	Purpose	Country and setting	Chronic/ Episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean Age	% Any AEs (% TAEs)	% Any SAEs (% TSAEs)	Conclusion	Risk of bias
					Name	Dose	Route of administration	Frequency							
	in the preventive treatment of CM	Germany, Israel, Italy, Mexico, Netherlands, Spain, Taiwan, UK, and USA				240mg	SC	Monthly	277	82	41.1	57	1.8		
Dodick 2014 [28]	To assess the safety and efficacy of Galcanezumab for migraine prevention	35 centres in the USA	Episodic	12 DB	Placebo	-	-	-	110	87	41.9	67	3.6	Adverse events were reported to a similar extent in both groups	Some concerns
					Galcanezumab	150mg	SC	Every 2 weeks	107	82	40.9	72	1.9		
Mulleners 2020 [29]	To assess the safety and efficacy of Galcanezumab in patients with migraine who had not benefited from preventive drugs from two to four categories.	64 sites in 12 countries	Episodic & Chronic	12 DB	Placebo	-	-	-	230	88	45.7	53 (15)	1	Galcanezumab was safe & well tolerated in patients for whom multiple previous standard-of-care preventive treatments had failed	Some concerns
					Galcanezumab	120mg	SC	Monthly	232	84	45.9	51 (16)	1		

Author, Year	Purpose	Country and setting	Chronic/ Episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean Age	% Any AEs (% TAEs)	% Any SAEs (% TSAEs)	Conclusion	Risk of bias
					Name	Dose	Route of administration	Frequency							
Sakai 2020 [30]	To assess the efficacy and safety of Galcanezumab for the prevention of migraine in patients with EM	40 sites in Japan	Episodic	24 DB	Placebo	-	-	-	230	85.2	44.2	64.8	0	Galcanezumab were safe and well tolerated in Japanese patients with episodic migraine	Low
					Galcanezumab	240mg	SC	Monthly	114	84.2	44.8	81.6	0.9		
Skljarevski 2018 [31]	To evaluate the efficacy and safety of two dosing regimens of Galcanezumab in patients with EM	109 study sites in 12 countries	Episodic	24 DB	Placebo	-	-	-	461	85.3	42.3	62.3	1.1	Galcanezumab 120mg or 240mg given once monthly was safe and well tolerated.	Some concerns
					Galcanezumab	120mg	SC	Monthly	226	85.3	40.9	65‡	2.2		
						240mg	SC	Monthly	228	85.7	41.9	71.5	3.1		
Stauffer 2018 [32]	To demonstrate Galcanezumab is superior to placebo in the prevention of EM with or without aura.	90 sites in North America	Episodic	24 DB	Placebo	-	-	-	432	83.6	41.3	60.4	1.16 (0)	The incidence rate of AEs was low, showing a favourable tolerability profile of Galcanezumab	Some concerns
					Galcanezumab	120mg	SC	Monthly	206	85	40.9	65.5	2.91 (0)		
						240mg	SC	Monthly	220	82.6	39.1	67.7	0 (0)		
			Episodic	12 DB	Placebo	-	-	-	222	89.2	40.3	56.8 (9)	0.9 (0)		Low

Author, Year	Purpose	Country and setting	Chronic/ Episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean Age	% Any AEs (% TAEs)	% Any SAEs (% TSAEs)	Conclusion	Risk of bias
					Name	Dose	Route of administration	Frequency							
Ailani 2021 [33]	To examine the efficacy and safety of Atogepant compared with placebo for the prevention of migraine in participants with EM	128 sites in the USA			Atogepant	10mg	Oral	Once daily	221	90.5	41.4	52.9 (23.1)	0.9 (0.5)	Most common adverse events were constipation, nausea across Atogepant patients	
						30mg	Oral	Once daily	228	89.5	42.1	52.2 (14.9)	0		
						60mg	Oral	Once daily	231	86.1	42.5	53.7 (19.5)	0		
Ashina 2023 [34]	To assess long-term safety, and efficacy of once-daily oral Atogepant in adults with migraine	111 study centers in the USA	Episodic	52 OL	Oral standard care[b]	-	-	-	196	87.8	41.1	78.6 (36.2)	3.6	Daily use of oral Atogepant 60mg during this 1-year study, was safe, well tolerated, and efficacious.	High
					Atogepant	60mg	Oral	Once daily	543	88.2	42.5	67 (18)	4.4		
Croop 2021 [35]	To assess the efficacy of for preventive	92 sites in the USA	Episodic	12 DB	Placebo	-	-	-	371	84	41.1	36 (9)	1 (0.26)	Tolerability was similar to that of placebo	Some concerns
					Rimegepant	75mg	Oral	Daily	370	81	41.3	36 (11)	1 (0)		

Author, Year	Purpose	Country and setting	Chronic/ Episodic	Treatment duration (week) and study design	Treatment				Number of participants (ITT)	Female (%)	Mean Age	% Any AEs (% TAEs)	% Any SAEs (% TSAEs)	Conclusion	Risk of bias
					Name	Dose	Route of administration	Frequency							
	treatment of migraine.														

Abbreviations: AEs - Adverse Events; AMG334 - Erenumab; BTA - Onabotulinumtoxin A; CM - Chronic migraine; DB - Double Blind; EM - episodic migraine; IM - Intramuscular; IV - Intravenous; OL - Open Label; SAEs - Serious Adverse Events; SC - Subcutaneous; TAEs - Treatment-related Adverse Events; TSAEs - Treatment-related Serious Adverse Events

a. This study is series of 3 sequential, RCTs. In study I, patients were randomised to treatment with placebo or BTA (7.5U, 25U, or 50U) in predetermined fixed injection sites on the front and sides of the head only. In study II, patients continued to receive, or were randomised to, 2 consecutive treatments with 25U or 50U. In study III, patients were randomised to placebo or continuation of 25U or 50U. Injection cycles were each 4 months long.

b. Oral standard care were permitted as initial treatments for participants included: Antiepileptic (valproic acid, sodium valproate, divalproex sodium, topiramate), Tricylic antidepressant (amitriptyline, nortriptyline), Beta-blockers (metoprolol, bisoprolol, atenolol, nadolol, propranolol, timolol), Calcium-channel blocker (flunarizine), Angiotensin receptor blocker (ARB) (candesartan), Serotonin-nor

Supplementary Table 2: Adverse Events classified by System Organ Class (SOC) (%)

Medications	Doses	Participants (N)	Investigations (%)	Skin and subcutaneous (%)	Gastrointestinal disorders (%)	Ear and labyrinth disorders (%)	Eye disorders (%)	Psychiatric Disorders (%)	Metabolism and nutrition disorders (%)	Vascular disorders (%)	Renal and urinary disorders (%)	Musculoskeletal and connective tissue disorders (%)	Nervous system disorders (%)	Infection and infestation (%)	General disorders and administration site conditions (%)	Respiratory, thoracic and mediastinal disorders (%)
Amitriptyline [1]	25mg to 100mg	169	**23 (13.6)**	0	**100 (59.2)**	0	0	0	8 (4.7)	0	0	0	73 (43.4)	40 (23.7)	41 (24.3)	7 (4.1)
Atogepant [33, 34]	10mg	221	8 (3.7)	0	28 (12.7)	0	0	2 (0.9)	0	0	0	0	7 (3.2)	25 (11.4)	3 (1.4)	1 (0.5)
	30mg	228	4 (1.8)	0	26 (11.4)	0	0	1 (0.4)	0	0	0	0	4 (1.8)	40 (17.5)	7 (3.1)	2 (0.9)
	60mg	774	47 (6.1)	0	30 (3.8)	0	0	21 (2.7)	0	14 (1.8)	0	35 (4.5)	21 (2.7)	109 (14.1)	9 (1.2)	4 (0.5)
BTA [3, 6]	155 U	907	0	0	1 (0.1)	0	**29 (3.2)**	5 (0.5)	0	0	0	141 (15.6)	5 (5.0)	14 (1.5)	23 (2.5)	0
Eptinezumab [7-11]	100mg	1238	5 (0.4)	0	32 (2.6)	0	0	0	0	0	0	19 (1.5)	38 (3.1)	148 (12)	26 (2.1)	19 (1.5)
Eptinezumab [7-10]	300mg	989	0	0	47 (4.8)	0	0	0	0	0	0	9 (0.9)	18 (1.8)	191 (19.3)	20 (2)	17 (1.7)
Erenumab [16]	21mg	105	0	0	2 (2)	0	0	0	0	0	0	0	4 (4)	12 (11)	2 (2)	1 (1)
Erenumab [16]	7mg	108	0	0	3 (3)	0	0	0	0	0	0	4 (4)	5 (5)	12 (11)	5 (5)	2 (2)
Erenumab [12, 13, 16-20]	70mg	1637	0	0	62 (3.4)	0	0	0	0	5 (0.3)	0	32 (1.3)	24 (1.6)	208 (10.1)	59 (3.9)	0

Erenumab [13-15, 17, 18]	140mg	1238	4 (0.3)	0	144 (11.6)	17 (1.4)	0	42 (3.4)	9 (0.7)	0	0	28 (2.3)	87 (7)	110 (8.9)	68 (5.5)	0
Fremanezumab [21-25]	Monthly	1263	4 (0.3)	8 (0.6)	24 (1.9)	0	0	8 (0.6)	0	1 (0.1)	0	11 (0.9)	19 (1.5)	155 (12.3)	**794 (62.9)**	63 (5)
	Quarterly	1251	8 (0.6)	4 (0.3)	48 (3.8)	0	0	9 (0.7)	0	3 (0.2)	0	13 (1)	18 (1.4)	170 (13.6)	762 (60.9)	8 (0.6)
Galcanezumab [26, 27, 29-32]	120mg	1313	13 (1)	8 (0.6)	56 (4.3)	7 (0.5)	0	5 (0.4)	0	0	**7 (0.5)**	32 (2.4)	34 (2.6)	197 (15)	284 (21.6)	11 (0.8)
Galcanezumab [27, 30-32]	240mg	844	2 (0.2)	13 (1.5)	37 (4.4)	4 (0.5)	0	0	0	0	0	19 (2.3)	20 (2.4)	101 (12)	272 (32.2)	18 (2.1)
Galcanezumab (LY2951742) [28]	150mg	107	0	**5 (5)**	15 (14)	0	3 (3)	0	0	**5 (5)**	0	**18 (17)**	5 (5)	**28 (26)**	28 (26)	0
Placebo [3, 7-14, 16-18, 20-33, 35]	-	7977	16 (0.2)	8 (0.1)	241 (3)	0	8 (0.1)	6 (0.1)	0	7 (0.1)	0	140 (1.8)	162(2)	942 (12)	996 (12.5)	55 (0.7)
Rimegepant [35]	75mg	370	0	0	11 (3)	0	0	0	0	0	0	0	0	30 (8)	0	0
Topiramate [1, 6, 15]	100mg	707	22 (3.1)	0	194 (27.4)	**23 (3.2)**	21 (2.9)	**88 (12.5)**	**63 (8.9)**	0	0	3 (0.4)	**426 (60.2)**	52 (7.3)	115 (16.3)	9 (1.3)

Supplementary Table 3: SAEs classified by System Organ Class (SOC) (%)

Medications	Doses	Participants (N)	Neoplasms benign malignant and unspecified (%)	Nervous system disorders (%)	Injury, poisoning and procedural complications (%)	Respiratory, thoracic and mediastinal disorders (%)	Gastrointestinal disorders (%)	Renal and urinary disorders (%)	Infections and infestations (%)	Cardiac disorders (%)	Congenital, familial and genetic disorders (%)	Hepatobiliary disorders (%)	Psychiatric disorders (%)	Musculoskeletal and connective tissue disorders (%)	Investigations (%)	Metabolism and nutrition disorders (%)	Reproductive system and breast disorders (%)	Skin and subcutaneous tissue disorders (%)	Vascular disorders (%)	General disorders and administration site conditions (%)	Eye disorders (%)	Ear and labyrinth disorders (%)	Immune system disorders (%)
Amitriptyline [1]	25 to 100mg	169	2 (1.18)	1 (0.59)	0	0	**1 (0.59)**	**1 (0.59)**	1 (0.59)	0	0	**1 (0.59)**	0	0	0	0	**1 (0.59)**	0	0	0	0	0	0
Atogepant [33, 34]	10mg	221	0	0	0	1 (0.45)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.45)	0	0
	30mg	228	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	60mg	774	5 (0.64)	**5 (0.64)**	3 (0.38)	2 (0.25)	1 (0.18)	0	4 (0.51)	0	0	1 (0.18)	3 (0.38)	0	0	**3 (0.38)**	2 (0.25)	0	0	0	0	**1 (0.18)**	0
BTA [4, 6]	150 U	907	**11 (1.21)**	5 (0.50)	2 (0.22)	7 (0.77)	3 (0.33)	1 (0.11)	1 (0.11)	**5 (0.50)**	0	0	**4 (0.44)**	1 (0.11)	0	1 (0.11)	1 (0.11)	0	1 (0.11)	**1 (0.11)**	0	0	0
Eptinezumab [7-11]	100mg	1238	1 (0.08)	3 (0.24)	**6 (0.48)**	0	2 (0.16)	0	1 (0.08)	1 (0.08)	0	3 (0.24)	5 (0.40)	0	0	0	0	0	0	0	1 (0.08)	0	0
Eptinezumab [7-10]	300mg	989	1 (0.10)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.10)
Erenumab [13-15, 17, 18]	140mg	1238	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**1 (0.08)**	0	0	0	0	0

Erenumab [12, 13, 16-20]	70mg	1555	2 (0.13)	3 (0.19)	4 (0.25)	0	2 (0.13)	1 (0.07)	2 (0.14)	0	0	1 (0.07)	0	1 (0.07)	0	0	2 (0.13)	0	1 (0.07)	0	0	0	1 (0.07)
Erenumab [16]	7mg	108	0	0	0	**1 (0.92)**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**1 (0.92)**	0	0
Erenumab [16]	21mg	105	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Fremanezumab [21-25]	Monthly	1262	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Quarterly	1251	11 (0.88)	5 (0.4)	2 (0.16	7 (0.56)	3 (0.24)	1 (0.08)	1 (0.08)	5 (0.4)	0	0	4 (0.32)	1 (0.08)	0	1 (0.08)	1 (0.08)	0	1 (0.08)	1 (0.08)	0	0	0
Galcanezumab [26, 27, 29-32]	120mg	1313	0	0	0	0	0	0	0	0	0	1 (0.08)	1 (0.08)	0	0	0	0	0	0	0	0	0	0
Galcanezumab [27, 30-32]	240mg	844	0	0	1 (0.12)	0	0	2 (0.23)	0	0	0	0	0	1 (0.12)	0	0	0	0	0	0	0	0	0	0
Galcanezum (LY2951742) [28]	150mg	107	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**1 (0.93)**	0	0	0	0
Placebo [3, 7-14, 16-33, 35]	-	7979	11 (0.14)	14 (0.17)	19 (0.24)	11 (0.14)	8 (0.1)	2 (0.03)	20 (0.24)	4 (0.05)	1 (0.01)	5 (0.06)	3 (0.04)	9 (0.12)	1 (0.01)	2 (0.03)	9 (0.12)	0	1 (0.01)	3 (0.04)	1 (0.01)	1 (0.01)	4 (0.05)
Rimegepant [35]	75mg	370	1 (0.27)	0	0	0	0	0	1 (0.27)	0	0	0	1 (0.27)	0	0	0	0	0	0	0	0	0	0
Topiramate [1, 6, 15]	100mg	707	1 (0.14)	1 (0.14)	1 (0.14)	2 (0.28)	2 (0.28)	1 (0.14)	**8 (1.13)**	1 (0.14)	0	1 (0.14)	1 (0.14)	**1 (0.14)**	**1 (0.14)**	2 (0.28)	4 (0.57)	0	2 (0.28)	0	4 (0.42)	0	**1 (0.14)**

Appendix 1-5

Appendix 1: Literature searches

Overview

Bibliographic databases and clinical trials registers		
Database	**Date searched**	**Number of records**
MEDLINE All (via Ovid)	08/09/21	4,029
Embase (via Ovid)	08/09/21	8,404
Cochrane CENTRAL (via Cochrane Library)	08/09/21	6,754
Science Citation Index (via Web of Science)	08/09/21	4,737
Global Index Medicus (via World Health Organization)	14/09/21	200
Clinicaltrials.gov	15/09/21	338
International Clinical Trials Registry Platform (ICTRP) (World Health Organization)	15/09/21	512
Total number of records retrieved: 24,974 **Duplicates removed (EndNote): 8,368** **Final number for screening: 16,606**		
Bibliographic databases and clinical trials registers; additional search for riboflavin, magnesium and coenzyme Q10		
Source	**Date searched**	**Number of records**
MEDLINE All (via Ovid)	08/02/22	163
Embase (via Ovid)	08/02/22	587
Cochrane CENTRAL (via Cochrane Library)	08/02/22	331
Science Citation Index (via Web of Science)	08/02/22	359
Global Index Medicus (via World Health Organization)	08/02/22	24
Clinicaltrials.gov	08/02/22	15
International Clinical Trials Registry Platform (ICTRP) (World Health Organization)	08/02/22	38
Total number of records retrieved: 1,517 **Duplicates removed within this set (EndNote): 481** **Duplicates removed against original search (EndNote): 448** **Final number for screening: 588**		
Pragmatic search for recent systematic reviews, to check reference lists/included studies		
Database	**Date searched**	**Number of records**
MEDLINE All (via Ovid)	14/02/22	114
Embase (via Ovid)	14/02/22	164
Cochrane Database of Systematic Reviews (via Cochrane Library)	14/02/22	4
Total number of records retrieved: 282 **Duplicates removed within this set (EndNote): 103** **Final number for screening: 179**		
Bibliographic databases and clinical trials registers; search update November 2022 (including all relevant drug terms)		
Database	**Date searched**	**Number of records**
MEDLINE All (via Ovid)	07/11/22	390
Embase (via Ovid)	07/11/22	710
Cochrane CENTRAL (via Cochrane Library)	07/11/22	713
Science Citation Index (via Web of Science)	07/11/22	440
Global Index Medicus (via World Health Organization)	07/11/22	222
Clinicaltrials.gov	08/11/22	390
International Clinical Trials Registry Platform (ICTRP) (World Health Organization)	08/11/22	631
Total number of records retrieved: 3,496		

Duplicates removed within this set (EndNote): 1,096 **Duplicates removed against previous searches (EndNote): 1,066** **Final number for screening: 1,334**		
Other sources; citation tracking		
Source	**Date searched**	**Number of records**
Reference lists – included studies (Web of Science)	23/11/22	875
Forwards citation tracking: Science Citation Index (Web of Science)	22-23/11/22	2,710
Forwards citation tracking: Google Scholar (for studies not found in Web of Science only)	23/11/22	23
Total number of records retrieved: 3,608 **Duplicates removed (both within this set and against previous searches) (Endnote): 2,122** **Final number for screening: 1,486**		
Checking for retraction notices, errata and comments relating to included studies		
Source	**Date searched**	**Number of records**
MEDLINE All (via Ovid)	22/11/22	23
Embase (via Ovid)	22/11/22	0
Retraction Watch website	22/11/22	0
Total number of records retrieved: 23		
Bibliographic databases and clinical trials registers; search update June 2023 (including all relevant drug terms)		
Database	**Date searched**	**Number of records**
MEDLINE All (via Ovid)	15/06/23	149
Embase (via Ovid)	15/06/23	408
Cochrane CENTRAL (via Cochrane Library)	15/06/23	169
Science Citation Index (via Web of Science)	15/06/23	191
Global Index Medicus (via World Health Organization)	15/06/23	234
Clinicaltrials.gov	15/06/23	413
International Clinical Trials Registry Platform (ICTRP) (World Health Organization)	15/06/23	663
Total number of records retrieved: 2,227 **Duplicates removed (both within this set and against previous searches) (EndNote): 1,644** **Final number for screening: 583**		

MEDLINE search strategy: original searches, September 2021

Date searched: 08/09/21

Database: Ovid MEDLINE(R) ALL <1946 to September 07, 2021>

Search Strategy:

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1 (headache* or head ache* or migrain* or cephalgi* or cephalalgi* or hemicrani*).ab,kf,ti. (112921)
2 Headache/ or exp Headache Disorders/ (61239)
3 1 or 2 [population: migraine/headache] (124144)
4 (((calcitonin gene-related peptide or CGRP) adj5 (antibod* or antagon* or inhibit* or block*)) or anti-CGRP or anti-calcitonin gene-related peptide or monoclonal antibod* or mAb or mAbs or moAb or moAbs).ab,kf,ti. (216437)
5 Calcitonin Gene-Related Peptide/ai (436)
6 Antibodies, Monoclonal/ or Antibodies, Monoclonal, Humanized/ (217039)
7 Calcitonin Gene-Related Peptide Receptor Antagonists/ (701)
8 (erenumab or galcanezumab or fremanezumab or eptinezumab).ab,kf,ti,nm. (507)
9 (rimegepant or ubrogepant or atogepant or gepant?).ab,kf,ti,nm. (214)
10 exp Botulinum Toxins/ (17105)
11 (botulin* adj toxin*).ab,kf,ti,nm. (21943)
12 (botulinum* or botox* or onabotulinum*).ab,kf,ti,nm. (25159)
13 (antidepress* or anti depress*).ab,kf,ti. (73890)
14 exp Antidepressive Agents/ (153122)
15 (amitriptyline or venlafaxine or mirtazapine or duloxetine).ab,kf,ti,nm. (17955)
16 exp "Serotonin and Noradrenaline Reuptake Inhibitors"/ (5005)
17 (SNRI or SNRIs or (serotonin adj2 (noradrenaline or norepinephrine) adj reuptake inhib*)).ab,kf,ti. (2908)
18 exp Angiotensin-Converting Enzyme Inhibitors/ (45324)
19 (Angiotensin Converting Enzyme Inhibit* or ACE inhibit*).ab,kf,ti. (37937)
20 acei.ab,kf,ti. (4344)
21 lisinopril.ab,kf,ti,nm. (3086)
22 ((angiotensin receptor or angiotensin II receptor) adj (block* or antagon*)).ab,kf,ti. (14474)
23 (ARB or ARBs).ab,kf,ti. (7873)
24 exp Angiotensin Receptor Antagonists/ (25403)
25 candesartan.ab,kf,ti,nm. (3374)
26 ((beta adj3 block*) or betablock*).ab,kf,ti. (55697)
27 ((adrenergic or adrenoreceptor* or adrenoceptor*) adj3 (antagon* or block*)).ab,kf,ti. (34997)
28 exp Adrenergic beta-Antagonists/ (85444)
29 (propranolol or metoprolol or timolol or atenolol or nadolol or nebivolol or pindolol).ab,kf,ti,nm. (67114)
30 (calcium adj2 (block* or antagon* or inhibit*)).ab,kf,ti. (41676)
31 (CCB or CCBs).ab,kf,ti. (2619)
32 exp Calcium Channel Blockers/ (88532)
33 (flunarizine or verapamil).ab,kf,ti,nm. (27700)
34 (anticonvuls* or antiepilep* or anti convuls* or anti epilep*).ab,kf,ti. (53599)
35 exp Anticonvulsants/ (147158)
36 (topiramate or valproate or divalproex or valproic acid or gabapentin).ab,kf,ti,nm. (31200)
37 Pizotyline/ (250)
38 (pizotifen or pizotyline).ab,kf,ti,nm. (418)
39 (alpha adj4 agonist*).ab,kf,ti. (15369)
40 exp Adrenergic alpha-Agonists/ (164069)
41 (clonidine or guanfacine).ab,kf,ti,nm. (19180)
42 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 [Interventions: named drugs/drug classes or types] (1098623)
43 randomized controlled trial.pt. (542809)
44 controlled clinical trial.pt. (94373)
45 randomized.ab. (533045)
46 placebo.ab. (221237)

47 clinical trials as topic.sh. (197235)
48 randomly.ab. (365421)
49 trial.ti. (247114)
50 43 or 44 or 45 or 46 or 47 or 48 or 49 (1392358)
51 exp animals/ not humans.sh. (4882975)
52 50 not 51 [RCTs filter] (1281368)
53 3 and 42 and 52 [population and interventions and RCTs filter] (3949)
54 ("in data review" or in process or publisher or "pubmed not medline").st. (4677722)
55 (random* or controlled trial* or clinical trial* or rct).ab,kf,ti. (1547833)
56 54 and 55 [pragmatic filter to pick up RCTs that have not been fully indexed for MEDLINE yet] (236445)
57 3 and 42 and 56 [population and interventions and non-MEDLINE RCT filter] (365)
58 53 or 57 (4029)

The migraine/headache search terms (lines 1-3) and botox search terms (lines 10-12) are based on those used in:
Herd CP, Tomlinson CL, Rick C, Scotton WJ, Edwards J, Ives N, Clarke CE, Sinclair A. Botulinum toxins for the prevention of migraine in adults. Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD011616. DOI: 10.1002/14651858.CD011616.pub2.

The search filter for RCTs (lines 43-52) is the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format: Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from: www.training.cochrane.org/handbook.

MEDLINE search strategy: additional searches for riboflavin, magnesium and coenzyme Q10, February 2022

Date searched: 08/02/22
Ovid MEDLINE(R) ALL <1946 to February 07, 2022>

1 (headache* or head ache* or migrain* or cephalgi* or cephalalgi* or hemicrani*).ab,kf,ti. 115846
2 Headache/ or exp Headache Disorders/ 62888
3 1 or 2 [population: migraine/headache] 127140
4 Riboflavin/ 9019
5 (riboflavin or vitamin b2 or vitamin b 2).ab,kf,ti,nm. 14667
6 Ubiquinone/ 9986
7 (coenzyme q* or co enzyme q* or ubidecarenone or ubiquino* or coq10 or co q10).ab,kf,ti,nm. 17133
8 Magnesium/ or exp Magnesium Compounds/ 83822
9 magnesium.ab,kf,ti,nm. 113129
10 4 or 5 or 6 or 7 or 8 or 9 [interventions: 3 drugs added February 2022] 147736
11 randomized controlled trial.pt. 558117
12 controlled clinical trial.pt. 94685
13 randomized.ab. 550007
14 placebo.ab. 225467
15 clinical trials as topic.sh. 199113
16 randomly.ab. 375668
17 trial.ti. 256318
18 11 or 12 or 13 or 14 or 15 or 16 or 17 1425517
19 exp animals/ not humans.sh. 4955382
20 18 not 19 [Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)] 1311348
21 3 and 10 and 20 [population + interventions + RCT filter] 161
22 ("in data review" or in process or publisher or "pubmed not medline").st. 4673502
23 (random* or controlled trial* or clinical trial* or rct).ab,kf,ti. 1597122

24 22 and 23 [filter to pick up RCTs that have not been fully indexed for MEDLINE yet] 231267
25 3 and 10 and 24 [population + interventions + RCT filter for non indexed studies] 18
26 21 or 25 163

MEDLINE search strategy: pragmatic search for recent systematic reviews, to check reference lists/included studies, February 2022

Date searched: 14/02/22
Ovid MEDLINE(R) ALL <1946 to February 11, 2022>
1 exp Migraine Disorders/pc 2569
2 "migrain*".ab,hw,kf,ti. 43508
3 ((prevent* or prophyla*) adj2 (treatment? or therap* or medication? or drug?)).ab,hw,kf,ti. 179039
4 2 and 3 3218
5 (migrain* adj4 (prevent* or prophyla*)).ab,hw,kf,ti. 3883
6 1 or 4 or 5 5846
7 (metaanalys* or "meta analys*").tw. 222321
8 (systematic* adj3 review*).mp. 276043
9 meta analysis.pt. 152804
10 7 or 8 or 9 [pragmatic systematic review filter] 392108
11 (((calcitonin gene-related peptide or CGRP) adj5 (antibod* or antagon* or inhibit* or block*)) or anti-CGRP or anti-calcitonin gene-related peptide or monoclonal antibod* or mAb or mAbs or moAb or moAbs).ab,kf,ti. 219332
12 Calcitonin Gene-Related Peptide/ai 452
13 Antibodies, Monoclonal/ or Antibodies, Monoclonal, Humanized/ 221635
14 Calcitonin Gene-Related Peptide Receptor Antagonists/ 781
15 (erenumab or galcanezumab or fremanezumab or eptinezumab).ab,kf,ti,nm. 588
16 (rimegepant or ubrogepant or atogepant or gepant?).ab,kf,ti,nm. 247
17 exp Botulinum Toxins/ 17563
18 (botulin* adj toxin*).ab,kf,ti,nm. 22444
19 (botulinum* or botox* or onabotulinum*).ab,kf,ti,nm. 25677
20 (antidepress* or anti depress*).ab,kf,ti. 75518
21 exp Antidepressive Agents/ 155320
22 (amitriptyline or venlafaxine or mirtazapine or duloxetine).ab,kf,ti,nm. 18204
23 exp "Serotonin and Noradrenaline Reuptake Inhibitors"/ 5141
24 (SNRI or SNRIs or (serotonin adj2 (noradrenaline or norepinephrine) adj reuptake inhib*)).ab,kf,ti. 2996
25 exp Angiotensin-Converting Enzyme Inhibitors/ 45974
26 (Angiotensin Converting Enzyme Inhibit* or ACE inhibit*).ab,kf,ti. 38458
27 acei.ab,kf,ti. 4519
28 lisinopril.ab,kf,ti,nm. 3114
29 ((angiotensin receptor or angiotensin II receptor) adj (block* or antagon*)).ab,kf,ti. 14830
30 (ARB or ARBs).ab,kf,ti. 8220
31 exp Angiotensin Receptor Antagonists/ 26157
32 candesartan.ab,kf,ti,nm. 3407
33 ((beta adj3 block*) or betablock*).ab,kf,ti. 56350
34 ((adrenergic or adrenoreceptor* or adrenoceptor*) adj3 (antagon* or block*)).ab,kf,ti. 35141
35 exp Adrenergic beta-Antagonists/ 85957
36 (propranolol or metoprolol or timolol or atenolol or nadolol or nebivolol or pindolol).ab,kf,ti,nm. 67483
37 (calcium adj2 (block* or antagon* or inhibit*)).ab,kf,ti. 41979
38 (CCB or CCBs).ab,kf,ti. 2692
39 exp Calcium Channel Blockers/ 89276
40 (flunarizine or verapamil).ab,kf,ti,nm. 27822
41 (anticonvuls* or antiepilep* or anti convuls* or anti epilep*).ab,kf,ti. 54399
42 exp Anticonvulsants/ 149062

43 (topiramate or valproate or divalproex or valproic acid or gabapentin).ab,kf,ti,nm. 31789
44 Pizotyline/ 250
45 (pizotifen or pizotyline).ab,kf,ti,nm. 420
46 (alpha adj4 agonist*).ab,kf,ti. 15482
47 exp Adrenergic alpha-Agonists/ 165206
48 (clonidine or guanfacine).ab,kf,ti,nm. 19260
49 Riboflavin/ 9020
50 (riboflavin or vitamin b2 or vitamin b 2).ab,kf,ti,nm. 14670
51 Ubiquinone/ 9995
52 (coenzyme q* or co enzyme q* or ubidecarenone or ubiquino* or coq10 or co q10).ab,kf,ti,nm. 17147
53 Magnesium/ or exp Magnesium Compounds/ 83845
54 magnesium.ab,kf,ti,nm. 113174
55 or/11-54 1249348
56 6 and 10 and 55 182
57 limit 56 to yr="2017 - 2022" 114

MEDLINE search strategy: update searches, November 2022 & June 2023

Date searched: 07/11/22

Ovid MEDLINE(R) ALL <1946 to November 04, 2022>

1 (headache* or head ache* or migrain* or cephalgi* or cephalalgi* or hemicrani*).ab,kf,ti. 121076
2 Headache/ or exp Headache Disorders/ 64821
3 1 or 2 [population: migraine/headache, based on Cochrane botox review] 132425
4 (((calcitonin gene-related peptide or CGRP) adj5 (antibod* or antagon* or inhibit* or block*)) or anti-CGRP or anti-calcitonin gene-related peptide or monoclonal antibod* or mAb or mAbs or moAb or moAbs).ab,kf,ti. 224346
5 Calcitonin Gene-Related Peptide/ai 463
6 Antibodies, Monoclonal/ or Antibodies, Monoclonal, Humanized/ 227720
7 Calcitonin Gene-Related Peptide Receptor Antagonists/ 887
8 (erenumab or galcanezumab or fremanezumab or eptinezumab).ab,kf,ti,nm. 730
9 (rimegepant or ubrogepant or atogepant or gepant?).ab,kf,ti,nm. 300
10 exp Botulinum Toxins/ 18153
11 (botulin* adj toxin*).ab,kf,ti,nm. 23232
12 (botulinum* or botox* or onabotulinum*).ab,kf,ti,nm. 26565
13 (antidepress* or anti depress*).ab,kf,ti. 78168
14 exp Antidepressive Agents/ 158352
15 (amitriptyline or venlafaxine or mirtazapine or duloxetine).ab,kf,ti,nm. 18641
16 exp "Serotonin and Noradrenaline Reuptake Inhibitors"/ 5336
17 (SNRI or SNRIs or (serotonin adj2 (noradrenaline or norepinephrine) adj reuptake inhib*)).ab,kf,ti. 3138
18 exp Angiotensin-Converting Enzyme Inhibitors/ 46764
19 (Angiotensin Converting Enzyme Inhibit* or ACE inhibit*).ab,kf,ti. 39244
20 acei.ab,kf,ti. 4749
21 lisinopril.ab,kf,ti,nm. 3155
22 ((angiotensin receptor or angiotensin II receptor) adj (block* or antagon*)).ab,kf,ti. 15370
23 (ARB or ARBs).ab,kf,ti. 8687
24 exp Angiotensin Receptor Antagonists/ 27181
25 candesartan.ab,kf,ti,nm. 3449
26 ((beta adj3 block*) or betablock*).ab,kf,ti. 57470
27 ((adrenergic or adrenoreceptor* or adrenoceptor*) adj3 (antagon* or block*)).ab,kf,ti. 35378
28 exp Adrenergic beta-Antagonists/ 86663
29 (propranolol or metoprolol or timolol or atenolol or nadolol or nebivolol or pindolol).ab,kf,ti,nm. 68123
30 (calcium adj2 (block* or antagon* or inhibit*)).ab,kf,ti. 42541
31 (CCB or CCBs).ab,kf,ti. 2828

32 exp Calcium Channel Blockers/ 90326
33 (flunarizine or verapamil).ab,kf,ti,nm. 28045
34 (anticonvuls* or antiepilep* or anti convuls* or anti epilep*).ab,kf,ti. 55690
35 exp Anticonvulsants/ 152010
36 (topiramate or valproate or divalproex or valproic acid or gabapentin).ab,kf,ti,nm. 32842
37 Pizotyline/ 252
38 (pizotifen or pizotyline).ab,kf,ti,nm. 425
39 (alpha adj4 agonist*).ab,kf,ti. 15644
40 exp Adrenergic alpha-Agonists/ 166795
41 (clonidine or guanfacine).ab,kf,ti,nm. 19418
42 Riboflavin/ 9260
43 (riboflavin or vitamin b2 or vitamin b 2).ab,kf,ti,nm. 15160
44 Ubiquinone/ 10256
45 (coenzyme q* or co enzyme q* or ubidecarenone or ubiquino* or coq10 or co q10).ab,kf,ti,nm. 17694
46 Magnesium/ or exp Magnesium Compounds/ 85028
47 magnesium.ab,kf,ti,nm. 115926
48 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 [Interventions: named drugs/drug classes or types] 1275840
49 randomized controlled trial.pt. 579949
50 controlled clinical trial.pt. 95083
51 randomized.ab. 580977
52 placebo.ab. 232922
53 clinical trials as topic.sh. 200534
54 randomly.ab. 394586
55 trial.ti. 273031
56 49 or 50 or 51 or 52 or 53 or 54 or 55 1482588
57 exp animals/ not humans.sh. 5060853
58 56 not 57 [Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)] 1364006
59 3 and 48 and 58 [population and interventions and RCT filter] 4313
60 ("in data review" or in process or publisher or "pubmed not medline").st. 4897386
61 (random* or controlled trial* or clinical trial* or rct).ab,kf,ti. 1688331
62 60 and 61 [filter to pick up RCTs that have not been fully indexed for MEDLINE yet] 242577
63 3 and 48 and 62 [population and interventions and non-MEDLINE RCT filter] 328
64 59 or 63 4390
65 limit 64 to ed=20210908-20221107 303
66 limit 64 to ep=20210908-20221107 211
67 limit 64 to dt=20210908-20221107 259
68 limit 64 to ez=20210908-20221107 259
69 limit 64 to da=20210908-20221107 366
70 65 or 66 or 67 or 68 or 69 390

Date searched: 15/06/23
Ovid MEDLINE(R) ALL <1946 to June 14, 2023>
As above, but lines 64-70 are:
64 59 or 63 4509
65 limit 64 to ed=20221107-20230615 101
66 limit 64 to ep=20221107-20230615 98
67 limit 64 to dt=20221107-20230615 127
68 limit 64 to ez=20221107-20230615 127
69 limit 64 to da=20221107-20230615 147
70 65 or 66 or 67 or 68 or 69 149

Appendix 2: The list of excluded studies

Publications	Reason(s) for exclusion
1.Pradalier A, Rancurel G, Dordain G, Verdure L, Rascol A, Dry J. Acute Migraine Attack Therapy: Comparison of Naproxen Sodium and an Ergotamine Tartrate Compound. Cephalalgia. 1985;5(2):107-113. [1] doi:10.1046/j.1468-2982.1985.0502107.x	Acute Migraine
2.Abbasi V, Atalu A, Seddighnia P. Comparison of Levetiracetam and sodium Valproate in the prevention of migraine: a randomized clinical trial study. International Journal of Basic & Clinical Pharmacology. 2018 Aug;7(8):1460. [2]	Small sample size of episodic migraine
3.Krakowski AJ, Engisch R. A new agent for chemotherapy of migraine headaches: a controlled study. Psychosomatics: Journal of Consultation and Liaison Psychiatry. 1973 Sep. [3]	Small sample size of episodic migraine
4.Adam EI, Gore SM, Price WH. Double blind trial of clonidine in the treatment of migraine in a general practice. The Journal of the Royal College of General Practitioners. 1978 Oct 1;28(195):587-90. [4]	Small sample size of episodic migraine
5.Soares AD, Louçana PM, Nasi EP, Sousa KM, Sá OM, Silva-Néto RP. A double-blind, randomized, and placebo-controlled clinical trial with omega-3 polyunsaturated fatty acids (OPFA ω-3) for the prevention of migraine in chronic migraine patients using amitriptyline. Nutritional neuroscience. 2018 Mar 16;21(3):219-23. [5]	Small sample size of chronic migraine
6.Afshari D, Rafizadeh S, Rezaei M. A comparative study of the effects of low-dose topiramate versus sodium valproate in migraine prophylaxis. International journal of Neuroscience. 2012 Jan 1;122(2):60-8. [6]	Small sample size of episodic migraine
7.Allais G, De Lorenzo C, Quirico PE, Airola G, Tolardo G, Mana O, Benedetto C. Acupuncture in the prophylactic treatment of migraine without aura: a comparison with flunarizine. Headache: The Journal of Head and Face Pain. 2002 Oct;42(9):855-61. [7]	Small sample size of episodic migraine
8. Chabi A, Zhang Y, Jackson S, Cady R, Lines C, Herring WJ, Connor KM, Michelson D. Randomized controlled trial of the orexin receptor antagonist filorexant for migraine prophylaxis. Cephalalgia. 2015 Apr;35(5):379-88. [8]	Not available in the market
9. Andersson PG, Dahl S, Hansen JH, Hansen PE, Hedman C, Nygaard Kristensen T, de Fine Olivarius B. Prophylactic treatment of classical and non-classical migraine with metoprolol—a comparison with placebo. Cephalalgia. 1983 Dec;3(4):207-12. [9]	Small sample size of episodic migraine
10. Camporeale A, Kudrow D, Sides R, Wang S, Van Dycke A, Selzler KJ, Stauffer VL. A phase 3, long-term, open-label safety study of Galcanezumab in patients with migraine. BMC neurology. 2018 Dec;18(1):1-2. [10]	A safety study, different Galcanezumab doses.
11.Ansell E, Fazzone T, Festenstein R, Johnson ES, Thavapalan M, Wilkinson M, Wozniak I. Nimodipine in migraine prophylaxis. Cephalalgia. 1988 Dec;8(4):269-72. [11]	Small sample size of episodic migraine
12.Bostani A, Rajabi A, Moradian N, Razazian N, Rezaei M. The effects of cinnarizine versus sodium valproate in migraine prophylaxis. International Journal of Neuroscience. 2013 Jul 1;123(7):487-93. [12]	Not clear if chronic, small sample size
13.Ashina M, Doležil D, Bonner JH, Zhou L, Klatt J, Picard H, Mikol DD. A phase 2, randomized, double-blind, placebo-controlled trial of AMG 301, a pituitary adenylate cyclase-activating polypeptide PAC1	Not available in the market

receptor monoclonal antibody for migraine prevention. Cephalalgia. 2021 Jan;41(1):33-44. [13]	
14.Assarzadegan F, Tabesh H, Hosseini-Zijoud SM, Beale AD, Shoghli A, Yazdi MG, Mansouri B, Hesami O, Moghadam NB, Kasmaei HD. Comparing zonisamide with sodium valproate in the management of migraine headaches: double-blind randomized clinical trial of efficacy and safety. Iranian Red Crescent Medical Journal. 2016 Sep;18(9). [14]	Small sample size of episodic migraine
15. Barrientos N, Chana P. Botulinum toxin type A in prophylactic treatment of migraine headaches: a preliminary study. The Journal of headache and pain. 2003 Dec;4(3):146-51. [15]	Small sample size of episodic migraine
16.Bavrasad R, Nejad SE, Yarahmadi AR, Sajedi SI, Rahim F. Assessment of the middle dose of topiramate in comparison with sodium valproate for migraine prophylaxis: a randomized-double-blind study. International Journal of Pharmacology. 2010 Sep 1;6(5):670-5. [16]	Small sample size of episodic migraine
17.Beran RG, Spira PJ. Levetiracetam in chronic daily headache: A double-blind, randomised placebo-controlled study: (The Australian KEPPRA Headache Trial [AUS-KHT]). Cephalalgia. 2011 Apr;31(5):530-6. [17]	Small sample size of chronic headache day
18. Bigal ME, Dodick DW, Krymchantowski AV, VanderPluym JH, Tepper SJ, Aycardi E, Loupe PS, Ma Y, Goadsby PJ. TEV-48125 for the preventive treatment of chronic migraine: efficacy at early time points. Neurology. 2016 Jul 5;87(1):41-8. [18]	Small sample size of chronic migraine and no outcome of interests
19. Blumenfeld AM, Stevanovic DM, Ortega M, Cohen JM, Seminerio MJ, Yang R, Jiang B, Tepper SJ. No "Wearing-Off Effect" Seen in Quarterly or Monthly Dosing of Fremanezumab: Subanalysis of a Randomized Long-Term Study. Headache: The Journal of Head and Face Pain. 2020 Nov;60(10):2431-43. [19]	Wearing-Off Effect study
20. Blumenfeld AM, Schim JD, Chippendale TJ. Botulinum toxin type A and divalproex sodium for prophylactic treatment of episodic or chronic migraine. Headache: The Journal of Head and Face Pain. 2008 Feb;48(2):210-20. [20]	Small size of mixed population
21. Brandes JL, Saper JR, Diamond M, Couch JR, Lewis DW, Schmitt J, Neto W, Schwabe S, Jacobs D, MIGR-002 Study Group, MIGR-002 Study Group. Topiramate for migraine prevention: a randomized controlled trial. Jama. 2004 Feb 25;291(8):965-73. [21]	The mixed population of adults and adolescence
22. Standnes B. The prophylactic effect of timolol versus propranolol and placebo in common migraine: beta-blockers in migraine. Cephalalgia. 1982 Sep;2(3):165-70. [22]	Small sample size of episodic migraine
23. Broessner G, Reuter U, Bonner JH, Dodick DW, Hallström Y, Picard H, Zhang F, Lenz RA, Klatt J, Mikol DD. The spectrum of response to erenumab in patients with episodic migraine and subgroup analysis of patients achieving≥ 50%,≥ 75%, and 100% response. Headache: The Journal of Head and Face Pain. 2020 Oct;60(9):2026-40. [23]	No report of Adverse Events
24. Bruno MA, Krymchantowski AV. Amitriptyline and intraoral devices for migraine prevention: a randomized comparative trial. Arquivos de Neuro-Psiquiatria. 2018;76:213-8. [24]	Small sample size of episodic migraine
25. R. K. Cady, C. P. Schreiber, J. A. H. Porter, A. M. Blumenfeld, and K. U. Farmer, "A multi-center double-blind pilot comparison of onabotulinumtoxinA and topiramate for the prophylactic treatment of chronic migraine," *Headache: The Journal of Head and Face Pain*, vol. 51, no. 1, pp. 21–32, 2011. [25]	Pilot study, small sample size of chronic migraine
26.Cady RK, Voirin J, Farmer K, Browning R, Beach ME, Tarrasch J. Two center, randomized pilot study of migraine prophylaxis comparing paradigms using pre-emptive frovatriptan or daily topiramate:	Small sample size of episodic migraine

research and clinical implications. Headache: The Journal of Head and Face Pain. 2012 May;52(5):749-64. [26]	
27.Cao K, Han F, Lin A, Yang W, Zhao J, Zhang H, Ding Y, Xie W, Xu Y, Yu T, Wang X. Zhengtian Capsule versus flunarizine in patients with migraine: a multi-center, double-blind, double-dummy, randomized controlled, non-inferior clinical trial. BMC complementary and alternative medicine. 2016 Dec;16(1):1-0. [27]	Herbal remedy
28. Chankrachang S, Arayawichanont A, Poungvarin N, Nidhinandana S, Boonkongchuen P, Towanabut S, Sithinamsuwan P, Kongsaengdao S. Prophylactic botulinum type A toxin complex (Dysport®) for migraine without aura. Headache: The Journal of Head and Face Pain. 2011 Jan;51(1):52-63. [28]	Small sample size of episodic migraine
29.Charles JA, Jotkowitz S, Byrd LH. Prevention of migraine with olmesartan in patients with hypertension/prehypertension. Headache: The Journal of Head and Face Pain. 2006 Mar;46(3):503-7. [29]	Small sample size of different doses of the same drug, no placebo/control
30. Christensen CE, Younis S, Deen M, Khan S, Ghanizada H, Ashina M. Migraine induction with calcitonin gene-related peptide in patients from erenumab trials. The Journal of Headache and Pain. 2018 Dec;19(1):1-9. [30]	question not relevant, not a trial of migraine prevention
31. Couch JR, Amitriptyline Versus Placebo Study Group. Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. Headache: The Journal of Head and Face Pain. 2011 Jan;51(1):33-51. [31]	Small sample size of episodic and chronic migraine
32. Yang CP, Chang MH, Liu PE, Li TC, Hsieh CL, Hwang KL, Chang HH. Acupuncture versus topiramate in chronic migraine prophylaxis: a randomized clinical trial. Cephalalgia. 2011 Nov;31(15):1510-21. [32]	Small sample size of chronic migraine, and compared with Chinese traditional medicines
33.d'Amato CC, Pizza V, Marmolo T, Giordano E, Alfano V, Nasta A. Fluoxetine for migraine prophylaxis: a double-blind trial. Headache: The Journal of Head and Face Pain. 1999 Nov;39(10):716-9. [33]	Small sample size of migraine
34.Buse DC, Lipton RB, Hallström Y, Reuter U, Tepper SJ, Zhang F, Sapra S, Picard H, Mikol DD, Lenz RA. Migraine-related disability, impact, and health-related quality of life among patients with episodic migraine receiving preventive treatment with Erenumab. Cephalalgia. 2018 Sep;38(10):1622-31. [34]	No report of Adverse Events
35. Diener HC, Krupp P, Schmitt T, Steitz G, Milde K, Freytag S, Study Group. Cyclandelate in the prophylaxis of migraine: a placebo-controlled study. Cephalalgia. 2001 Feb;21(1):66-70. [35]	No report of Adverse Events
36. Diener HC, F" h M, Laccarino C, Wessely P, Isler H, Stienge H, Fischer M, Wedekind W, Taneri Z. Cyclandelate in the prophylaxis of migraine: a randomized, parallel, double-blind study in comparison with placebo and propranolol. Cephalalgia. 1996 Oct;16(6):441-7. [36]	Small sample size of episodic or chronic migraine
37.Diener HC, Hartung E, Chrubasik JO, Evers S, Schoenen J, Eikermann A, Latta G, Hauke W, Study Group. A comparative study of oral acetylsalicyclic acid and metoprolol for the prophylactic treatment of migraine. A randomized, controlled, double-blind, parallel group phase III study. Cephalalgia. 2001 Mar;21(2):120-8. [37]	No report of Adverse Events
38. Diener HC, Bussone G, Oene JV, Lahaye M, Schwalen S, Goadsby PJ. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. Cephalalgia. 2007 Jul;27(7):814-23. [38]	Small sample size of chronic migraine
39. Dodick DW, Mauskop A, Elkind AH, DeGryse R, Brin MF, Silberstein SD, Botox CDH Study Group. Botulinum toxin type A for the prophylaxis of chronic daily headache: Subgroup analysis of patients	Chronic daily headache

not receiving other prophylactic medications: A randomized double-blind, placebo-controlled study. Headache: The Journal of Head and Face Pain. 2005 Apr;45(4):315-24. [39]	
40. Domingues RB, Silva AL, Domingues SA, Aquino CC, Kuster GW. A double-blind randomized controlled trial of low doses of propranolol, nortriptyline, and the combination of propranolol and nortriptyline for the preventive treatment of migraine. Arquivos de neuro-psiquiatria. 2009;67:973-7. [40]	Small sample size of episodic or chronic migraine
41. Magalhães E, Menezes C, Cardeal M, Melo A. Botulinum toxin type A versus amitriptyline for the treatment of chronic daily migraine. Clinical neurology and neurosurgery. 2010 Jul 1;112(6):463-6. [41]	Small sample size of chronic migraine, and no outcomes of interest
42. Lipton RB, Pozo-Rosich P, Blumenfeld AM, Dodick DW, McAllister P, Li Y, Lu K, Dabruzzo B, Miceli R, Severt L, Finnegan M. Rates of response to atogepant for migraine prophylaxis among adults: a secondary analysis of a randomized clinical trial. JAMA Network Open. 2022 Jun 1;5(6):e2215499-. [42]	Episodic migraine
43. Faraji F, Zarinfar N, Zanjani AT, Morteza A. The effect of Helicobacter pylori eradication on migraine: a randomized, double blind, controlled trial. Pain physician. 2012;15(6):495. [43]	This is the eradication of HP not use of a prophylactic treatment
44. Ford JH, Ayer DW, Zhang Q, Carter JN, Leroux E, Skljarevski V, Aurora SK, Tockhorn-Heidenreich A, Lipton RB. Two randomized migraine studies of galcanezumab: effects on patient functioning and disability. Neurology. 2019 Jul 30;93(5):e508-17. [44]	No report of Adverse Events
45. Freitag FG, Diamond S, Diamond M, Urban G. Botulinum toxin type A in the treatment of chronic migraine without medication overuse. Headache: The Journal of Head and Face Pain. 2008 Feb;48(2):201-9. [45]	Small sample size of chronic migraine
46. Lauretti GR, Rosa CP, Kitayama A, Lopes BC. Comparison of botox® or prosigne® and facial nerve blockade as adjuvant in chronic migraine. Journal of Biomedical Science and Engineering. 2014 Jun 26;2014. [46]	Small sample size of chronic migraine
47. Ganji R, Majdinasab N, Hesam S, Rostami N, Sayyah M, Sahebnasagh A. Does atorvastatin have augmentative effects with sodium valproate in prevention of migraine with aura attacks? A triple-blind controlled clinical trial. Journal of pharmaceutical health care and sciences. 2021 Dec;7(1):1-0. [47]	Small sample size of episodic migraine
48. Gawel MJ, Kreeft J, Nelson RF, Simard D, Arnott WS. Comparison of the efficacy and safety of flunarizine to propranolol in the prophylaxis of migraine. Canadian journal of neurological sciences. 1992 Aug;19(3):340-5. [48]	Small sample size of episodic migraine
49. Keyvan G, Abolfazl MB. Comparison of treatment effect of sodium valproate, propranolol and tricyclic antidepressants in migraine. Pakistan journal of biological sciences: PJBS. 2009 Aug 1;12(15):1098-101. [49]	Small sample size of episodic or chronic migraine
50. Hussein HS, Alsalihi NJ, Al Gawwam G. Flunarizine Vs Propranolol in the Prevention of Migrainous Headache Attacks. Age (years). 2021;30(9):30-4. [50]	Small sample size of migraine
51. Ghose K, Niven BE, Berry D. A double-blind crossover comparison of the effects of vigabatrin with placebo in the prevention of migraine headache. The Journal of Headache and Pain. 2002 Sep;3(2):79-85. [51]	Small sample size of migraine
52. Goadsby PJ, Silberstein SD, Yeung PP, Cohen JM, Ning X, Yang R, Dodick DW. Long-term safety, tolerability, and efficacy of fremanezumab in migraine: a randomized study. Neurology. 2020 Nov 3;95(18):e2487-99. [52]	Comparing the dosing regime of same drug

53. Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, Wright IK, Chou DE, Klatt J, Picard H, Lenz RA. One-year sustained efficacy of erenumab in episodic migraine: results of the STRIVE study. Neurology. 2020 Aug 4;95(5):e469-79. [53]	Reporting the active treatment phase with dose blinding not the RCT part
54. Goadsby PJ, Reuter U, Lanteri-Minet M, da Silva Lima GP, Hours-Zesiger P, Fernandes C, Wen S, Tenenbaum N, Kataria A, Ferrari MD, Klatt J. Long-Term efficacy and safety of Erenumab: results from 64 weeks of the liberty study. Neurology. 2021 Jun 1;96(22):e2724-35. [54]	Not RCT
55. Grahame R. Drug prophylaxis in migraine. British Medical Journal. 1960 Oct 10;2(5207):1203. [55]	Small sample size of episodic migraine
56. Rompel, H. & Bauermeister PW. Aetiology of migraine and prevention with carbamazepine (Tegretol): results of a double-blind, cross-over study. South African Medical Journal. 1970 Jan 1;44(4):75-80. [56]	Small sample size of episodic migraine
57. Havanka-Kanniainen H, Hokkanen E, Myllylä VV. Efficacy of nimodipine in comparison with pizotifen in the prophylaxis of migraine. Cephalalgia. 1987 Mar;7(1):7-13. [57]	Small sample size of episodic migraine
58. Silberstein SD, Rapoport AM, Loupe PS, Aycardi E, McDonald M, Yang R, Bigal ME. The effect of beginning treatment with fremanezumab on headache and associated symptoms in the randomized phase 2 study of high frequency episodic migraine: Post-hoc analyses on the first 3 weeks of treatment. Headache: The Journal of Head and Face Pain. 2019 Mar;59(3):383-93. [58]	Small sample size of episodic migraine
59. Hering R, Kuritzky A. Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. Cephalalgia. 1992 Apr;12(2):81-4. [59]	Small sample size of episodic migraine
60. Hirata K, Takeshima T, Sakai F, Tatsuoka Y, Suzuki N, Igarashi H, Nakamura T, Ozeki A, Yamazaki H, Skljarevski V. A long-term open-label safety study of galcanezumab in Japanese patients with migraine. Expert Opinion on Drug Safety. 2021 Jun 3;20(6):721-33. [60]	Not RCT
61. Hollanda L, Monteiro L, Melo A. Botulinum toxin type a for cephalic cutaneous allodynia in chronic migraine: a randomized, double-blinded, placebo-controlled trial. Neurology International. 2014 Dec 5;6(4):5133. [61]	Assesses cutaneous allodynia rather than headache improvement
62. Hou M, Xie JF, Kong XP, Zhang Y, Shao YF, Wang C, Ren WT, Cui GF, Xin L, Hou YP. Acupoint injection of onabotulinumtoxin A for migraines. Toxins. 2015 Oct 30;7(11):4442-54. [62]	Small sample size of episodic migraine
63. Mehvari J, Rafieian-Kopaei M. Prophylactic activity of cyproheptadine and Bellergal on migraine headache. Iranian Journal of Medical Sciences. 2005 Jun 1;30(2). [63]	Small sample size of episodic migraine
64. Song JH, Zhang GB, Ding XD, Huang L, Hong Y, Chen HX. Efficacy of type a botulinum toxin injections and infrared polarized light on treating chronic migraine. Eur Rev Med Pharmacol Sci. 2015 Jan 1;19(11):1976-82. [64]	Small sample size of chronic migraine
65. Gomersall JD, Stuart A. Amitriptyline in migraine prophylaxis: changes in pattern of attacks during a controlled clinical trial. Journal of Neurology, Neurosurgery & Psychiatry. 1973 Aug 1;36(4):684-90. [65]	Small sample size of episodic migraine
66. Jedynak J, Eross E, Gendolla A, Rettiganti M, Stauffer VL. Shift from high-frequency to low-frequency episodic migraine in patients treated with galcanezumab: results from two global randomized clinical trials. The Journal of Headache and Pain. 2021 Dec;22(1):1-0. [66]	No report of Adverse Events
67. Grotemeyer KH, Schlake HP, Husstedt IW. Etilefrine Pivalate vs. Dihydroergotamin and Flunarizin in Prophylactic Treatment of	Small sample size of episodic migraine

Migraine in Patients with Low Blood Pressure—A Randomized Double-Blind-Study. Cephalalgia. 1989 Oct;9(10_suppl):433-4. [67]	
68. Welch KM. 11: Naproxen Sodium in the Treatment of Migraine. Cephalalgia. 1986 Apr;6(4_suppl):85-92. [68]	Small sample size of episodic migraine
69. Kuruppu DK, Tobin J, Dong Y, Aurora SK, Yunes-Medina L, Green AL. Efficacy of galcanezumab in patients with migraine who did not benefit from commonly prescribed preventive treatments. BMC neurology. 2021 Dec;21(1):1-9. [69]	No report of Adverse Events
70. Lai KL, Niddam DM, Fuh JL, Chen SP, Wang YF, Chen WT, Wu JC, Wang SJ. Flunarizine versus topiramate for chronic migraine prophylaxis: a randomized trial. Acta Neurologica Scandinavica. 2017 Apr;135(4):476-83. [70]	Small sample size of chronic migraine
71. Landy S, McGinnis J, Curlin D, Laizure SC. Selective serotonin reuptake inhibitors for migraine prophylaxis. Headache: The Journal of Head and Face Pain. 1999 Jan;39(1):28-32. [64, 71]	Small sample size of episodic migraine
72. Lepcha A, Amalanathan S, Augustine AM, Tyagi AK, Balraj A. Flunarizine in the prophylaxis of migrainous vertigo: a randomized controlled trial. European Archives of Oto-Rhino-Laryngology. 2014 Nov;271(11):2931-6. [72]	Vertigo migraine
73. Lipton RB, Cohen JM, Galic M, Seminerio MJ, Yeung PP, Aycardi E, Bigal ME, Bibeau K, Buse DC. Effects of fremanezumab in patients with chronic migraine and comorbid depression: subgroup analysis of the randomized HALO CM study. Headache: The Journal of Head and Face Pain. 2021 Apr;61(4):662-72. [73]	Content of this paper is out of scope
74. Loeb LM, Amorim RP, Mazzacoratti MD, Scorza FA, Peres MF. Botulinum toxin A (BT-A) versus low-level laser therapy (LLLT) in chronic migraine treatment: a comparison. Arquivos de neuro-psiquiatria. 2018;76:663-7. [74]	Small sample size of chronic migraine
75. Louis P, Spierings EL. Comparison of flunarizine (Sibelium®) and pizotifen (Sandomigran®) in migraine treatment: A double-blind study. Cephalalgia. 1982 Dec 1;2(4):197-203. [75]	Small sample size of episodic migraine
76. Luo N, Di W, Zhang A, Wang Y, Ding M, Qi W, Zhu Y, Massing MW, Fang Y. A randomized, one-year clinical trial comparing the efficacy of topiramate, flunarizine, and a combination of flunarizine and topiramate in migraine prophylaxis. Pain Medicine. 2012 Jan 1;13(1):80-6. [76]	Small sample size of chronic migraine
77. Siniatchkin M, Andrasik F, Kropp P, Niederberger U, Strenge H, Averkina N, Lindner V, Stephani U, Gerber WD. Central mechanisms of controlled-release metoprolol in migraine: a double-blind, placebo-controlled study. Cephalalgia. 2007 Sep;27(9):1024-32. [77]	Small sample size of episodic migraine
78. Bigal ME, Dodick DW, Rapoport AM, Silberstein SD, Ma Y, Yang R, Loupe PS, Burstein R, Newman LC, Lipton RB. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. The Lancet Neurology. 2015 Nov 1;14(11):1081-90. [78]	Small sample size of episodic migraine
79. Simmonds MK, Rashiq S, Sobolev IA, Dick BD, Gray DP, Stewart BJ, Jamieson-Lega KI. The effect of single-dose propofol injection on pain and quality of life in chronic daily headache: a randomized, double-blind, controlled trial. Anesthesia & Analgesia. 2009 Dec 1;109(6):1972-80. [79]	Small sample size of chronic daily headache
80. Mathew NT, Frishberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C, Botox CDH Study Group. Botulinum toxin type A (BOTOX®) for the prophylactic treatment of chronic daily headache: A randomized, double-blind, placebo-controlled trial. Headache: The Journal of Head and Face Pain. 2005 Apr;45(4):293-307. [80]	Chronic daily headache

81. Mathew NT, Jaffri SF. A double-blind comparison of onabotulinumtoxina (BOTOX®) and topiramate (TOPAMAX®) for the prophylactic treatment of chronic migraine: A pilot study. Headache: The Journal of Head and Face Pain. 2009 Nov;49(10):1466-78. [81]	Small sample size of chronic migraine
82. Mazdeh M, Mahmudian R, Vafaei SY, Taheri M, Ghafouri-Fard S. Effect of propranolol with and without rosuvastatin on migraine attacks: a triple blind randomized clinical trial. Future Neurology. 2020 May;15(2):FNL44. [82]	Small sample size of episodic or chronic migraine
83. Homam M, Farajpour A, Khadem S, Mostafavian Z. The experiential comparison of levetiracetam efficacy in migraine headache with sodium valproate. Caspian Journal of Neurological Sciences. 2016 Jun 10;2(2):42-9. [83]	Small sample size of episodic migraine
84. Millan-Guerrero RO, Isais-Millan R, Barreto-Vizcaino S, Rivera-Castano L, Garcia-Solorzano A, López-Blanca C, Membrila-Maldonado M, Muñoz-Solis R. Subcutaneous histamine versus sodium valproate in migraine prophylaxis: A randomized, controlled, double-blind study. European journal of neurology. 2007 Oct;14(10):1079-84. [84]	Small sample size of episodic migraine
85. Millán-Guerrero RO, Isais-Millán S, Barreto-Vizcaíno S, Rivera-Castaño L, Rios-Madariaga C. Subcutaneous histamine versus botulinum toxin type A in migraine prophylaxis: a randomized, double-blind study. European journal of neurology. 2009 Jan;16(1):88-94. [85]	Small sample size of episodic migraine
86. Mogollón J, Serrano A, Padrón de Freitez A, Uzcátegui E, Baptista T. Olanzapine as an add-on treatment in migraine status: A randomized double-blind, placebo-controlled, pilot study. The European Journal of Psychiatry. 2012 Dec;26(4):260-5. [86]	Acute Migraine
87. Hasan MK, Khan I, Salam T, Sharmin M. The Sociodemographic Characteristics of Migraine Patients in Bangladesh. Int J Med Res Prof. 2019:59-62. [87]	Small sample size of episodic migraine
88. Choudhary MU, Nawaz J, Saddique MU, Zameer A. Comparison between topiramate and sodium valproate efficacy in the treatment of migraine. Pak J Med Health Sci. 2017 Jul 1;11(3):1005-7. [88]	Small sample size of episodic migraine
89. Naderinabi B, Saberi A, Hashemi M, Haghighi M, Biazar G, Gharehdaghi FA, Sedighinejad A, Chavoshi T. Acupuncture and botulinum toxin A injection in the treatment of chronic migraine: a randomized controlled study. Caspian Journal of Internal Medicine. 2017;8(3):196. [89]	Small sample size of chronic migraine
90. Nappi G, Sandrini G, Savoini G, Cavallini A, De Rysky C, Micieli G. Comparative efficacy of cyclandelate versus flunarizine in the prophylactic treatment of migraine. Drugs. 1987 Mar;33(2):103-9. [90]	Small sample size of episodic migraine
91. Nichols R, Doty E, Sacco S, Ruff D, Pearlman E, Aurora SK. Analysis of initial nonresponders to galcanezumab in patients with episodic or chronic migraine: results from the EVOLVE-1, EVOLVE-2, and REGAIN randomized, double-blind, placebo-controlled studies. Headache: The Journal of Head and Face Pain. 2019 Feb;59(2):192-204. [91]	Mixed population
92. Olsson JE, Behring HC, Forssman B, Hedman C, Hedman G, Johansson FA, Kinnman J, Pålhagen SE, Samuelsson M, Strandman E. Metoprolol and propranolol in migraine prophylaxis: a double-blind multicentre study. Acta neurologica scandinavica. 1984 Sep;70(3):160-8. [92]	Small sample size of episodic migraine
93. Omranifard M, Abdali H, Ardakani MR, Talebianfar M. A comparison of outcome of medical and surgical treatment of migraine headache: In 1 year follow-up. Advanced Biomedical Research. 2016;5. [93]	Small sample size of chronic migraine

94. Ondo WG, Vuong KD, Derman HS. Botulinum toxin A for chronic daily headache: a randomized, placebo-controlled, parallel design study. Cephalalgia. 2004 Jan;24(1):60-5. [94]	Mixed of chronic tension type and chronic migraine headaches.
95. Ozyalcin SN, Talu GK, Kiziltan E, Yucel B, Ertas M, Disci R. The efficacy and safety of venlafaxine in the prophylaxis of migraine. Headache: The Journal of Head and Face Pain. 2005 Feb;45(2):144-52. [95]	Small sample size of migraine
96. Kangasniemi P, Hedman C. Metoprolol and propranolol in the prophylactic treatment of classical and common migraine. A double-blind study. Cephalalgia. 1984 Jun;4(2):91-6. [96]	Small sample size of migraine
97. Kangasniemi PJ, Nyrke T, Lang AH, Petersen E. Femoxetine-a new 5-HT uptake inhibitor-and propranolol in the prophylactic treatment of migraine. Acta neurologica scandinavica. 1983 Oct;68(4):262-7. [97]	Drug not available and small sample size of migraine
98. Goadsby PJ, Dodick DW, Ailani J, Trugman JM, Finnegan M, Lu K, Szegedi A. Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: a double-blind, randomised phase 2b/3 trial. The Lancet Neurology. 2020 Sep 1;19(9):727-37. [98]	Small sample size of episodic migraine
99. Pijpers JA, Kies DA, Louter MA, van Zwet EW, Ferrari MD, Terwindt GM. Acute withdrawal and botulinum toxin A in chronic migraine with medication overuse: a double-blind randomized controlled trial. Brain. 2019 May 1;142(5):1203-14. [99]	Small sample size of chronic migraine
100. Pradalier A, Serratrice G, Collard M, Hirsch E, Feve J, Masson M, Masson C, Dry J, Koulikovsky G, Nguyen G, Schbath J. Long-acting propranolol in migraine prophylaxis: results of a double-blind, placebo-controlled study. Cephalalgia. 1989 Dec;9(4):247-53. [100]	Small sample size of episodic or chronic migraine
101. Pradalier A, Lantéri-Minet M, Géraud G, Attain H, Lucas C, Delgado A. The PROMISE study: PROphylaxis of migraine with SEglor®(dihydroergotamine mesilate) in French primary care. CNS drugs. 2004 Dec;18(15):1149-63. [101]	No report of Adverse Events
102. Rahimdel A, Zeinali A, Yazdian-Anari P, Hajizadeh R, Arefnia E. Effectiveness of vitamin B2 versus sodium valproate in migraine prophylaxis: a randomized clinical trial. Electronic Physician. 2015 Oct;7(6):1344. [102]	Small sample size of migraine
103. Rapoport A, Mauskop A, Diener HC, Schwalen S, Pfeil J. Long-term migraine prevention with topiramate: open-label extension of pivotal trials. Headache: The Journal of Head and Face Pain. 2006 Jul;46(7):1151-60. [103]	Mixed population of adults and adolescence
104. Rasmussen MJ, Holt Larsen B, Borg L, Soelberg Sørensen P, Hansen PE. Tolfenamic acid versus propranolol in the prophylactic treatment of migraine. Acta neurologica scandinavica. 1994 Jun;89(6):446-50. [104]	Small sample size of episodic or chronic migraine
105. Kaushik R, Kaushik RM, Mahajan SK, Rajesh V. Biofeedback assisted diaphragmatic breathing and systematic relaxation versus propranolol in long term prophylaxis of migraine. Complementary therapies in medicine. 2005 Sep 1;13(3):165-74. [105]	Small sample size of episodic or chronic migraine
106. Lipton RB, Silberstein S, Dodick D, Cady R, Freitag F, Mathew N, Biondi DM, Ascher S, Olson WH, Hulihan J. Topiramate intervention to prevent transformation of episodic migraine: the topiramate INTREPID study. Cephalalgia. 2011 Jan;31(1):18-30. [106]	Mixed population of adults and adolescence
107. Ryan Sr RE. Comparative study of nadolol and propranolol in prophylactic treatment of migraine. American Heart Journal. 1984 Oct 1;108(4):1156-9. [107]	Small sample size of episodic or chronic migraine
108. Ryan RE, Diamond S, Ryan RE. Double blind study of clonidine and placebo for the prophylactic treatment of migraine. Headache: The Journal of Head and Face Pain. 1975 Oct;15(3):202-6. [108]	Small sample size of migraine

109. Ildefonso RL, Martín SA, Francisco HS, Mandeville Peter B, del Rocío RL, Manuel SM, Humberto TP. Topiramate vs. Amitriptyline in prophylactic treatment of migraine: A controlled clinical trial. Rev Mex Neurosci. 2010;11(5):338-42. [109]	Small sample size of migraine
110. Weber RB, Reinmuth OM. The treatment of migraine with propranolol. Neurology. 1972 Apr 1;22(4):366-9. [110]	Small sample size of migraine
111. Ruff DD, Ford JH, Tockhorn-Heidenreich A, Stauffer VL, Govindan S, Aurora SK, Terwindt GM, Goadsby PJ. Efficacy of galcanezumab in patients with episodic migraine and a history of preventive treatment failure: results from two global randomized clinical trials. European journal of neurology. 2020 Apr;27(4):609-18. [111]	No report of Adverse Events
112. Evers S, Vollmer-Haase J, Schwaag S, Rahmann A, Husstedt IW, Frese A. Botulinum toxin A in the prophylactic treatment of migraine–a randomized, double-blind, placebo-controlled study. Cephalalgia. 2004 Oct;24(10):838-43. [112]	Small sample size of migraine
113. Ghobadi SH, Jivad N. The prophylactic activity of propranol and nimodipineon migraine headache. World J Med Sci. 2013;8(2):144-6. [113]	Small sample size of migraine
114. Sadeghian H, Motiei-Langroudi R. Comparison of Levetiracetam and sodium Valproate in migraine prophylaxis: A randomized placebo-controlled study. Annals of Indian Academy of Neurology. 2015 Jan;18(1):45. [114]	Mixed population of adolescent and adult
115. Sakai F, Takeshima T, Tatsuoka Y, Hirata K, Lenz R, Wang Y, Cheng S, Hirama T, Mikol DD. A randomized phase 2 study of erenumab for the prevention of episodic migraine in Japanese adults. Headache: The Journal of Head and Face Pain. 2019 Nov;59(10):1731-42. [115]	Small sample size of episodic migraine
116. Sakai F, Takeshima T, Tatsuoka Y, Hirata K, Cheng S, Numachi Y, Peng C, Xue F, Mikol DD. Long-term efficacy and safety during open-label erenumab treatment in Japanese patients with episodic migraine. Headache: The Journal of Head and Face Pain. 2021 Apr;61(4):653-61. [116]	Small sample size of episodic migraine
117. Santiago MD, Carvalho DD, Gabbai AA, Pinto MM, Moutran AR, Villa TR. Amitriptyline and aerobic exercise or amitriptyline alone in the treatment of chronic migraine: a randomized comparative study. Arquivos de neuro-psiquiatria. 2014;72:851-5. [117]	Small sample size of chronic migraine
118. Saper JR, Lake III AE, Cantrell DT, Winner PK, White JR. Chronic daily headache prophylaxis with tizanidine: a double-blind, placebo-controlled, multicenter outcome study. Headache: The Journal of Head and Face Pain. 2002 Jun;42(6):470-82. [118]	Small sample size of chronic daily headache
119. Schellenberg R, Lichtenthal A, Wöhling H, Graf C, Brixius K. Nebivolol and Metoprolol for Treating Migraine: An Advance on β-Blocker Treatment?. Headache: The Journal of Head and Face Pain. 2008 Jan;48(1):118-25. [119]	Small sample size of episodic or chronic migraine
120. Seng EK, Holroyd KA. Behavioral migraine management modifies behavioral and cognitive coping in people with migraine. Headache: The Journal of Head and Face Pain. 2014 Oct;54(9):1470-83. [120]	Not drug trial
121. Bulut S, Berilgen MS, Baran A, Tekatas A, Atmaca M, Mungen B. Venlafaxine versus amitriptyline in the prophylactic treatment of migraine: randomized, double-blind, crossover study. Clinical neurology and neurosurgery. 2004 Dec 1;107(1):44-8. [121]	Small sample size of episodic migraine
122. Sonbolestan SA, Heshmat K, Javanmard SH, Saadatnia M. Efficacy of enalapril in migraine prophylaxis: a randomized, double-blind, placebo-controlled trial. International Journal of Preventive Medicine. 2013 Jan;4(1):72. [122]	Small sample size of episodic migraine

123. Rafie S, Karimian F, Ghomifar A, Karimian A. Effect of Pramipexole on Headache Relief in Patients with Concomitant Migraine and Restless Legs Syndrome; A Randomized, Controlled, Clinical Trial. Jundishapur Journal of Natural Pharmaceutical Products. 2019 Aug 31;14(3). [123]	Small sample size of episodic or chronic migraine
124. Shehata HS, Esmail EH, Abdelalim A, El-Jaafary S, Elmazny A, Sabbah A, Shalaby NM. Repetitive transcranial magnetic stimulation versus botulinum toxin injection in chronic migraine prophylaxis: a pilot randomized trial. Journal of pain research. 2016;9:771. [124]	Small sample size of chronic migraine
125. Silberstein SD, Collins SD, Long-term Safety of Depakote in Headache Prophylaxis Study Group. Safety of divalproex sodium in migraine prophylaxis: An open-label, long-term study. Headache: The Journal of Head and Face Pain. 1999 Oct;39(9):633-43. [125]	Not a RCT
126. Silberstein SD, Neto W, Schmitt J, Jacobs D, MIGR-001 Study Group. Topiramate in migraine prevention: results of a large controlled trial. Archives of Neurology. 2004 Apr 1;61(4):490-5. [126]	Mixed population of adults and adolescence
127. Silberstein SD, Dodick DW, Lindblad AS, Holroyd K, Harrington M, Mathew NT, Hirtz D. Randomized, placebo-controlled trial of propranolol added to topiramate in chronic migraine. Neurology. 2012 Mar 27;78(13):976-84. [127]	Small sample size of chronic migraine
128. Silvestrini M, Bartolini M, Coccia M, Baruffaldi R, Taffi R, Provinciali L. Topiramate in the treatment of chronic migraine. Cephalalgia. 2003 Oct;23(8):820-4. [128]	Small sample size of chronic migraine
129. Skljarevski V, Oakes TM, Zhang QI, Ferguson MB, Martinez J, Camporeale A, Johnson KW, Shan Q, Carter J, Schacht A, Goadsby PJ. Effect of different doses of galcanezumab vs placebo for episodic migraine prevention: a randomized clinical trial. JAMA neurology. 2018 Feb 1;75(2):187-93. [129]	Small sample size of episodic migraine
130. Sørensen PS, Hansen K, Olesen J. A placebo-controlled, double-blind, cross-over trial of flunarizine in common migraine. Cephalalgia. 1986 Mar;6(1):7-14. [130]	Small sample size of migraine
131. Silberstein SD, Loder E, Forde G, Papadopoulos G, Fairclough D, Greenberg S. The impact of migraine on daily activities: effect of topiramate compared with placebo. Current medical research and opinion. 2006 Jun 1;22(6):1021-9. [131]	No report of Adverse Events
132. Silberstein S, Goode-Sellers S, Twomey C, Saiers J, Ascher J. Randomized, double-blind, placebo-controlled, phase II trial of gabapentin enacarbil for migraine prophylaxis. Cephalalgia. 2013 Jan;33(2):101-11. [132]	Small sample size of episodic migraine
133. Stovner LJ, Linde M, Gravdahl GB, Tronvik E, Aamodt AH, Sand T, Hagen K. A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study. Cephalalgia. 2014 Jun;34(7):523-32. [133]	Small sample size of episodic or chronic migraine
134. Sujan MU, Rao MR, Kisan R, Abhishekh HA, Nalini A, Raju TR, Sathyaprabha TN. Influence of hydrotherapy on clinical and cardiac autonomic function in migraine patients. Journal of neurosciences in rural practice. 2016 Jan;7(01):109-13. [134]	Not drug trial
135. Zain S, Khan M, Alam R, Zafar I, Ahmed S. Comparison of efficacy and safety of topiramate with gabapentin in migraine prophylaxis: randomized open label control trial. J Pak Med Assoc. 2013 Jan 1;63(1):3-7. [135]	Small sample size of episodic migraine
136. Tatsuoka Y, Takeshima T, Ozeki A, Matsumura T. Treatment Satisfaction of Galcanezumab in Japanese Patients with Episodic Migraine: A Phase 2 Randomized Controlled Study. Neurology and therapy. 2021 Jun;10(1):265-78. [136]	No report of Adverse Events

137. Oakes TM, Skljarevski V, Zhang Q, Kielbasa W, Hodsdon ME, Detke HC, Camporeale A, Saper JR. Safety of galcanezumab in patients with episodic migraine: a randomized placebo-controlled dose-ranging phase 2b study. Cephalalgia. 2018 May;38(6):1015-25. [137]	Small sample size of episodic migraine
138. Titus F, Dávalos A, Alom J, Codina A. 5-hydroxytryptophan versus methysergide in the prophylaxis of migraine. European neurology. 1986;25(5):327-9. [138]	Small sample size of migraine
139. Steiner TJ, Ahmed F, Findley LJ, MacGregor EA, Wilkinson M. S-fluoxetine in the prophylaxis of migraine: a phase II double-blind randomized placebo-controlled study. Cephalalgia. 1998 Jun;18(5):283-6. [139]	Small sample size of migraine
140. Vahedi K, Taupin P, Djomby RF, El-Amrani M, Lutz G, Filipetti V, Landais P, Massiou H, Bousser MG. Efficacy and tolerability of acetazolamide in migraine prophylaxis: a randomised placebo-controlled trial. Journal of neurology. 2002 Feb;249(2):206-11. [140]	Small sample size of episodic migraine
141. Todorov V, Bogdanova D, Tonchev P, Milanov I. Repetitive transcranial magnetic stimulation over two target areas, sham stimulation and topiramate in the treatment of chronic migraine. Comptes rendus de l'Académie bulgare des Sciences. 2020 Jan 1;73(9). [141]	Small sample size of chronic migraine
142. Villani V, Prosperini L, Palombini F, Orzi F, Sette G. Single-blind, randomized, pilot study combining shiatsu and amitriptyline in refractory primary headaches. Neurological Sciences. 2017 Jun;38(6):999-1007. [142]	Small sample size of episodic migraine
143. Wammes-van der EA, Smidt MH, Tijssen CC, Van 't Hoff AR, Lenderink, PharmD AW, Egberts, PharmD AC. Effect of low-intensity acenocoumarol on frequency and severity of migraine attacks. Headache: The Journal of Head and Face Pain. 2005 Feb;45(2):137-43. [143]	Small sample size of episodic or chronic migraine
144. Xu JH, Mi HY. A randomized controlled trial of acupressure as an adjunctive therapy to sodium valproate on the prevention of chronic migraine with aura. Medicine. 2017 Jul;96(27). [144]	Not a drug trial
145. Yurekli VA, Akhan G, Kutluhan S, Uzar E, Koyuncuoglu HR, Gultekin F. The effect of sodium valproate on chronic daily headache and its subgroups. The journal of headache and pain. 2008 Feb;9(1):37-41. [145]	Small sample size on chronic daily headache
146. Zidan A, Hussaini S, Gibson S, Brooks G, Mejico L. Onabotulinumtoxin Type A reconstitution with preserved versus preservative-free saline in chronic migraine (B-RECON). A randomised, double-blind trial. International Journal of Clinical Practice. 2020 Sep;74(9):e13522. [146]	Trial of Botox preservative on injection site pain
147. Silberstein SD, Hulihan J, Karim MR, Wu SC, Jordan D, Karvois D, Kamin M. Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults: a randomized, placebo-controlled, double-blind, 12-week pilot study. Clinical therapeutics. 2006 Jul 1;28(7):1002-11. [147]	Small sample size of episodic migraine
148. Askari G, Nasiri M, Mozaffari-Khosravi H, Rezaie M, Bagheri-Bidakhavidi M, Sadeghi O. The effects of folic acid and pyridoxine supplementation on characteristics of migraine attacks in migraine patients with aura: A double-blind, randomized placebo-controlled, clinical trial. Nutrition. 2017 Jun 1;38:74-9. [148]	Acute migraine
149. Hajihashemi P, Askari G, Khorvash F, Reza Maracy M, Nourian M. The effects of concurrent Coenzyme Q10, L-carnitine supplementation in migraine prophylaxis: A randomized, placebo-	Small sample size of episodic migraine

controlled, double-blind trial. Cephalalgia. 2019 Apr;39(5):648-54. [149]	
150. Bredfeldt RC, Sutherland JE, Kruse JE. Efficacy of transdermal clonidine for headache prophylaxis and reduction of narcotic use in migraine patients. J Fam Pract. 1989;29(2):153-6. [150]	Small sample size of episodic migraine Small episodic migraine
151. Centonze V, Macinagrossa G, Attolini E, Magrone D, Trizio T, Tesauro P, Campanozzi F, Altomare E, Albano O. Terapia preventiva dell'emicrania: flunarizina versus verapamil [Preventive therapy of migraine: flunarizine versus verapamil]. Clin Ter. 1985 Dec 15;115(5):333-9. Italian. PMID: 3830537. [151]	Small sample size of episodic migraine
152. Maizels M, Blumenfeld A, Burchette R. A combination of riboflavin, magnesium, and feverfew for migraine prophylaxis: a randomized trial. Headache: The Journal of Head and Face Pain. 2004 Oct;44(9):885-90. [152]	Small sample size of episodic migraine
153. Chitsaz A, Ghorbani A, Hoseinzadeh H, Nazari F, Norouzi R, Tajic S. Comparison of botulinum toxin type-A and divalproex sodium for prevention of chronic and episodic migraine. Neurology Asia. 2012 Jun 1;17(2). [153]	Small sample size of episodic or chronic migraine
154. Matin H, Taghian F, Chitsaz A. Artificial intelligence analysis to explore synchronize exercise, cobalamin, and magnesium as new actors to therapeutic of migraine symptoms: a randomized, placebo-controlled trial. Neurological Sciences. 2022 Feb 3:1-2. [154]	Small sample size of episodic migraine
155. Croop R, Lipton RB, Kudrow D, Stock DA, Kamen L, Conway CM, Stock EG, Coric V, Goadsby PJ. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. The Lancet. 2021 Jan 2;397(10268):51-60. [155]	Small sample size of episodic or chronic migraine
156. Diamond S, Kudrow L, Stevens J, Shapiro DB. Long-term study of propranolol in the treatment of migraine. Headache: The Journal of Head and Face Pain. 1982 Nov;22(6):268-71. [156]	No outcome of interests
157. Mottaghi T, Askari G, Khorvash F, Maracy MR. Effect of Vitamin D supplementation on symptoms and C-reactive protein in migraine patients. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2015 May;20(5):477. [157]	Mixed population of adults and adolescence
158. Nattagh-Eshtivani E, Dahri M, Hashemilar M, Tarighat-Esfanjani A. The effect of coenzyme Q10 supplementation on serum levels of lactate, pyruvate, matrix metalloproteinase 9 and nitric oxide in women with migraine. A double blind, placebo, controlled randomized clinical trial. European Journal of Integrative Medicine. 2018 Aug 1;21:70-6. [158]	Small sample size of episodic migraine
159. Shoeibi A, Olfati N, Soltani Sabi M, Salehi M, Mali S, Akbari Oryani M. Effectiveness of coenzyme Q10 in prophylactic treatment of migraine headache: an open-label, add-on, controlled trial. Acta Neurologica Belgica. 2017 Mar;117(1):103-9. [159]	Small sample size of episodic migraine
160. Tarighat Esfanjani A, Mahdavi R, Ebrahimi Mameghani M, Talebi M, Nikniaz Z, Safaiyan A. The effects of magnesium, l-carnitine, and concurrent magnesium–l-carnitine supplementation in migraine prophylaxis. Biological trace element research. 2012 Dec;150(1):42-8. [160]	Small sample size of episodic migraine
161. Hsieh LL, Liou HH, Lee LH, Chen TH, Yen AM. Effect of acupressure and trigger points in treating headache: a randomized controlled trial. The American Journal of Chinese Medicine. 2010;38(01):1-4. [161]	Small sample size of episodic migraine
162. Langohr HD, Gerber WD, Koletzki E, Mayer K, Schroth G. Clomipramine and Metoprolol in Migraine Prophylaxis—A Double-	Small sample size of episodic migraine

blind Crossover Study. Headache: The Journal of Head and Face Pain. 1985 Mar;25(2):107-12. [162]	
163. Sândor PS, Di Clemente L, Coppola G, Saenger U, Fumal A, Magis D, Seidel L, Agosti RM, Schoenen J. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. Neurology. 2005 Feb 22;64(4):713-5. [163]	Small sample size of episodic migraine
164. Mathew NT. Prophylaxis of migraine and mixed headache. A randomized controlled study. Headache: The Journal of Head and Face Pain. 1981 May;21(3):105-9. [164]	Small sample size of migraine
165. Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis A randomized controlled trial. Neurology. 1998 Feb 1;50(2):466-70. [165]	Small sample size of episodic migraine
166. Cao K, Yu L, Gao Y, Fan Y, Zhao J, Zhang X, Xie W, Yang W, Dong M, Li T, Qiao X. Efficacy of zhengtian pill for migraine prophylaxis: a randomized, multicenter, double-blind, placebo-controlled, parallel-group study. European Journal of Integrative Medicine. 2014 Jun 1;6(3):259-67. [166]	Episodic, is large enough for Safety, but unless Zhengtian is in main analysis no need to collect SAEs
167. Nelson CF, Bronfort G, Evans R, Boline P, Goldsmith C, Anderson AV. The efficacy of spinal manipulation, amitriptyline and the combination of both therapies for the prophylaxis of migraine headache. Journal of manipulative and physiological therapeutics. 1998 Oct 1;21(8):511-9. [167]	Small sample size of episodic migraine
168. Diener HC, Kronfeld K, Boewing G, Lungenhausen M, Maier C, Molsberger A, Tegenthoff M, Trampisch HJ, Zenz M, Meinert R, GERAC Migraine Study Group. Efficacy of acupuncture for the prophylaxis of migraine: a multicentre randomised controlled clinical trial. The Lancet Neurology. 2006 Apr 1;5(4):310-6. [168]	Episodic, Control treatment not standardized
169. Shukla R, Garg RK, Nag D, Ahuja RC. Nifedipine in migraine and tension headache: a randomised double blind crossover study. The Journal of the Association of Physicians of India. 1995 Nov 1;43(11):770-2. [169]	Small sample size of episodic migraine
170. Silberstein SD, Stark SR, Lucas SM, Christie SN, Degryse RE, Turkel CC, BoNTA-039 Study Group. Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. InMayo Clinic Proceedings 2005 Sep 1 (Vol. 80, No. 9, pp. 1126-1137). Elsevier. [170]	Paper has included mixed patients (77% chronic migraine, 18% chronic tension type headache, 3% new daily persistent headache and 1% other headaches). Hence, not all patients were chronic migraineurs.
171. Ford JH, Stauffer VL, McAllister P, Akkala S, Sexson M, Ayer DW, Wang S. Functional impairment and disability among patients with migraine: evaluation of galcanezumab in a long-term, open-label study. Quality of Life Research. 2021 Feb;30(2):455-64. [171]	Small sample size of episodic migraine
172. Anthony M. Interesting uses of beta blockers. 1. Beta blockers in migraine prevention. Australian family physician. 1981 Apr;10(4):258-62. [172]	Not RCT
173. Arthur GP, Hornabrook RW. The treatment of migraine with BC 105 (pizotifen): a double blind trial. The New Zealand Medical Journal. 1971 Jan 1;73(464):5-9. [173]	Small sample size of episodic migraine
174. Ashkenazi A, Silberstein S. Botulinum toxin type A for the treatment of headache: why we say yes. Archives of neurology. 2008 Jan 1;65(1):146-9. [174]	Not an RCT
175. Bademosi O, Osuntokun BO. Pizotifen in the management of migraine. The Practitioner. 1978 Feb 1;220(1316):325-7. [175]	Small sample size of episodic migraine

176. Behan PO, Reid M. Propranolol in the treatment of migraine. The Practitioner. 1980 Feb;224(1340):201-3. [176]	Small sample size of episodic migraine
177. Chen SP, Fuh JL, Wang SJ. OnabotulinumtoxinA: preventive treatment for chronic migraine. Current pain and headache reports. 2011 Feb;15(1):4-7. [177]	Not an RCT
178. Diamond S, Freitag FG. A double-blind trial of flunarizine in migraine prophylaxis. Headache Quarterly-Current Treatment and Research. 1993 Jan 1;4(2):169-72. [178]	Small sample size of episodic migraine
179. Feuerstein T, Quebe-Fehling E. A double-blind, placebo-controlled, parallel-group, multicenter study of the safety and efficacy of gabapentin (CI-945) as a prophylactic interval therapy in patients with common migraine (Protocols 879-201,-205,-206,-207,-209). Research Report No. RR 4301-00066. Freiburg: Goedecke AG Research and Development. Available at: http://dida. library. ucsf. edu/pdf/brr13j10 1990. Accessed May 26; 2015. [179]	Small sample size of episodic migraine
180. Hübbe P. Controlled clinical trials of drugs for use in the prophylaxis of migraine. Danish Medical Bulletin. 1975 Mar 1;22(3):92-6. [180]	Not an RCT
181. Lance JW, Curran DA, Anthony M. Investigations into the mechanism and treatment of chronic headache. Medical journal of Australia. 1965 Nov;2(22):909-14. [181]	Not an RCT
182. Magnus-Miller L, Bernstein P, Caswell K. Double-blind, randomized, placebo-controlled, multicenter trial to determine the efficacy and safety of Neurontin®(gabapentin) in migraine prophylaxis administered in doses divided three times a day (TID)(protocol 945-220). Research Report No. RR 995-00074. [182]	Small sample size of episodic migraine
183. Morris Plains, NJ: Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company Medical and Scientific Affairs Department; August 24, 1999. Available at: http://dida. library. ucsf. edu/pdf/arr13j10. 1999 Aug 24. [183]	Small sample size of episodic migraine
184. Linde K, Rossnagel K. WITHDRAWN: Propranolol for migraine prophylaxis. Cochrane Database Syst Rev. 2017;2(2):CD003225. Published 2017 Feb 17. doi:10.1002/14651858.CD003225.pub3 [184]	Not an RCT
185. Nair KG. A pilot study of the value of propranolol in migraine. Journal of postgraduate medicine. 1975 Jul;21(3):111-3. [185]	Small sample size of episodic migraine
186. Pita E, Higueras A, Bolanos J, Perez N, Mundo A. Propranolol and migraine. A clinical trial. Archivos de Farmacologia y Toxicologia. 1977 Dec 1;3(3):273-8. [186]	Small sample size of episodic migraine
187. Verstraete M, Verhaeghe R. 20 Drugs acting on the cerebral and peripheral. Side Effects of Drugs Annual. 1977;10:172. [187]	Small sample size of episodic migraine
188. Rothrock JF. Topiramate for migraine prevention: an update. Headache: The Journal of Head and Face Pain. 2012 May;52(5):859-60. [188]	Not an RCT
189. Ryan Sr RE, Ryan Jr RE, Sudilovsky A. Nadolol and placebo comparison study in the prophylactic treatment of migraine. Panminerva medica. 1982;24(2):89-94. [189]	Small sample size of episodic migraine
190. Saper JR, Good DC, Michalek J, Kaplan RJ, Xiao Y, Nadler S. Efficacy and tolerability of tizanidine as adjunctive therapy in the prophylaxis of chronic daily headache. Round Table Series-Royal Society of Medicine. 2002 Jan 1(75):13-22. [190]	Small sample size of episodic migraine
191. Yuan C, Wang JX, Yu JP, Yan F, Su SH. A double-blind trial of 5 calcium channel blockers in prophylaxis of migraine. CHINESE JOURNAL OF CLINICAL PHARMACOLOGY. 1998;14:14-7. [191]	Small sample size of episodic migraine
192. Mattimoe D, Newton W. High-dose riboflavin for migraine prophylaxis. The Journal of Family Practice. 1998 Jul 1;47(1):11-. [192]	Small sample size of episodic migraine

193. Gonçalves DA, Camparis CC, Speciali JG, et al.Treatment of comorbid migraine and temporo-mandibular disorders: A factorial, double-blind, ran-domized, placebo-controlled study.J Orofac Pain.2013;27:325-335. [193]	Small sample size of episodic migraine
194. Schoenen J, Jacquy J, Lenaerts M. High-dose riboflavin is effective in migraine prophylaxis: Results from a double blind, randomized, placebo controlled trial. InNeurology 1997 Mar 1 (Vol. 48, No. 3, pp. 8005-8005). 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106: LIPPINCOTT-RAVEN PUBL. [194]	Small sample size of episodic migraine
195. Hübbe P. The prophylactic treatment of migraine with an antiserotonin pizotifen (BC 105). Acta Neurologica Scandinavica. 1973 Mar;49(1):108-14. [195]	Small sample size of episodic migraine
196. Schoenen J, Jacquy J, Lenaerts ME, Loder E. High-dose riboflavin reduced the frequency of migraine headaches. Evidence-Based Medicine. 1998 Sep;3(5):151. [196]	Small sample size of episodic migraine
197. Rezaeiashtiani A, Jadidi A, Khanmohammadi-Hezaveh A, Aghaeipour SM, Pourandish Y, Malekhosseini S, Ghassami K, Mohammadbeigi A. Is the treatment of constipation can relieve the migraine symptoms? A randomized clinical trial study. Journal of Pediatric Neurosciences. 2019 Oct;14(4):186. [197]	Small sample size of episodic migraine
198. Shimell CJ, Fritz VU, Levien SL. A comparative trial of flunarizine and propranolol in the prevention of migraine. South African Medical Journal, 1990 Jan 1;77(2):75-7. [198]	Small sample size of episodic migraine
199. Wang LP, Zhang XZ, Guo J, Liu HL, Zhang Y, Liu CZ, Yi JH, Wang LP, Zhao JP, Li SS. Efficacy of acupuncture for migraine prophylaxis: a single-blinded, double-dummy, randomized controlled trial. PAIN®. 2011 Aug 1;152(8):1864-71. [199]	Small sample size of episodic migraine
200. Yang CP, Chang MH, Li TC, Hsieh CL, Hwang KL, Chang HH. Predicting prognostic factors in a randomized controlled trial of acupuncture versus topiramate treatment in patients with chronic migraine. The Clinical Journal of Pain. 2013 Nov 1;29(11):982-7. [200]	Small sample size of chronic migraine
201. Manzoni, GC, et all., Multicentric, double-blind, randomized study on the efficacy and tolerance of dothiepin and amitriptyline for the prophylaxis of chronic migraine. Giornale di neuropsicofarmacologia. 1990; 12(5):179-184. [201]	Small sample size of chronic migraine
202. Lipton RB, Croop R, Stock EG, Stock DA, Morris BA, Frost M, Dubowchik GM, Conway CM, Coric V, Goadsby PJ. Rimegepant, an oral calcitonin gene–related peptide receptor antagonist, for migraine. New England Journal of Medicine. 2019 Jul 11;381(2):142-9. [202]	Acute migraine
203. Diener HC, Tfelt-Hansen P, Dahlöf C, et al. Topiramate in migraine prophylaxis. J Neurol 251, 943– 950 (2004). https://doi.org/10.1007/s00415-004-0464-6. [203]	Mixed population of adult and adolescents
204. Ailani J, Andrews JS, Tockhorn-Heidenreich A, Wenzel R, Rettiganti M. Effect of Galcanezumab on Total Pain Burden in Patients Who Had Previously Not Benefited from Migraine Preventive Medication (CONQUER Trial): A Post Hoc Analysis. Advances in Therapy. 2022 Oct;39(10):4544-55. [204]	No safety data for adverse events review and a small sample size of chronic migraine
205. Igarashi H, Shibata M, Ozeki A, Matsumura T. Galcanezumab Effects on Migraine Severity and Symptoms in Japanese Patients with Episodic Migraine: Secondary Analysis of a Phase 2 Randomized Trial. Neurology and Therapy. 2022 Oct 20:1-5. [205]	No safety data for adverse events review
206. Chowdhury D, Chaudhuri JR, Ghosh P, Kulkarni R, Singh S, Thakur S, Thorat AV. Efficacy and tolerability of erenumab for	Small sample of episodic migraine

prevention of episodic migraine in India. Annals of Indian Academy of Neurology. 2022 May;25(3):433. [206]	
207. Igarashi H, Shibata M, Ozeki A, Day KA, Matsumura T. Early Onset and Maintenance Effect of Galcanezumab in Japanese Patients with Episodic Migraine. Journal of Pain Research. 2021;14:3555. [207]	No safety data for adverse events review
208. Sakai F, Takeshima T, Tatsuoka Y, Hirata K, Cheng S, Numachi Y, Peng C, Xue F, Mikol DD. Long-term efficacy and safety during open-label erenumab treatment in Japanese patients with episodic migraine. Headache: The Journal of Head and Face Pain. 2021 Apr;61(4):653-61. [208]	Small sample of episodic migraine
209. Okonkwo R, Tockhorn-Heidenreich A, Stroud C, Paget MA, Matharu MS, Tassorelli C. Efficacy of galcanezumab in patients with migraine and history of failure to 3–4 preventive medication categories: subgroup analysis from CONQUER study. The journal of headache and pain. 2021 Dec;22(1):1-1. [209]	No safety data for adverse events review
210. Okonkwo R, Tockhorn-Heidenreich A, Stroud C, Paget MA, Matharu MS, Tassorelli C. Efficacy of galcanezumab in patients with migraine and history of failure to 3–4 preventive medication categories: subgroup analysis from CONQUER study. The journal of headache and pain. 2021 Dec;22(1):1-1. [210]	No safety data for adverse events review
211. Couch JR, Amitriptyline Versus Placebo Study Group. Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. Headache: The Journal of Head and Face Pain. 2011 Jan;51(1):33-51. [211]	Definition for AEs and SAEs
212. Diener HC, Matias-Guiu J, Hartung E, Pfaffenrath V, Ludin HP, Nappi G, De Beukelaar F, Study Group. Efficacy and tolerability in migraine prophylaxis of flunarizine in reduced doses: a comparison with propranolol 160 mg daily. Cephalalgia. 2002 Apr;22(3):209-21. [212]	Definition for AEs and SAEs
213. Kalita J, Bhoi SK, Misra UK. Amitriptyline vs divalproate in migraine prophylaxis: a randomized controlled trial. Acta Neurologica Scandinavica. 2013 Jul;128(1):65-72. [213]	Definition for AEs and SAEs
214. Yang CP, Chang MH, Li TC, Hsieh CL, Hwang KL, Chang HH. Predicting prognostic factors in a randomized controlled trial of acupuncture versus topiramate treatment in patients with chronic migraine. The Clinical Journal of Pain. 2013 Nov 1;29(11):982-7. [214]	Not pharmacological intervention
215. Lucking CH, Oestreich W, Schmidt R, Soyka D. Flunarizine vs. propranolol in the prophylaxis of migraine: two double-blind comparative studies in more than 400 patients. Cephalalgia. 1988 Sep;8(8_suppl):21-6. [215]	Definition for AEs and SAEs
216. Relja M, Poole AC, Schoenen J, Pascual J, Lei X, Thompson C. A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A (BoNTA) for the prophylaxis of episodic migraine headaches. Cephalalgia. 2007 Jun;27(6):492-503. [216]	Definition for AEs and SAEs
217. Rapoport A, Mauskop A, Diener HC, Schwalen S, Pfeil J. Long-term migraine prevention with topiramate: open-label extension of pivotal trials. Headache: The Journal of Head and Face Pain. 2006 Jul;46(7):1151-60. [217]	The mixed population of adults and adolescence
218. Lipton RB, Silberstein S, Dodick D, Cady R, Freitag F, Mathew N, Biondi DM, Ascher S, Olson WH, Hulihan J. Topiramate intervention to prevent transformation of episodic migraine: the topiramate INTREPID study. Cephalalgia. 2011 Jan;31(1):18-30. [218]	Definition for AEs and SAEs
219. Ruff DD, Ford JH, Tockhorn-Heidenreich A, Stauffer VL, Govindan S, Aurora SK, Terwindt GM, Goadsby PJ. Efficacy of galcanezumab in patients with episodic migraine and a history of preventive treatment	No report of Adverse Events

failure: results from two global randomized clinical trials. European Journal of Neurology. 2020 Apr;27(4):609-18. [219]	
220. Sakai F, Takeshima T, Tatsuoka Y, Hirata K, Cheng S, Numachi Y, Peng C, Xue F, Mikol DD. Long-term efficacy and safety during open-label erenumab treatment in Japanese patients with episodic migraine. Headache: The Journal of Head and Face Pain. 2021 Apr;61(4):653-61. [220]	Small sample size of episodic migraine
221. Silberstein SD, Loder E, Forde G, Papadopoulos G, Fairclough D, Greenberg S. The impact of migraine on daily activities: effect of topiramate compared with placebo. Current medical research and opinion. 2006 Jun 1;22(6):1021-9. [221]	No adverse events reported
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223. Tatsuoka Y, Takeshima T, Ozeki A, Matsumura T. Treatment satisfaction of galcanezumab in Japanese patients with episodic migraine: a phase 2 randomized controlled study. Neurology and Therapy. 2021 Jun;10:265-78. [223]	No adverse events reported
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Appendix 3: More details on baseline characteristics of the included studies

First author, year/ Country	Study design and Date	Key inclusion criteria	Key exclusion criteria
Author, year: Rothrock, 2019 [6] **Country:** USA	**Study design:** multicenter, randomised, parallel-group, post-authorisation, open-label prospective study. After 12 weeks, patients initially randomised to topiramate could cross over to BTA treatment **Date:** August 2014 to September 2017	• Adults (18-65) had to record ≥20 diary days during 28 days baseline screening • Reported ≥15 headache days. • Patients taking other preventive treatments were eligible for enrolment if the dose had been stable and well tolerated for ≥12 weeks before screening and the patient was willing to maintain a stable dose. • Patients were permitted to take prescription or over the counter acute headache pain medication, recording use in their daily diary	• Taking opioid-containing products for acute headache treatment more than 8 days during a 28-day period • Previous treatment with botulinum toxin of any serotype for any reason • Previous treatment with topiramate • On a ketogenic diet (high in fat, low in carbohydrates) • History of acute myopia or increased intraocular pressure • Diagnosis of myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis or any other significant disease that might interfere with neuromuscular function • Acupuncture, transcutaneous electrical stimulation (TENS), cranial traction, dental splints for headache, or injection of anesthetics/steroids in the 4 weeks prior to screening.
Author, year: Tepper, 2017 [17] **Country:** North America (Canada and the USA) and Europe (Czech Republic, Denmark, Finland, Germany, Norway, Poland, Sweden, and the UK	**Study design:** phase 2, randomised, double-blind, placebo-controlled, multicentre **Date:** April 2014, to Dec 2016	• History of at least 5 attacks of migraine without aura and/or migraine with visual sensory, speech and/or language, retinal or brainstem aura. • History of ≥ 15 headache days per month of which ≥ 8 headache days were assessed by the subject as migraine day. • ≥ 4 distinct headache episodes, each lasting ≥ 4 hours OR if shorter, associated with use of a triptan or ergot-derivative on the same calendar day based on the eDiary calculations.	• History of cluster headache or hemiplegic migraine headache • Unable to differentiate migraine from other headaches • Failed > 3 medication categories due to lack of efficacy for prophylactic treatment of migraine. • Received botulinum toxin in head or neck region within 4 months prior to screening. • Used a prohibited migraine prophylactic medication, device or procedure within 2 months prior to the start of the baseline phase

		• Demonstrated at least 80% compliance with the eDiary.	
Author, year: Dodick, 2019 [9] **Country:** 82 in the United States, four in Australia, and three each in New Zealand and the Republic of Georgia	**Study design:** phase 2b, parallel-group, double-blind, randomised, placebo-controlled, dose-ranging clinical trial. **Date:** December 2014 to December 2016	• Adults 18–55 years with CM according ICHD-3b • Established at age >=35 years and history of CM of >=1 year. • >=15 headache days, of which>=8 were assessed as migraine days during baseline priod. • Use of hormonal therapy and preventive medications for headache except botulinum toxin, was allowed if the dosing has been stable for >3 months before screening, and was maintained at the same dosing level throughout the trial • The use of barbiturates or opioids for the acute treatment of CM was allowed if the dosing had been stable for 3 months before screening, and dosing did not exceed 4 days/month. • Patients with CM who were diagnosed with medication overuse headache	• Confounding pain syndromes (e.g. fibromyalgia, chronic low back pain, complex regional pain syndrome) or any pain syndrome that requires regular analgesia • Psychiatric conditions that are uncontrolled and untreated, including conditions that are not controlled for a minimum of 6 months prior to screening. • History or diagnosis of complicated migraine (ICHD-III beta version, 2013), chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, migraine with brainstem aura, sporadic and familial hemiplegic migraine • Unable to differentiate migraine from other headaches • Subject has received botulinum toxin for migraine or for any other medical/cosmetic reasons requiring injections in the head, face, or neck within 4 months prior to screening. • Have any clinically significant concurrent medical condition
Author, year: Detke, 2018 [27] **Country:** Argentina, Canada, Czech Republic, Germany, Israel, Italy, Mexico, the Netherlands, Spain, Taiwan, the United Kingdom, and the United States	**Study design:** phase 3, randomised, double-blind, placebo-controlled study **Date:** January 2016 to March 2017	• Adults 18 to 65 years with CM as defined by ICHD-3 beta with at least 15 headache days • Migraine onset before 50 years of age. • Patients could take acute headache medication as needed throughout the trial but could take opioid or barbiturate containing medications no more than 3 days per month, could not take oral corticosteroids, and could receive no more than 1 steroid	• Are currently enrolled in or have participated within the last 30 days or within 5 half-lives (whichever is longer) in a clinical trial involving an investigational product. • Current use or prior exposure to galcanezumab or another calcitonin gene-related peptide (CGRP) antibody. • Known hypersensitivity to multiple drugs, monoclonal antibodies or other therapeutic proteins, or to galcanezumab.

		injection during the study and only if in an emergency setting. • Patients had to wash out all migraine preventive medications except topiramate or propranolol • Patients also needed at least 1 headache-free day per month within 3 months before screening period.	• History of persistent daily headache, cluster headache or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, and migraine with brainstem aura (basilar-type migraine) defined by IHS ICHD-3 beta
Author, year: Dodick 2010 [3]; [pooled Aurora 2010 [4], Diener 2010 [5]] **Country:** 56 North American sites	**Study design:** phase 3 study, with a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week, open-label phase **Date:** 23 January 2006 to 16 July 2008 and 7 February 2006 to 11 August 2008	• Adults (18 to 65 years) with a history of migraine according ICHD-II • Randomised patients provided diary data on >20 of 28 days during baseline. • Having >15 headache days with each day consisting of >4 hours of continuous headache and with >50% of days being migraine or probable migraine days and >4 distinct headache episodes, each lasting >4 hours.	• Previous use of botulinum toxin of any serotype or immunisation to any botulinum toxin serotype • Any medical condition that puts the patient at increased risk with exposure to BTA • Diagnosis of complicated migraine, chronic tension-type headache, hypnic headache, hemicrania continua, new daily persistent headache • Use of prophylactic headache medication within 28 days prior to week -4 • Unremitting headache lasting continuously throughout the 4-week baseline period • Known or suspected Temporomandibular Disorders (TMD) • Diagnosis of fibromyalgia • Beck depression inventory score >24 at week-4 • Psychiatric problems that may have interfered with study participation
Author, year: Ferrari, 2019 [22] **Country:** Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, Netherlands,	**Study design:** Phase 3 FOCUS trial, randomised, double-blind, placebo-controlled, parallel-group **Date:** October 2017 to May 2019	• Adults (18–70 years), had a diagnosis of migraine with onset at or before age 50 years. • Chronic migraine history at least 12 months before screening. • > 15 headache days per month, with at least 8 migraine days	• At the time of screening visit, participant is receiving any preventive migraine medications, regardless of the medical indication for more than 5 days and expects to continue with these medications. • Participant has received onabotulinumtoxinA for migraine or for any medical or cosmetic reasons requiring injections in the head, face,

Poland, Spain, Sweden, Switzerland, UK, and the USA.		• Participants with and without overuse of acute headache medication • With failure to two to four classes of migraine preventive medications in the past 10 years.	or neck during the 3 months before screening visit. • Participant has used an intervention/device (for example; scheduled nerve blocks and transcranial magnetic stimulation) for migraine during the 2 months prior to screening. • Participant uses triptans/ergots as preventive therapies for migraine. • Participant uses non-steroidal anti-inflammatory drugs (NSAIDs) as preventive therapy for migraine on nearly daily basis for other indications. Note: Low dose aspirin (for example; 81 mg) used for cardiovascular disease prevention is allowed.
Author, year: Sakai F, 2021 [23] **Country:** Japan and Korea	**Study design:** multicenter, randomised, double-blind, placebo-controlled, parallel-group **Date:** November 2017 and November 2019	• Patient with migraine onset at ≤50 years of age • Headache occurring on ≥15 days and fulfilling any of the following on ≥8 days: (ICHD-3 beta diagnostic criteria C and D for 1.1 Migraine without aura, criteria B and C for 1.2 Migraine with aura, Probable migraine. • Not using preventive migraine medications for migraine or other medical conditions or using no more than 1 preventive migraine medication for migraine or other medical conditions if the dose and regimen have been stable for at least 2 months prior to giving informed consent.	• The lack of efficacy of at least two of four clusters of preventive medications despite an ade-quate treatment • Unremitting headaches with duration more than 80% of waking hours and with less than 4 days without headache per month • Clinically significant major organ disease • Patient has received onabotulinumtoxin A for migraine or for any medical or cosmetic reason requiring injection in the head, face, or neck during the 4 months prior to giving informed consent • Patient is using medications containing opioids or barbiturates on more than 4 days per month for the treatment of migraine or for any other reason • Patient has used an intervention or device for migraine during the 2 months prior to giving informed consent.
Author, year: Silberstein SD, 2017 [25]	**Study design:**	• Adults (18 to 70 years), a history of migraine according to ICHD-3 beta for at least 12 months.	• The use of BTA during the 4 months before screening

Country: 132 sites in nine countries	randomised, double-blind, placebo-controlled, parallel-group trial **Date:** March 2016 through January 2017	• ≥15 headache days with ≥8 migraine days. • The protocol allowed inclusion of up to 30% of patients using a stable dose of one migraine-preventive medication (hereafter referred to as preventive medication) for at least 2 months before the beginning of the pre-intervention period to continue these medications	• The use of interventions or devices for migraine, such as nerve blocks and transcranial magnetic stimulation, during the 2 months before screening • The use of opioid or barbiturate medications on more than 4 days during the pre-intervention period and a lack of efficacy, after an adequate therapeutic trial, of at least two of four clusters of preventive medications
Author, year: Lipton, 2020 [10] **Country:** 13 countries (United States, Spain, Ukraine, Russian Federation, United Kingdom, Republic of Georgia, Hungary, Italy, Slovakia, Germany, Czech Republic, Denmark, and Belgium)	**Study design:** phase 3, double-blind, randomised, placebo-controlled, parallel-group **Date:** November 2016 to April 2018.	• Adults (18 to 65 years) of age (inclusive) with a diagnosis of migraine at or before 50 years of age if they had a history of CM for ≥12 months before screening, • Completed the headache electronic diary (eDiary) on ≥24 of the 28 days and experienced ≥15 to ≤26 headache days and ≥8 migraine days during the 28-day screening period. • Migraine preventive medication use had to be stable for ≥3 months before screening. Hormonal therapy was also permitted if it was stable and ongoing ≥3 months before screening. • Patients using barbiturates or prescription opioids ≤4 d/mo were eligible for participation if use was stable for ≥2 months before screening. • Patients with CM and medication-overuse headache with the exception of the overuse of barbiturates or opioids	• Patients using opioids or barbiturates ≥5 d/mo • With a confounding pain disorder or clinically significant pain syndromes; uncontrolled or untreated psychiatric conditions; acute or active temporomandibular disorders; history or diagnosis of a headache or migraine disorders that did not meet the ICHD-3 criteria • Present or previous malignancies, any active, progressive, or unstable cardiovascular, neurologic, or autoimmune disorder; newly diagnosed or uncontrolled hypertension. • Women who were pregnant, breastfeeding, or planning to become pregnant during the study • positive for HIV, hepatitis B surface antigen, or hepatitis C • A concurrent medical condition or laboratory abnormality during the screening period or before dosing on day 0; • Body mass index ≥39 kg/m2 • Or recent or planned surgery requiring general anaesthesia within 8 weeks before screening or during the duration of the study

			• Botulinum toxin (any type) for migraine or for any other medical cosmetic reasons requiring injections within 4 months before screening or during the screening period • Any monoclonal antibody treatment within 6 months of screening; or Eptinezumab or any monoclonal antibody targeting the CGRP pathway.
Author, year: Ailani, 2021 [33] **Country:** United States	**Study design:** multicentre, double-blind, parallel group, randomised, placebo-controlled trial **Date:** December 2018 to June 2020	• Adults 18 to 80 years of age with 4 to 14 migraine days per month in the 3 months before visit 1 and 4 to 14 migraine days during the 28- day baseline period according to an electronic diary • Participants had to have at least a 1-year history of migraine with or without aura, diagnosed as specified in the International Classification of Headache Disorders, 3rd edition (ICHD-3), and with migraine onset before 50 years of age.	• Diagnosis of chronic migraine, new daily persistent headache, trigeminal autonomic cephalalgia, or painful cranial neuropathy as defined by the ICHD-3 or if they averaged 15 or more headache days per month across the 3 months before visit 1 or during the 28-day baseline period. • An inadequate response to more than four oral medications prescribed for the preventive treatment of migraine, two of which needed to have different mechanisms of action. • Participants who used opioids or barbiturates on more than 2 days per month, triptans or ergots on 10 or more days per month, or simple analgesic agents on 15 or more days per month in the 3 months before visit 1 or during the 28-day baseline period. • Use of barbiturates 30 days before screening • Pregnant, planning to become pregnant, or lactating.
Author, year: Sun, 2016 [16] **Country:** North America (Canada, USA) and Europe (Denmark, Finland, Germany, Norway, Sweden, and Portugal)	**Study design:** multicentre, randomised, double-blind, placebo-controlled trial **Date:**	• Adults, 18 to 60 years • History of migraine for more than 12 months prior to screening • Migraine frequency: ≥ 4 and ≤ 14 migraine days per month in each of the 3 months prior to screening and during baseline phase	• Older than 50 years of age at migraine onset • History of cluster headache or basilar or hemiplegic migraine headache • Unable to differentiate migraine from other headaches • No therapeutic response with > 2 of the following eight medication categories for

	August 2013 to November 2019	• Headache frequency: < 15 headache days per month (with > 50% of the headache days being migraine days) in each of the 3 months prior to screening and during baseline phase • Demonstrated at least 80% compliance with the eDiary during baseline phase	prophylactic treatment of migraine after an adequate therapeutic trial. Medication categories are: (Category 1: Divalproex sodium, sodium valproate, Category 2: Topiramate, Category 3: Beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol), Category 4: Tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline), Category 5: Venlafaxine, desvenlafaxine, duloxetine, milnacipran, Category 6: Flunarizine, verapamil, Category 7: Lisinopril, candesartan, Category 8: Butterbur, feverfew, magnesium (≥ 600 mg/day), riboflavin (≥ 100 mg/day) • Overuse of acute migraine medications in any month during the 3 months prior to screening or during screening
Author, year: Ashina, 2020 [7] **Country:** USA and the Republic of Georgia	**Study design:** multicenter, randomised, double-blind, placebo-controlled, parallel-group study **Date:** September 2015 to December 2017	• Adults, 18 to 75 years • Diagnosis of migraine at ≤ 50 years of age • History of migraine ≥ 12 months with ○ ≤ 14 headache days of which at least 4 have to be migraine days (migraine days count as headache days) in each 28-day period in the 3 months prior to screening ○ During the 28 days following the screening visit, the subject experiences ≤ 14 headache days of which at least 4 have to be migraine days (migraine days count as headache days) as recorded in the eDiary • No use of any botulinum toxin for migraine or for any other medical/cosmetic reasons requiring	• Confounding pain syndromes, e.g. fibromyalgia, complex regional pain syndrome or any pain syndrome that requires regular analgesia • Psychiatric conditions that are uncontrolled and untreated, including conditions that are not controlled for a minimum of 6 months prior to screening • History or diagnosis of complicated migraine (ICHD- II, 2004 Section 1), chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, migraine with brainstem aura, sporadic and familial hemiplegic migraine • Unable to differentiate migraine from other headaches

		injections in the head, face, or neck 4 months prior to screening and during the 28-day period prior to randomisation • Headache eDiary was completed on at least 25 of the 28 days prior to randomisation	• Have any clinically significant concurrent medical condition • Receipt of any monoclonal antibody treatment within 6 months of screening (within or outside a clinical trial) • Previously dosed with ALD403 or any monoclonal antibody targeting the CGRP pathway
Author, year: Dodick, 2014 [28] **Country:** USA	**Study design:** randomised, double-blind, placebo-controlled, phase 2 proof-of-concept study, parallel assignment. **Date:** July 2012 to September 2013	• Adults 18–65 years with four to 14 migraine headache days per month • Have a history of migraine as defined by ICHD-II, of at least 1 year prior to enrolment, migraine onset prior to age 50, and a moderate frequency of migraine headaches • Women of child-bearing potential (not surgically sterile or at least 1-year post-menopause) must test negative for pregnancy at the time of screening based on a serum pregnancy test and must agree to use a reliable method of birth control during the study and for 3 months following completion of participation in the study • Have clinical laboratory test results within normal reference ranges or, if outside the normal range, judged not clinically significant by the Investigator • Must not be on any migraine prevention therapy, including botulinum toxin • Agree not to post any personal medical data related to the study or information related to the study on any website or social media site.	• Current enrolment in, or discontinuation within the last 30 days from, a clinical trial involving any investigational drug or device, or concurrent enrolment in any other type of medical research judged not to be scientifically or medically compatible with this study • Previous completion or withdrawal from this study or any other study investigating LY2951742 or other therapeutic antibodies that target calcitonin gene-related peptide • History of chronic migraine or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, and basilar-type migraine • Evidence of significant active psychiatric disease including, but not limited to, manic depressive illness, schizophrenia, generalized anxiety disorder, obsessive compulsive disorder, personality disorders, or other serious mood, anxiety, depression, or substance use disorders • Have a history or presence of any other medical illness • Women who are pregnant or nursing • Confirmed corrected QT (QTc) interval >470 milliseconds (msec) for women and >450 for men

Author, year: Dodick, 2018 [12] **Country:** 69 sites across North America and Europe (including Russia)	**Study design:** multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial **Date:** July 2015 to March 2017	• Adults 18–65 years • Migraine onset prior to age 50 • History of migraines (with or without aura) for ≥ 12 months • Migraine frequency: ≥ 4 and < 15 migraine days per month on average across the 3 months prior to screening • Headache (i.e., migraine and non-migraine headache) frequency: < 15 headache days per month on average across the 3 months prior to screening • Demonstrated compliance with the eDiary	• History of cluster headache or hemiplegic migraine headache. • No therapeutic response with > 2 categories for prophylactic treatment of migraine after an adequate therapeutic trial. • Concomitant use of 2 or more medications with possible migraine prophylactic effects within 2 months prior to the start of the baseline phase or during the baseline phase. • Used a prohibited medication, device, or procedure within 2 months prior to the start of the baseline phase or during the baseline phase. • Received botulinum toxin • Active chronic pain syndromes (such as fibromyalgia and chronic pelvic pain). • History of major psychiatric disorder, seizure, HIV • Myocardial infarction (MI), stroke, transient ischemic attack (TIA), unstable angina, or coronary artery bypass surgery or other revascularization procedure within 12 months prior to screening.
Author, year: Dodick, 2009 [1] **Country:** United States	**Study design:** multicentre, randomised, double-blind, double-dummy, parallel-group noninferiority study **Date:** February 2004 to October 2005	• Adults (age ≥18 years) with a history of migraine without or with aura (International Headache Society class 1.1 and 1.2, respectively) for at least 6 months before the screening • Washout period, along with ~3 to 12 migraines per month in the 3 months before the screening • Washout period, from 3 to 12 migraine episodes during the 28-day prospective baseline period, and no	• With previously failed >2 adequate trials of migraine-preventive medications or had failed an adequate trial of topiramate or amitriptyline because of lack of efficacy or AEs. • Acute abortive medication uses on >15 treatment days per month • Migraine aura only (without headache) • History of cluster headache, a progressive neurologic disorder other than migraine, or a condition more painful than headache

		more than 15 headache days (migraine and nonmigraine) during the prospective baseline period, based on headache records. • Onset of migraine prior the age of 50 years	• History of a medical condition in which use of amitriptyline is contraindicated • History of an unstable medical condition within the past 2 years or of a major psychiatric disorder within the past 6 months that could impair reliable participation in the study or necessitate the use of medications not permitted in the study • History of drug or alcohol abuse within the past 2 years • History of nephrolithiasis, active liver disease, or liver function tests ≥2 times the upper limit of normal • Pregnant or nursing women and those who were not practicing a medically accepted method of birth control
Author, year: Dodick, 2018 [21] **Country:** Canada, Czech Republic, Finland, Israel, Japan, Poland, Russia, Spain, United States	**Study design:** randomised, double-blind, placebo-controlled, parallel group. **Date:** March 2016 to April 2017	• Males or females aged 18 to 70 years, inclusive, with migraine onset at ≤50 years of age (ICHD-3 beta) • Patient signs and dates the informed consent document • Patient has history of migraine according to International Classification of Headache Disorders, or clinical judgment suggests a migraine diagnosis • 85% e-diary compliance • Total body weight between 99 and 265 lbs, inclusive • A subset of patients was allowed to use 1 concomitant preventive migraine medication if the dosing was stable for at least 2 months prior to the beginning of the pre-treatment period and without any change in dose during the study.	• Clinically significant haematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease, at the discretion of the investigator • History of clinically significant psychiatric issues • History of cardiovascular disease or vascular ischemia or thromboembolic events, such as cerebrovascular accident, deep vein thrombosis, or pulmonary embolism • History of human immunodeficiency virus, tuberculosis, or chronic hepatitis B or C infection • Pregnant or nursing females • Using onabotulinumtoxinA during the 4 months before screening, • Using opioids or barbiturates on more than 4 days during the pre-treatment baseline period

		• Acute headache medications were permitted	• Having previous failure of 2 or more of the following medication clusters after at least 3 months of treatment for episodic or chronic migraine: divalproex sodium and sodium valproate; flunarizine and pizotifen; amitriptyline, nortriptyline, venlafaxine, and duloxetine; and atenolol, nadolol, metoprolol, propranolol, and timolol
Author, year: Goadsby, 2017 [13] **Country:** 121 sites across North America, Europe, and Turkey	**Study design:** Multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial **Date:** July 2015 to September 2016	• Adults 18 to 65 years • History of migraine (with or without aura) for ≥ 12 months prior to screening according to the International Headache Society (IHS) International Classification of Headache Disorders (ICHD-3) classification • Migraine frequency: ≥ 4 and < 15 migraine days per month on average across the 3 months prior to screening and during baseline • Headache frequency: < 15 headache days per month on average across the 3 months prior to screening and baseline • Demonstrated at least 80% compliance with the eDiary.	• Older than 50 years of age at migraine onset • History of cluster headache or hemiplegic migraine headache • Unable to differentiate migraine from other headache • No therapeutic response with > 2 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial • Used a prohibited medication, device, or procedure within 2 months prior to the start of the baseline phase or during the baseline phase • Concomitant use of 2 or more medications with possible migraine prophylactic effects within 2 months prior to the start of the baseline phase or during the baseline phase. If only 1 prophylactic medication is used, the dose must be stable within 2 months prior to the start of the baseline phase and throughout the study
Author, year: Sakai 2020 [30] **Country:** Japan from 40 sites	**Study design:** Phase 2, randomised, double-blind, placebo-controlled parallel-design study **Date:**	• Adults 18 to 65 years • Have a diagnosis of migraine as defined by International Headache Society (IHS) International Classification of Headache Disorders (ICHD)-3 beta guidelines (1.1 or 1.2) (ICHD-3 2013)	• Are currently enrolled in or have participated within the last 30 days or within 5 half-lives (whichever is longer) in a clinical trial involving an investigational product. • Current use or prior exposure to Galcanezumab or other antibodies to CGRP or its receptor.

	December 2016 to January 2019	• History of migraine headaches of at least 1 year prior to screening, and migraine onset prior to age 50 • Patients had to demonstrate ≥80% compliance (completion of daily entries) with the ePRO diary, and all patients agreed to use reliable methods of contraception during the study and for 5 months after the last dose	• Known hypersensitivity to multiple drugs, monoclonal antibodies or other therapeutic proteins, or to Galcanezumab and the excipients in the investigational product. • History of persistent daily headache, cluster headache or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, and migraine with brainstem aura (basilar-type migraine) defined by IHS ICHD-3 beta.
Author, year: Sakai, 2021 [24] **Country:** Japan and Korea	**Study design:** multicentred, randomised, double-blind, placebo-controlled, parallel-group Phase 2b/3 trial **Date:** November 2017 and November 2019	• Adults 18 to 70 years • Patient with migraine onset at ≤50 years of age • Patient has a history of migraine, based on [ICHD-3 beta] criteria or clinical judgment suggests a migraine diagnosis for ≥ 12 months prior to giving informed consent • Patient fulfils the criteria for Episodic migraine in baseline information collected during the 28-day screening period • Not using preventive migraine medications for migraine or other medical conditions or using no more than 1 preventive migraine medication for migraine or other medical conditions (e.g., propranolol used for hypertension) if the dose and regimen have been stable for at least 2 months prior to giving informed consent.	• Patients who have previously failed (lack of efficacy) 2 or more of the clusters of the medications for treatment of migraine after use for at least 3 months at accepted migraine therapeutic doses • Haematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease considered clinically significant in the judgment of the investigator • Female patient who is nursing at the time informed consent is obtained or who tests positive in pregnancy test at screening or baseline. • History of hypersensitivity reactions to injected proteins, including monoclonal antibodies.
Author, year: Stauffer, 2018 [32] **Country:** 90 sites in North America	**Study design:** phase 3, randomised, double-blind, placebo-controlled study, parallel design	• Adults 18 to 65 years • Have a diagnosis of episodic migraine as defined by International Headache Society (IHS) International	• Are currently enrolled in or have participated within the last 30 days or within 5 half-lives (whichever is longer) in a clinical trial involving an investigational product.

	Date: November 2015 to August 2018	Classification of Headache Disorders (ICHD)-3 beta guidelines (1.1 or 1.2) • History of migraine headaches of at least 1 year prior to screening, • Migraine onset prior to age 50 • Monthly frequency of 4-14 Migraine Headache Days (MHD).	• Current use or prior exposure to Galcanezumab or another CGRP antibody. • Known hypersensitivity to multiple drugs, monoclonal antibodies or other therapeutic proteins, or to Galcanezumab. • History of persistent daily headache, cluster headache or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine, and migraine with brainstem aura (basilar-type migraine) defined by IHS ICHD-3 beta.
Author, year: Skljarevski, 2018 [31] **Country:** 109 study sites in the United States, United Kingdom, Netherlands, Spain, Czech Republic, Germany, Argentina, Israel, Korea, Taiwan, and Mexico	**Study design:** Phase 3, multicentre, placebo-controlled, double-blind, randomised **Date:** January 2016 and March 2017	• Adults 18 to 65 years • Have a diagnosis of episodic migraine as defined by International Headache Society (IHS) International Classification of Headache Disorders (ICHD)-3 beta guidelines (1.1 or 1.2) • History of migraine headaches of at least 1 year prior to screening, • Migraine onset prior to age 50 • Monthly frequency of 4-14 Migraine Headache Days (MHD). • 80% compliance rate in using the electronic diary • patients had to agree to use an acceptable method of birth control during the study and for at least 5 months afterwards	• Having failed treatment with three or more migraine prevention drugs from different classes (level A or B evidence per American Academy of Neurology guidelines for episodic migraine prevention) • Using opioids or barbiturates more than twice per month. • If participation were in another clinical trial within the past 30 days, prior exposure to galcanezumab or any another CGRP antibody, taking any therapeutic antibody in the past 12 months, known hypersensitivity to multiple drugs • Presence of any medical or psychiatric illness that would preclude study participation
Author, year: Reuter, 2018 [14] **Country:** 59 sites in 16 countries across Europe and Australia	**Study design:** randomised, double-blind, placebo-controlled, phase 3b study **Date:** March 2017 to January 2021	• Adults 18 – 65 years • Documented history of migraine in the 12 months prior to screen • 4-14 days per month of migraine symptoms • >=80% diary compliance during the Baseline period	• >50 years old at migraine onset • Pregnant or nursing • History of cluster or hemiplegic headache • Evidence of seizure or psychiatric disorder • Score of over 19 on Beck Depression Inventory-2 • Active chronic pain syndrome

		• Failure of previous migraine prophylactic treatments	• Cardiac or hepatic disease
Author, year: Reuter, 2022 [15] **Country:** 82 study sites in Germany	**Study design:** randomised, double-blind, double dummy, active-controlled, parallel-group phase 4 **Date:** February 2019 to July 2020	• Adults • Documented history of migraine in the 12 months prior to screen according ICHD-3 episodic and chronic migraine • at least 4 days per month of migraine symptoms • >=80% diary compliance during the Baseline period • If patients had not received prior prophylactic migraine treatment (naıve) or, due to lack of efficacy or tolerability, had failed or had not been suitable for up to three previous prophylactic treatments from the following: Metoprolol/propranolol, amitriptyline, and flunarizine	• Older than 50 years of age at migraine onset • Pregnant or nursing • History of cluster or hemiplegic headache, or if they were unable to differentiate migraine from other headaches • History or evidence of major psychiatric disorder • Score of 19 or higher on Beck Depression Inventory (BDI) • Having previously received valproate or, in the event of chronic migraine, onabotulinumtoxin A, in line with recommendations of the German HTA bod
Author, year: Wang, 2021 [18] **Country:** 83 sites across 11 countries in Asia, the Middle East, and Latin America	**Study design:** multicentre, randomised, double-blind, placebo controlled, parallel-group, phase 3 study **Date:** February 2018 to January 2020	• Adults 16- 65 years old with migraine diagnosis according with ICHD-3 beta • ≥4 and <15 migraine days per month and <15 headache days in the 12 months prior to screening • 4-14 days per month of migraine symptoms • >=80% diary compliance during the Baseline period	• >50 years old at migraine onset • Pregnant or nursing • History of cluster or hemiplegic headache • Evidence of seizure or major psychiatric disorder • Score of 19 or higher on the BDI • Active chronic pain syndrome • Cardiac or hepatic disease • No therapeutic response to >2 of the seven categories of migraine-preventive treatments after an adequate therapeutic trial • Use of a prohibited medication, device, or procedure prior to the start of the study • Use of botulinum toxin within 4 months, ergotamines or triptans on ≥10 days per month, simple analgesics on ≥15 days per

			month, or opioid or butalbital-containing analgesics on ≥4 days per month.
Author, year: Elkind, 2006 [2] **Country:** -	**Study design:** A series of 3 sequential, randomised, controlled studies **Date:** -	• Adults 18 to 65 years, with International Headache Society–defined migraines with or without aura. • Having an average of 4 to 8 moderate to severe migraines per month that occurred with a stable frequency and severity and had begun at least 1 year prior to the study. • Patients were first diagnosed with migraine before age 50 years and could distinguish between migraine and nonmigraine headaches. • Eligible patients were in stable medical condition and, if taking chronic medications (including prophylactic migraine medications), were on stable doses and regimens for at least 3 months prior to enrolment, which they agreed to continue throughout the study.	• Patients with more than 15 headache days per month. • History of complicated migraine or typical migraine pain localized predominantly to the occipital or suboccipital region. • Patients were ineligible if they were consistently refractory to multiple acute therapies or had never tried any acute therapies. • Patients who overused symptomatic medications, as were those who used caffeine excessively or abused alcohol/drugs. • Any medical condition or use of any agent that might have put the patient at increased risk with exposure to BTA or interfered with study participation or the results • Women who were pregnant, breastfeeding, or planning a pregnancy • Those with infection or skin problems at the injection site.
Author, year: Mulleners, 2020 [29] **Country:** 64 sites (hospitals, clinics, or research centres) in 12 countries (Belgium, Canada, Czech Republic, France, Germany, Hungary, Japan, the Netherlands, South Korea, Spain, the UK, and the USA)	**Study design:** multicentre, randomised, double-blind, placebo-controlled, phase 3b trial **Date:** Sept 2018 to March 21, 2019	• Adults 18–75 years with a diagnosis of migraine with aura or without aura, or chronic migraine defined ICHD-3, with a history of migraine headaches of at least 1 year before screening, and migraine onset before the age of 50 years. • History of at least four migraine headache days and at least one headache-free day per month on average within the past 3 months. • History of documented treatment failure of two to four standard-of-care	• History of cluster headache or migraine subtypes including hemiplegic migraine, ophthalmoplegic migraine, and migraine with brainstem aura, history of head or neck injury within 6 months before the screening visit, or history of traumatic head injury associated with significant change in the quality or frequency of headaches • Current use or prior exposure to galcanezumab or another calcitonin gene-related peptide (CGRP) antibody. • Pregnant or nursing.

		migraine preventive medication categories in the past 10 years owing to inadequate efficacy, or safety or tolerability reasons, or both, were eligible. • Treatment failure did not include contraindications; patients had to have taken the medications. • The medication categories were: propranolol or metoprolol, topiramate, valproate or divalproex, amitriptyline, flunarizine, candesartan, botulinum toxin A or B, and medications locally approved for prevention of migraine.	• Having acute cardiovascular events or a serious cardiovascular risk, or both, based on electrocardiogram (ECG) results during the screening visit, myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft or stroke within 6 months before screening, hepatic disease based on liver tests, or serious or unstable medical or psychiatric condition.
Author, year: Croop, 2021 [35] **Country:** 92 sites in the USA	**Study design:** multicentre, randomised, double-blind, placebo-controlled trial **Date:** November 2018 to August 2019	• Adults 18 years and older • Subject has at least 1 year history of migraine (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition, including the following: o Age of onset of migraines prior to 50 years of age o Migraine attacks, on average, lasting 4 - 72 hours if untreated o Per subject report, 4 - 18 migraine attacks of moderate to severe intensity per month within the last 3 months prior to the Screening Visit o 6 or more migraine days during the Observation Period o Not more than 18 headache days during the Observation Period o Ability to distinguish migraine attacks from tension/cluster headaches	• History of HIV disease • Subject history with current evidence of uncontrolled, unstable or recently diagnosed cardiovascular disease, such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia. Subjects with Myocardial Infarction (MI), Acute Coronary Syndrome (ACS), Percutaneous Coronary Intervention (PCI), cardiac surgery, stroke or transient ischemic attack (TIA) during the 6 months prior to screening • Uncontrolled hypertension (high blood pressure), or uncontrolled diabetes (however subjects can be included who have stable hypertension and/or diabetes for at least 3 months prior to screening). • Subjects with major depressive episode within the last 12 months, major depressive disorder or any anxiety disorder requiring more than 1 medication for each disorder. Medications to treat major depressive disorder or an anxiety disorder must have

		○ Subjects on prophylactic migraine medication are permitted to remain on 1 medication with possible migraine-prophylactic effects if the dose has been stable for at least 3 months prior to the Screening Visit, and the dose is not expected to change during the course of the study.	been at a stable dose for at least 3 months prior to the Screening visit. • Subjects with other pain syndromes, psychiatric conditions, dementia, or significant neurological disorders (other than migraine) that, in the Investigator's opinion, might interfere with study assessments • Subject has a history of gastric, or small intestinal surgery (including Gastric Bypass, Gastric Banding, Gastric Sleeve, Gastric Balloon, etc.), or has disease that causes malabsorption • Subject has current diagnosis of major depressive disorder requiring treatment with atypical antipsychotics, schizophrenia, bipolar disorder, or borderline personality disorder • History of gallstones or cholecystectomy. • The subject has a history or current evidence of any unstable medical conditions (e.g., history of congenital heart disease or arrhythmia, known or suspected infection, hepatitis B or C, or cancer) that, in the investigator's opinion, would expose them to undue risk of a significant adverse event (AE) or interfere with assessments of safety or efficacy during the course of the trial
Author, year: Winner, 2021 [11] **Country:** 47 sites in the United States and the country of Georgia	**Study design:** Phase 3, multicentre, parallel-group, double-blind, randomised, placebo-controlled trial **Date:** November 2019 to July 2020	• Greater than 1-year history of migraine, with or without aura, with onset of first migraine before age 50. • Migraine on 4 to 15 days per month in the 3 months prior to screening. • Headache free for at least 24 hours prior to onset of a qualifying migraine. • Adults 18 Years to 75 Years	• Use of the following medication, for any indication, within the 24-hour period prior to dosing with study drug: ○ triptans, ergotamines and ergot-derivatives, analgesics and other acute migraine medication(s), antiemetic medications, antihistamines, devices, neuromodulation, neurostimulation, or injectable therapy

		• Diagnosis of migraine based on ICHD-3 criteria1 for migraine with or without aura	• Use of the following medication, for any indication, in each of the 3 months prior to screening: o opioids/narcotics or butalbital containing products (including combinations) on more than 4 days per month o triptans, ergotamines, or combination analgesics for 10 or more days per month o acetaminophen, aspirin or NSAIDs for 15 or more days per month (except if participant is taking 81 mg dose of aspirin for cardiac prophylaxis) • History or diagnosis of chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, or unusual migraine subtypes that are not typical of migraine aura. • Any use of approved devices, neuromodulation, neurostimulation, or injectable therapy within the 24-hour period prior to treatment with study drug (Day 0). • Any use of botulinum toxin for migraine or for any other medical/cosmetic reasons requiring injections within 7 days prior to treatment with study drug (Day 0). • Any use of systemic corticosteroid for migraine or any other reason within 3 months prior to treatment with study drug (Day 0). • History of clinically significant psychiatric diseases • Receipt of any monoclonal antibody treatment, for migraine or any other indication within 6 months prior to screening.
Author, year: Bo Hu, 2022 [26]	**Study design:**	• Participants must have a diagnosis of migraine as defined by International	• Are currently enrolled in any other clinical trial involving an investigational product or

Country: 40 centres in China (n=26), India (n=10), and Russia (n=4)	Phase 3, randomised, double-blind, placebo-controlled study **Date:** July 2019 to March 2022	Headache Society (IHS) International Classification of Headache Disorders (ICHD)-3 (1.1 or 1.2) (ICHD-3 2018) with a history of migraine of at least 1 year prior to screening and migraine onset prior to age 50 • Prior to screening, participants must have a history of 4-14 migraine headache days and at least 2 migraine attacks per month on average within the past 3 months • Adults 18 to 65 years	any other type of medical research judged not to be scientifically or medically compatible with this study • Current use or prior exposure to galcanezumab or another calcitonin gene-related peptide antibody, including those who have previously completed or withdrawn from this study or any other study investigating a CGRP antibody • Participants who are taking, or are expected to take, therapeutic antibodies during the course of the study (for example, adalimumab, infliximab, trastuzumab, bevacizumab, etc.) • Known hypersensitivity to multiple drugs, monoclonal antibodies or other therapeutic proteins, or to galcanezumab • Women who are pregnant or nursing • History of chronic migraine, daily persistent headache, cluster headache, medication overuse headache, migraine with brainstem aura, or hemiplegic migraine.
Author, year: Ashina, 2022 [8] **Country:** 96 study locations across Europe (n=93) and the USA (n=3)	**Study design:** multicentre, multi-arm, double-blind, placebo-controlled **Date:** June 2020 to Oct 2021	• Diagnosis of migraine, with a history of chronic or episodic migraines of at least 12 months prior to the screening visit • History of migraine onset of ≤50 years of age. • The participant has ≥4 migraine days per month for each month within the past 3 months prior to the screening visit. • The participant has demonstrated compliance with the Headache eDiary by entry of data for at least 24 of the 28 days following the Screening Visit.	• History of failure on a previous treatment targeting the CGRP pathway. • Participant has a treatment failure on valproate/divalproex or botulinum toxin A/B and the treatment is not the latest preventive medication prior to study inclusion. The medication is regarded as the latest if the medication start date is after the start date of the other preventive medications and the medication stop date is after the stop date of the other preventive medications. • Participant has confounding and clinically significant pain syndromes

		• The participant fulfils the following criteria for CM or EM in prospectively collected information in the eDiary during the screening period: • For CM participants: Migraine occurring on ≥8 days and headache occurring on >14 days • For EM participants: Migraine occurring on ≥4 days and headache occurring on ≤14 days • Participant has documented evidence of treatment failure (must be supported by medical record or by physician's confirmation specific to each treatment) in the past 10 years of 2-4 different migraine preventive medications. • Participant has a history of either previous or active use of triptans for migraine.	• History of acute or active temporomandibular disorder. • History or diagnosis of chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, or unusual migraine subtypes such as hemiplegic migraine, ophthalmoplegic migraine, and migraine with neurological accompaniments that are not typical of migraine aura. • Participant has a psychiatric condition • Participants with a lifetime history of psychosis and/or mania in the last 5 years prior to the screening visit are excluded. • History of clinically significant cardiovascular disease or vascular ischaemia or thromboembolic events.
Author, year: Ashina 2023 [34] **Country:** United state	**Study design:** A 52-week, multicenter, randomized, open-label trial **Date:** September 2016 to April 2018	• Has at least a 1-year history of migraine with or without aura • Age of the patient at the time of migraine onset < 50 years • History of 4 to 14 migraine days (migraine/probable migraine headache days) per month on average in the 3 months prior to Visit 1 in the Investigator's judgment • Demonstrated compliance with e-diary •	• Has a history of migraine accompanied by diplopia or decreased level of consciousness and retinal migraine • Has a current diagnosis of chronic migraine, new persistent daily headache, trigeminal autonomic cephalgia (eg, cluster headache), or painful cranial neuropathy • Difficulty distinguishing migraine headache from other headaches • Has a history of malignancy in the prior 5 years, except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer • Has a history of gastric or small intestinal surgery, or has a disease that causes malabsorption

			• Has a history of hepatitis within previous 6 months • Usage of opioids or barbiturates > 2 days/month, triptans or ergots ≥ 10 days/month, or simple analgesics (eg, aspirin, non-steroidal anti-inflammatory drugs [NSAIDs], acetaminophen) ≥ 15 days/month in the 3 months prior to Visit 1 • Pregnant or nursing females
Author, year: Takeshima 2021 [19] **Country:** Japan	**Study design:** Phase 3, randomized, double-blind, placebo-controlled **Date:** April 2019 to November 2020	• Japanese patients ≥20 to ≤65 years of age • History of migraine (with or without aura) for ≥12 months before screening, according to International Classification of Headache Disorders, 3rd edition (ICHD-3). • During the 4-week baseline phase, patients had to have the same migraine type as assessed by their handheld electronic diary (eDiary) during screening and had to have demonstrated ≥80% compliance with their eDiary	• Subjects greater than 50 years of age at migraine onset. • History of cluster headache or hemiplegic migraine headache. • Unable to differentiate migraine from other headaches. • Migraine with continuous pain, in which the subject does not experience any pain-free periods (of any duration) during the 1 month before the screening period. • Malignancy, except non-melanoma skin cancers, cervical or breast ductal carcinoma in situ within the last 5 years.
Author, year: Shengyuan Yu 2022 [20] **Country:** Mainland China, India, the Republic of Korea, Malaysia, the Philippines, Singapore, Taiwan, Tailand, and Vietnam	**Study design:** phase 3, randomised, double-blind, placebo-controlled **Date:** August 2019 and August 2021	• Adults aged 18–65 years with a history of CM with or without aura for at least 12 months before screening as defned by the International Classifcation of Headache Disorders, 3rd edition (ICHD-3). • Patients with a history of≥15 headache days/month, of which≥8 headache days met criteria as migraine days during the baseline period, and who had demonstrated at least 80% compliance with the eDiary during the baseline period.	• Participants older than 50 years at migraine onset. • History of cluster or hemiplegic migraine headache; CM with continuous pain; unable to diferentiate migraine from other headaches; opioid and/or opioid-containing analgesic (for>4 days per month) or butalbital-containing analgesic (for>2 days per month) for any indication within one month before the start of or during the baseline period; • prior migraine preventive treatment failure in>3 medication categories (categories provided in Supplementary Table 2);

		• Concomitant therapies with possible migraine prophylactic efects taken for indications other than migraine must have been administered at a stable dose within the 3 months prior to the start of the baseline period and throughout the study.	• prior botulinum toxin A treatment in the head/ neck region within 4 months before the start of or during the baseline period, active chronic pain syndromes (such as fibromyalgia and chronic pelvic pain), or other medical conditions. • Pregnant or nursing (lactating) women, and women of childbearing potential

Appendix 4: Further results for adverse events (AEs)

Table 1: Arm level data on adverse events and treatment-related AEs (%)

Author	Year	Intervention	Participants	Any AEs	Treatment-related AEs
Ashina [34]	2023	Atogepant 60 mg	543	67	18
Ashina [34]	2023	Standard care	196	78.6	36.2
Shengyuan Yu [20]	2022	Erenumab 70mg	279	45.5	12.9
Shengyuan Yu [20]	2022	Placebo	278	47.5	13.3
HO [26]	2022	Galcanezumab 120 mg	261	49.8	
HO [26]	2022	Placebo	259	43.2	
Ashina [8]	2022	Eptinezumab 100 mg	299	42	3
Ashina [8]	2022	Eptinezumab 300 mg	294	41	1
Ashina [8]	2022	Placebo	298	40	3
Takeshima [19]	2021	Erenumab 70mg	130	65.4	
Takeshima [19]	2021	Placebo	131	58.8	
Sakai [23]	2021	Fremanezumab-M	188	61.7	29.3
Sakai [23]	2021	Fremanezumab-Q	190	61.1	32.1
Sakai [23]	2021	Placebo	191	61.8	28.3
Ailani [33]	2021	Atogepant 10 mg	221	52.9	23.1
Ailani [33]	2021	Atogepant 30 mg	228	52.2	14.9
Ailani [33]	2021	Atogepant 60 mg	231	53.7	19.5
Ailani [33]	2021	Placebo	222	56.8	9
Sakai [24]	2021	Fremanezumab-M	121	57	26.4
Sakai [24]	2021	Fremanezumab-Q	118	62.7	31.4
Sakai [24]	2021	Placebo	117	65.8	23.9
Reuter [15]	2021	Erenumab 140 mg	388		55.4
Reuter [15]	2021	Topiramate 100 mg	388		81.2
Wang [18]	2021	Erenumab 70 mg	335	34.9	11.3
Wang [18]	2021	Erenumab 140 mg	224	34.4	10.7
Wang [18]	2021	Placebo	335	36.7	9.6
Winner [11]	2021	Eptinezumab 100 mg	238	10.9	
Winner [11]	2021	Placebo	242	10.3	
Lipton [10]	2020	Eptinezumab 100 mg	356	43.5	
Lipton [10]	2020	Eptinezumab 300 mg	350	52	
Lipton [10]	2020	Placebo	366	46.7	
Ashina [7]	2020	Eptinezumab 100 mg	223	63.2	
Ashina [7]	2020	Eptinezumab 300 mg	224	57.6	
Ashina [7]	2020	Placebo	222	59.5	
Sakai [30]	2020	Galcanezumab 120 mg	115	85.2	
Sakai [30]	2020	Galcanezumab 240 mg	114	81.6	
Sakai [30]	2020	Placebo	230	64.8	
Mulleners [29]	2020	Galcanezumab 120 mg	232	51	15

Mulleners [29]	2020	Placebo	230	53	16
Croop [35]	2020	Rimegepant 75 mg	370	36	11
Croop [35]	2020	Placebo	371	36	9
Dodick [9]	2019	Eptinezumab 100 mg	122	57.5	19.8
Dodick [9]	2019	Eptinezumab 300 mg	121	63.6	17.4
Dodick [9]	2019	Placebo	121	56.2	14
Ferrari [22]	2019	Fremanezumab-Q	276	55	21
Ferrari [22]	2019	Fremanezumab-M	285	45	19
Ferrari [22]	2019	Placebo	277	48	20
Rothrock [6]	2019	BTA 150 U	220	48	17
Rothrock [6]	2019	Topiramate 100 mg	142	79	70
Detke [27]	2018	Galcanezumab 120 mg	273	58	
Detke [27]	2018	Galcanezumab 240 mg	282	57	
Detke [27]	2018	Placebo	558	50	
Dodick [12]	2018	Erenumab 70 mg	283	48.1	
Dodick [12]	2018	Placebo	289	54.7	
Dodick [21]	2018	Fremanezumab-M	290	66.2	47.6
Dodick [21]	2018	Fremanezumab-Q	291	66.3	47.1
Dodick [21]	2018	Placebo	293	58.4	37.2
Stauffer [32]	2018	Galcanezumab 120 mg	206	65.5	
Stauffer [32]	2018	Galcanezumab 240 mg	220	67.7	
Stauffer [32]	2018	Placebo	432	60.4	
Vladimir [31]	2018	Galcanezumab 120 mg	226	65	
Vladimir [31]	2018	Galcanezumab 240 mg	228	71.5	
Vladimir [31]	2018	Placebo	461	62.3	
Reuter [14]	2018	Erenumab 140 mg	119	55	
Reuter [14]	2018	Placebo	124	54	
Silberstein [25]	2017	Fremanezumab-Q	376	70	49
Silberstein [25]	2017	Fremanezumab-M	379	71	51
Silberstein [25]	2017	Placebo	375	64	42
Tepper [17]	2017	Erenumab 70 mg	190	44	
Tepper [17]	2017	Erenumab 140 mg	188	47	
Tepper [17]	2017	Placebo	282	39	
Goadsby [13]	2017	Erenumab 70 mg	314	57.3	
Goadsby [13]	2017	Erenumab 140 mg	319	55.5	
Goadsby [13]	2017	Placebo	319	63	
Hong Sun [16]	2016	Erenumab 7 mg	108	50	
Hong Sun [16]	2016	Erenumab 21 mg	105	51	
Hong Sun [16]	2016	Erenumab 70 mg	106	54	
Hong Sun [16]	2016	Placebo	153	54	
Dodick [28]	2014	Galcanezumab 150 mg	107	72	
Dodick [28]	2014	Placebo	110	67	

Dodick [3]	2010	BTA 150 U	687	62.4	29.4
Dodick [3]	2010	Placebo	692	51.7	12.7
Dodick [1]	2009	Topiramate 100 mg	177	85.9	68.4
Dodick [1]	2009	Amitriptyline 100 mg	169	88.8	75.7

Table 2: Details for investigations of system organ class (SOC) (%)

Author(s)	Year of Publication	Intervention	Participants	Weight increase	Weight decrease	Increased blood creatine kinase	Blood creatinine phosphokinase	INR increased	Alanine aminotransferase ≥3x ULN	Aspartate aminotransferase ≥3x ULN	Total bilirubin ≥2x ULN
Ashina [34]	2023	Atogepant 60 mg	543		2.6				2	2.4	
Ashina [34]	2023	Oral standard care	196	5.6							
HO [26]	2022	Galcanezumab 120 mg	261				1.5			1.9	
HO [26]	2022	Placebo	259				0			0	
Ashina [8]	2022	Eptinezumab 100 mg	299				1.5				
Ashina [8]	2022	Eptinezumab 300 mg	294				0				
Ashina [8]	2022	Placebo	298								
Ailani [33]	2021	Atogepant 10 mg	221			2.3			1.4		
Ailani [33]	2021	Atogepant 30 mg	228			0.9			0.9		
Ailani [33]	2021	Atogepant 60 mg	231			3			0.9		
Ailani [33]	2021	Placebo	222			0.9			2.7		
Reuter [15]	2021	Erenumab	388		0.8						
Reuter [15]	2021	Topiramate	388		5.7						
Ferrari [22]	2019	Fremanezumab-Q	276					1			
Ferrari [22]	2019	Fremanezumab-M	285					0.5			
Ferrari [22]	2019	Placebo	277					0.5			
Stauffer [32]	2018	Galcanezumab 120 mg	206	1.9							
Stauffer [32]	2018	Galcanezumab 240 mg	220	0.9							
Stauffer [32]	2018	Placebo	432	1.4							
Silberstein [25]	2017	Fremanezumab-Q	376						0.26	0.26	0.6
Silberstein [25]	2017	Fremanezumab-M	379						0.26	0.26	0
Silberstein [25]	2017	Placebo	375						0	0	0

Table 1: Details for injury, poisoning and procedural complications of system organ class (SOC) (%)

First Author	Year of Publication	Intervention	Participants	Ecchymosis	Injury	Contusion
Stauffer [32]	2018	Galcanezumab 120mg	206			2.4
Ashina [34]	2023	Oral standard care	196			3.1
Stauffer [32]	2018	Placebo	432			1.2

Table 4: Details for metabolism and nutrition disorders of system organ class (SOC) (%)

Author	Year of Publication	Intervention	Participants	Anorexia	Decreased appetite
Reuter [15]	2021	Erenumab 140 mg	388		2.1
Reuter [15]	2021	Topiramate 100 mg	388		9

Rothrock [6]	2019	BTA 150 U	220		0
Rothrock [6]	2019	Topiramate 100 mg	142		11

Table 5: Details for reproductive system and breast disorders of system organ class (SOC) (%)

Author(s)	Year of Publication	Intervention	Participants	Menstrual irregularity	Dysmenorrhea
Stauffer [32]	2018	Galcanezumab 120 mg	206		0.6
Stauffer [32]	2018	Galcanezumab 240 mg	220		2.2
Stauffer [32]	2018	Placebo	432		0.6

Table 6: Details for skin and subcutaneous of system organ class (SOC) (%)

Author(s)	Year of Publication	Intervention	Participants	Eczema	Urticaria	Pruritus	Hair fall	Skin tightness	Rash	Alopecia	Sweat discoloration
HO [26]	2022	Galcanezumab 120 mg	261			1.5					
HO [26]	2022	Placebo	259			0.8					
Sakai [24]	2021	Fremanezumab-M	121	2.5							
Sakai [24]	2021	Fremanezumab-Q	118	0.8							
Sakai [24]	2021	Placebo	117	0							
Saka i [30]	2020	Galcanezumab 120 mg	115		1.7						
Sakai [30]	2020	Galcanezumab 240 mg	114		6.1						
Sakai [30]	2020	Placebo	230		0						
Ferrari [22]	2019	Fremanezumab-Q	276						0.5	0.5	
Ferrari [22]	2019	Fremanezumab-M	285						1	0.5	
Ferrari [22]	2019	Placebo	277						0.5	0.5	
Stauffer [32]	2018	Galcanezumab 120 mg	206			1					
Stauffer [32]	2018	Galcanezumab 240 mg	220			2.7					
Stauffer [32]	2018	Placebo	432			0.2					
Dodick [28]	2014	Galcanezumab 150 mg	107						5		
Dodick [28]	2014	Placebo	110						0		

Fremanezumab-Q, Fremanezumab quarterly; Fremanezumab-M, Fremanezumab monthly

Table 7: Details for eye disorders of system organ class (SOC) (%)

Author	Year of Publication	Intervention	Participants	Belpharotosis	Abnormal vision	Visual disturbance	Vision blurred	Eyelid edema
Rothrock [6]	2019	BTA 150U	220				3	
Rothrock [6]	2019	Topiramate 100 mg	142				8	
Dodick [28]	2014	Galcanezumab 150 mg	107			3		
Dodick [28]	2014	Placebo	110			2		

Table 8: Details for renal and urinary disorders of system organ class (SOC) (%)

Author	Year of Publication	Intervention	Participants	Urinary retention	Protein urine present
HO [26]	2022	Galcanezumab 120 mg	261		2.3
HO [26]	2022	Placebo	259		1.5

Table 9: Details for vascular disorders and Cardiac Disorders of system organ class (SOC) (%)

Author	Year	Intervention	Vascular disorders			Cardiac Disorders
			Participants	Hypotension	Hypertension	Tachycardia
Ashina [34]	2023	Atogepant 60 mg	543		2.6	
Ferrari [22]	2019	Fremanezumab quarterly	276		1	
Ferrari [22]	2019	Fremanezumab monthly	285		0.5	
Ferrari [22]	2019	Placebo	277		0.5	
Goadsby [13]	2017	Erenumab 70 mg	314		1.6	
Goadsby [13]	2017	Erenumab 140 mg	319		0	
Goadsby [13]	2017	Placebo	319		2.5	
Dodick [28]	2014	Galcanezumab 150 mg	107		5	
Dodick [28]	2014	Placebo	110		0	

Table 10: Details for respiratory, thoracic and mediastinal disorders of system organ class (SOC)(%)

Author	Year of Publication	Intervention	Participants	Nasal congestion	Bronchitis	Rhinitis	Sinus congestion	Cough	Asthma
Sakai [23]	2021	Fremanezumab-M	188						1.1
Sakai [23]	2021	Fremanezumab-Q	190						2.1
Sakai [23]	2021	Placebo	191						0
Ailani [33]	2021	Atogepant 10 mg	221				0.5		
Ailani [33]	2021	Atogepant 30 mg	228				0.9		
Ailani [33]	2021	Atogepant 60 mg	231				1.7		
Ailani [33]	2021	placebo	222				2.3		
Ashina [7]	2020	Eptinezumab 100 mg	223		2.7			3.6	
Ashina [7]	2020	Eptinezumab 300 mg	224		3.1			2.7	
Ashina [7]	2020	Placebo	222		3.6			3.2	
Mulleners [29]	2020	Galcanezumab 120 mg	232		1				
Mulleners [29]	2020	Placebo	230		2				
Dodick [9]	2019	Eptinezumab 100 mg	122		3.3				
Dodick [9]	2019	Eptinezumab 300 mg	121		3.3				
Dodick [9]	2019	Placebo	121		7.4				
Dodick [21]	2018	Fremanezumab-M	290		21				
Dodick [21]	2018	Fremanezumab-Q	291		1.4				
Dodick [21]	2018	Placebo	293		1				
Stauffer [32]	2018	Galcanezumab 120 mg	206	0.5	1.5			1.9	
Stauffer [32]	2018	Galcanezumab 240 mg	220	2.3	3.2			2.7	
Stauffer [32]	2018	Placebo	432	0.9	1.4			1.6	
Hong Sun [16]	2016	Erenumab 7 mg	108					2	
Hong Sun [16]	2016	Erenumab 21 mg	105					1	
Hong Sun [16]	2016	Erenumab 70 mg	106					0	
Hong Sun [16]	2016	Placebo	153					2	
Dodick [1]	2009	Topiramate 100 mg	177					5.1	
Dodick [1]	2009	Amitriptyline 100 mg	169					4.1	

Fremanezumab-Q, Fremanezumab quarterly; Fremanezumab-M, Fremanezumab monthly

Table 11: Details for gastrointestinal disorders of system organ class (SOC) (%)

Author	Year of Publication	Intervention	Participants	Abdominal pain	Oropharyngeal pain	Abdominal discomfort	Diarrhoea	Flatulence	Dry mouth	Oropharyngeal pain	Toothache	Upper abdominal pain	Dyspepsia	Nausea	Dry mucous membrane	Constipation	Vomiting	Gastrointestinal symptoms	Vertigo	Giddiness
Ashina [34]	2023	Oral standard care	196				3.1		4.1				6.1			3.1				
HO [26]	2022	Galcanezumab 120 mg	261			1.9	1.5													
HO [26]	2022	Placebo	259			0.8	2.3													
Ashina [8]	2022	Eptinezumab 100	299				0					2		1						
Ashina [8]	2022	Eptinezumab 300 mg	294				2					1		2						
Ashina [8]	2022	Placebo	298				2					1		1						
Takeshima [19]	2021	Erenumab 70 mg	130				3.8									4.6				
Takeshima [19]	2021	Placebo	131				0.8									0.8				
Shengyuan Yu [20]	2022	Erenumab 70 mg	279													8.6				
Shengyuan Yu [20]	2022	Placebo	278													3.2				
Sakai [23]	2021	Fremanezumab-M	188				1.6							1.1						
Sakai [23]	2021	Fremanezumab-Q	190				2.1							2.6						
Sakai [23]	2021	Placebo	191				0							1						
Ailani [33]	2021	Atogepant 10 mg	221											5		7.7				
Ailani [33]	2021	Atogepant 30 mg	228											4.4		7				
Ailani [33]	2021	Atogepant 60 mg	231											6.1		6.9				
Ailani [33]	2021	Placebo	222											1.8		0.5				
Sakai [24]	2021	Fremanezumab-M	121				0					0.8		0.8						
Sakai [24]	2021	Fremanezumab-Q	118				2.5					2.5		0						
Sakai [24]	2021	Placebo	117				0					0		2.6						
Reuter [15]	2021	Erenumab 140mg	388				1.8		2.1			2.8	1.5	6.7		11.3			4.4	
Reuter [15]	2021	Topiramate	388				4.1		4.6			2.6	2.3	6.7		3.1			5.9	
Wang [18]	2021	Erenumab 70 mg	335													5.7				

Wang [18]	2021	Erenumab 140 mg	224													5.4				
Wang [18]	2021	Placebo	335													1.5				
Winner [11]	2021	Eptinezumab 100mg	238											0						
Winner [11]	2021	Placebo	242											0.8						
Lipton [10]	2020	Eptinezumab 100 mg	356											1.7						
Lipton [10]	2020	Eptinezumab 300 mg	350											3.4						
Lipton [10]	2020	Placebo	366											1.9						
Ashina [7]	2020	Eptinezumab 100 mg	223				1.3							2.2						
Ashina [7]	2020	Eptinezumab 300 mg	224				3.6							2.2						
Ashina [7]	2020	Placebo	222				1.4							3.6						
Mulleners [29]	2020	Galcanezumab 120 mg	232		1					1				2		2			2	
Mulleners [29]	2020	Placebo	230		2					2				2		2			0.004	
Croop [35]	2020	Rimegepant	370											3						
Croop [35]	2020	Placebo	371											1						
Dodick [9]	2019	Eptinezumab 100 mg	122											7.4						
Dodick [9]	2019	Eptinezumab 300 mg	121											6.6						
Dodick [9]	2019	Placebo	121											7.4						
Ferrari [22]	2019	Fremanezumab-Q	276				3					1		1		3				
Ferrari [22]	2019	Fremanezumab-M	285				0.5					0.5		0.5		0.5				
Ferrari [22]	2019	Placebo	277				1					0		2		0.5				
Rothrock [6]	2019	BTA	220											0.5						
Rothrock [6]	2019	Topiramate	142											13						
Detke [27]	2018	Galcanezumab 120 mg	273	2	1		1			1										
Detke [27]	2018	Galcanezumab 240 mg	282	1	2		2			2										
Detke [27]	2018	Placebo	558	2	1		1			1										
Dodick [12]	2018	Erenumab 70 mg	283											2.5		1.4				
Dodick [12]	2018	Placebo	289											4.5		2.1				
Dodick [21]	2018	Fremanezumab-M	290											1.4						
Dodick [21]	2018	Fremanezumab-Q	291											2.4						
Dodick [21]	2018	Placebo	293											1.7						
Stauffer [32]	2018	Galcanezumab 120 mg	206		1.9					1.9				2.4					1	

Stauffer [32]	2018	Galcanezumab 240 mg	220		1.4					1.4				3.6					1.8	
Stauffer [32]	2018	Placebo	432		0.7					0.7				3.5					0.5	
Vladimir [31]	2018	Galcanezumab 120 mg	226				3.1													
Vladimir [31]	2018	Galcanezumab 240 mg	228				1.3													
Vladimir [31]	2018	Placebo	461				2.4													
Silberstein [25]	2017	Fremanezumab-Q	376											1						
Silberstein [25]	2017	Fremanezumab-M	379											2						
Silberstein [25]	2017	Placebo	375											3						
Tepper [17]	2017	Erenumab 70 mg	190											2		0				
Tepper [17]	2017	Erenumab 140 mg	188											3		4				
Tepper [17]	2017	Placebo	282											2		0.5				
Goadsby [13]	2017	Erenumab 70 mg	314											2.2		1.6				
Goadsby [13]	2017	Erenumab 140 mg	319											1.9		3.4				
Goadsby [13]	2017	Placebo	319											1.9		1.3				
Hong Sun [16]	2016	Erenumab 7 mg	108				0							3						
Hong Sun [16]	2016	Erenumab 21 mg	105				1							1						
Hong Sun [16]	2016	Erenumab 70 mg	106				1							3						
Hong Sun [16]	2016	Placebo	153				3							1						
Dodick [28]	2014	Galcanezumab 150 mg	107	6							4			4						
Dodick [28]	2014	Placebo	110	3							1			9						
Dodick [1]	2009	Topiramate 100mg	177						6.8				5.1	10.2		3.4				

Dodick [1]	2009	Amitriptyline 100mg	169						35.5				8.3	7.1		8.3				

Table 12: Details for psychiatric disorders of system organ class (SOC) (%)

Author	Year of Publication	Intervention	Participants	Anxiety	Agitation	Sleep disorder	Nervousness	Insomnia	Mood swings	Irritability	Confusion	Depressed mood	Depression
Ashina [34]	2023	Atogepant 60 mg	543	2.9									
Ashina [34]	2023	Oral standard care	196	5.6				3.6					
Reuter [15]	2021	Erenumab 140 mg	388			4.1		1.5	2.1	1.3		0.3	1.5
Reuter [15]	2021	Topiramate 100 mg	388			1.5		2.6	4.1	4.6		3.6	4.1
Mulleners [29]	2020	Galcanezumab 120 mg	232					2					
Mulleners [29]	2020	Placebo	230					0					
Ferrari [22]	2019	Fremanezumab-quarterly	276	1				2					
Ferrari [22]	2019	Fremanezumab-monthly	285	0.5				2					
Ferrari [22]	2019	Placebo	277	0				0.5					
Rothrock [6]	2019	BTA 155U	220										2
Rothrock [6]	2019	Topiramate 100 mg	142										6
Lipton [10]	2011	Topiramate 100mg	176								5.7		
Lipton [10]	2011	Placebo	185								1.6		

Table 13: Details for musculoskeletal and connective tissue disorders of system organ class (SOC) (%)

Author	Year of Publication	Intervention	Participants	Muscular weakness	Muscle spasms	Muscle tightness	Myalgia	Musculoskel etal stiffness	Back pain	Musculoskel etal pain	Arthralgia	Neck pain	Arm pain
Ashina [34]	2023	Atogepant 60 mg	543			2			2.4		2		
Ashina [34]	2023	Oral standard care	196						2.6				
Ashina [8]	2022	Eptinezumab 100	299						2		2		
Ashina [8]	2022	Eptinezumab 300 mg	294						1		1		
Ashina [8]	2022	Placebo	298						1		0		
Takeshima [19]	2021	Erenumab 70 mg	130					3.8	5.4				
Takeshima [19]	2021	Placebo	131					0.8	4,6				
Sakai [23]	2021	Fremanezumab-M	188						2.7				
Sakai [23]	2021	Fremanezumab-Q	190						0.5				
Sakai [23]	2021	Placebo	191						0.5				
Sakai [24]	2021	Fremanezumab-M	121							0			
Sakai [24]	2021	Fremanezumab-Q	118							2.5			
Sakai [24]	2021	Placebo	117							0			
Winner [11]	2021	Eptinezumab 100 mg	238						0				
Winner [11]	2021	Placebo	242						0.8				
Ashina [7]	2020	Eptinezumab 100 mg	223						3.1				
Ashina [7]	2020	Eptinezumab 300 mg	224						1.3				
Ashina [7]	2020	Placebo	222						3.2				
Mulleners [29]	2020	Galcanezumab 120 mg	232						3				
Mulleners [29]	2020	Placebo	230						2				

Ferrari [22]	2019	Fremanezumab-Q	276						2		0.5	0.5	
Ferrari [22]	2019	Fremanezumab-M	285						0.5		0.5	1	
Ferrari [22]	2019	Placebo	277						2		1	0	
Rothrock [6]	2019	BTA 155 U	220									4	
Rothrock [6]	2019	Topiramate 100 mg	142									2	
Dodick [3]	2010	BTA 155U	687	5.5			2.6	2.3		2.2		6.7	
Dodick [3]	2010	Placebo	692	0.3			0.3	0.7		0.7		2.2	
Detke [27]	2018	Galcanezumab 120 mg	273						3		0	3	
Detke [27]	2018	Galcanezumab 240 mg	282						1		2	0	
Detke [27]	2018	Placebo	558						3		1	1	
Stauffer [32]	2018	Galcanezumab 120 mg	206						2.4			1.5	
Stauffer [32]	2018	Galcanezumab 240 mg	220						3.2			1.8	
Stauffer [32]	2018	Placebo	432						1.4			0.9	
Reuter [14]	2018	Erenumab 140 mg	119						4			3	
Reuter [14]	2018	Placebo	124						2			0	
Tepper [17]	2017	Erenumab 70 mg	190		<1								
Tepper [17]	2017	Erenumab 140 mg	188		4								
Tepper [17]	2017	Placebo	282		1								
Goadsby [13]	2017	Erenumab 70 mg	314						1.9		2.2		
Goadsby [13]	2017	Erenumab 140 mg	319						1.9		2.2		
Goadsby [13]	2017	Placebo	319						2.2		1.9		

Hong Sun [16]	2016	Erenumab 70 mg	108			0			3		1		
Hong Sun [16]	2016	Erenumab 21 mg	105			0					0		
Hong Sun [16]	2016	Erenumab 70 mg	106			0					1		
Hong Sun [16]	2016	Placebo	153			2					3		
Dodick [28]	2014	Galcanezumab 150 mg	107						7		6	4	
Dodick [28]	2014	Placebo	110						7		6	2	

Fremanezumab-Q, Fremanezumab quarterly; Fremanezumab-M, Fremanezumab monthly

Table 14: Details for nervous system disorders of system organ class (SOC) (%)

Author	Year	Intervention	Participants	Neck rigidity	Dysesthesia	Paraesthesia	Hypertonia	Hypoesthesia	Difficulty with memory	Difficulty with concentration	Taste perversion	Migraine	Dizziness	Aphasia	Dysgeusia	Cognitive disorder	Headache	Somnolence	Drowsiness	Facial paralysis
Ashina [34]	2023	Atogepant 60 mg	543										3.1							
Ashina [34]	2023	Oral standard care	196									3.1	11.2					4.1		
HO [26]	2022	Galcanezumab 120 mg	261										3.4							
HO [26]	2022	Placebo	259										2.3							
Ashina [8]	2022	Eptinezumab 100	299										1							
Ashina [8]	2022	Eptinezumab 300 mg	294										1							
Ashina [8]	2022	Placebo	298										2							
Shengyuan Yu [20]	2022	Erenumab 70 mg	298										1.8							
Shengyuan Yu [20]	2022	Placebo	297										4.3							
Ailani [33]	2021	Atogepant 10 mg	221															3.2		
Ailani [33]	2021	Atogepant 30 mg	228															1.8		
Ailani [33]	2021	Atogepant 60 mg	231															1.7		
Ailani [33]	2021	Placebo	222															0.9		

Sakai [24]	2021	Fremanezumab-M	121									0	0				1.7			
Sakai [24]	2021	Fremanezumab-Q	118									0	0.8				1.7			
Sakai [24]	2021	Placebo	117									2.6	2.6				3.4			
Reuter [15]	2021	Erenumab 140 mg	388		0.5	4.4		0.5	0.3	4.6	0		5.2	0.5	0.8		0.5			
Reuter [15]	2021	Topiramate 100 mg	388		2.1	39.9		3.4	2.6	16.2	6.2		13.1	2.8	5.7		2.1			
Wang [18]	2021	Erenumab 70 mg	335										0.9							
Wang [18]	2021	Erenumab 140 mg	224										3.1							
Wang [18]	2021	Placebo	335										1.8							
Lipton [10]	2020	Eptinezumab 100 mg	356									1.7								
Lipton [10]	2020	Eptinezumab 300 mg	350									2.3								
Lipton [10]	2020	Placebo	366									4.4								
na [7]	2020	Eptinezumab 100 mg	223										4.5							
Ashina [7]	2020	Eptinezumab 300 mg	224										1.8							
Ashina [7]	2020	Placebo	222										3.6							
Mulleners [29]	2020	Galcanezumab 120 mg	232									2								
Mulleners [29]	2020	Placebo	230									0								
Dodick [9]	2019	Eptinezumab 100 mg	122									5.7	9.8							
Dodick [9]	2019	Eptinezumab 300 mg	121									0.8	1.7							
Dodick [9]	2019	Placebo	121									1.7	7.4							
Ferrari [22]	2019	Fremanezumab-Q	276									0.5	2							
Ferrari [22]	2019	Fremanezumab-M	285									1	1							
Ferrari [22]	2019	Placebo	277									3	1							
Rothrock [6]	2019	BTA 155 U	220			0.5				0		3	3			5				
Rothrock [6]	2019	Topiramate 100 mg	142			31				8		2	13			13				
Dodick [3]	2010	BTA 155U	687														2.9			
Dodick [3]	2010	Placebo	692														1.6			
Detke [27]	2018	Galcanezumab 120 mg	273									2								
Detke [27]	2018	Galcanezumab 240 mg	282									1								
Detke [27]	2018	Placebo	558									1								
Dodick [12]	2018	Erenumab 70 mg	283									2.1								
Dodick [12]	2018	Placebo	289									2.8								
Stauffer [32]	2018	Galcanezumab 120 mg	206									1	2.6							

Stauffer [32]	2018	Galcanezumab 240 mg	220									2.3	2.3							
Stauffer [32]	2018	Placebo	432									0.9	2.6							
Vladimir [31]	2018	Galcanezumab 120 mg	226										3.5							
Vladimir [31]	2018	Galcanezumab 240 mg	228										3.1							
Vladimir [31]	2018	Placebo	461										2.2							
Reuter [14]	2018	Erenumab 140 mg	119										3							
Reuter [14]	2018	Placebo	124										2							
Silberstein [25]	2017	Fremanezumab-Q	376										2							
Silberstein [25]	2017	Fremanezumab-M	379										3							
Silberstein [25]	2017	Placebo	375										1							
Tepper [17]	2017	Erenumab 70 mg	190									2								
Tepper [17]	2017	Erenumab 140 mg	188									3								
Tepper [17]	2017	Placebo	282									1								
Goadsby [13]	2017	Erenumab 70 mg	314									1.3								
Goadsby [13]	2017	Erenumab 140 mg	319									0.9								
Goadsby [13]	2017	Placebo	319									3.1								
Hong Sun [16]	2016	Erenumab 7 mg	108									1					4			
Hong Sun [16]	2016	Erenumab 21 mg	105									3					1			
Hong Sun [16]	2016	Erenumab 70 mg	106									3					3			
Hong Sun [16]	2016	Placebo	153									1					1			
Dodick [28]	2014	Galcanezumab 150 mg	107										5							
Dodick [28]	2014	Placebo	110										3							
Dodick [1]	2009	Topiramate 100mg	177			29.9		10.7		6.8	5.6		8.5				5.1	11.9		
Dodick [1]	2009	Amitriptyline 100mg	169			4.7		3.6		3	3.6		10.7				0	17.8		

Fremanezumab-Q, Fremanezumab quarterly; Fremanezumab-M, Fremanezumab monthly

Table 15: Details for infection and infestation of system organ class (SOC) (%)

Author	Year of Publication	Intervention	Participants	Infection	Nasopharyngitis	Sinus infection	Pharyngitis	Sinusitis	Upper respiratory tract infection	Urinary tract infection	Cystitis	Influenza	Pyrexia	COVID-19	Viral infection	Viral gastroenteritis	Flu syndrome	Gastroenteritis
Ashina [34]	2023	Atogepant 60 mg	543		4.4			2.8				3.3						2.4
Ashina [34]	2023	Oral standard care	196		5.1			3.1	12.2	4.6		2.6						
HO [26]	2022	Galcanezumab 120 mg	261		2.7				5.4				2.3					
HO [26]	2022	Placebo	259		3.5				5				1.2					
Ashina [8]	2022	Eptinezumab 100	299		2					0.33				7				
Ashina [8]	2022	Eptinezumab 300 mg	294		3					2				6				
Ashina [8]	2022	Placebo	298		1					1				5				
Takeshima [19]	2021	Erenumab 70 mg	130		26.9		3.8											
Takeshima [19]	2021	Placebo	131		28.2		0.8											
Shengyuan Yu [20]	2022	Erenumab 70 mg	298		3.6				5.4									
Shengyuan Yu [20]	2022	Placebo	297		1.8				7.2									
Sakai [23]	2021	Fremanezumab-M	188		16.6						0	2.1						
Sakai [23]	2021	Fremanezumab-Q	190		21.1						2.5	1.1						
Sakai [23]	2021	Placebo	191		18.8						1	1.6						
Ailani [33]	2021	Atogepant 10 mg	221		1.8			1.8	4.1	1.4		1.4						0.9
Ailani [33]	2021	Atogepant 30 mg	228		3.5			1.3	5.7	3.9		0.9						2.2
Ailani [33]	2021	Atogepant 60 mg	231		3.5			2.2	3.9	3.9		2.2						1.3
Aliani [33]	2021	Placebo	222		3.6			1.4	4.5	3.6		0.9						1.8
Sakai [24]	2021	Fremanezumab-M	121		14							5						

Sakai [24]	2021	Fremanezumab-Q	118		12.7							1.7						
Sakai [24]	2021	Placebo	117		13.7							0.9						
Wang [18]	2021	Erenumab 70 mg	335		0.6				2.7				3					
Wang [18]	2021	Erenumab 140 mg	224		3.6				1.8				2.2					
Wang [18]	2021	Placebo	335		2.4				2.1				4.5					
Winner [11]	2021	Eptinezumab 100 mg	238						0.8			0.8						
Winner [11]	2021	Placebo	242						0.8			0.8						
Lipton [10]	2020	Eptinezumab 100 mg	356		5.3			2	4.2	2.2								
Lipton [10]	2020	Eptinezumab 300 mg	350		9.4			2.6	5.4	3.4								
Lipton [10]	2020	Placebo	366		6			4.1	5.5	1.6								
Ashina [7]	2020	Eptinezumab 100 mg	223		7.6			2.7	9.9			1.8						
Ashina [7]	2020	Eptinezumab 300 mg	224		6.3			4.9	10.3			3.6						
Ashina [7]	2020	Placebo	222		5.4			6.3	7.2			2.3						
Sakai [30]	2020	Galcanezumab 120 mg	115									7.8						
Sakai [30]	2020	Galcanezumab 240 mg	114									0.9						
Sakai [30]	2020	Placebo	230									1.3						
Mulleners [29]	2020	Galcanezumab 120 mg	232		9			2	2	2		3						1
Mulleners [29]	2020	Placebo	230		7			2	2	1		5						2
Croop [35]	2020	Rimegepant 75 mg	370		4				2	2								
Croop [35]	2020	Placebo	371		2				3	2								
Dodick [9]	2019	Eptinezumab 100 mg	122		6.6			2.5	6.6									
Dodick [9]	2019	Eptinezumab 300 mg	121		7.4			6.6	10.7									

Dodick [9]	2019	Placebo	121		5			5	5								
Ferrari [22]	2019	Fremanezumab-Q	276		5				1	1		0.5					1
Ferrari [22]	2019	Fremanezumab-M	285		2				3	1		2					1
Ferrari [22]	2019	Placebo	277		4				1	2		0.5					3
Rothrock [6]	2019	BTA 155 U	220					6									
Rothrock [6]	2019	Topiramate 100 mg	142					7									
Detke [27]	2018	Galcanezumab 120 mg	273		6			1	3	2		2	2				
Detke [27]	2018	Galcanezumab 240 mg	282		3			3	3	1		1	0				
Detke [27]	2018	Placebo	558		5			1	2	1		1	2				
Dodick [12]	2018	Erenumab 70 mg	283		5.3			2.1	6.4			3.9					
Dodick [12]	2018	Placebo	289		5.9			2.1	4.8			3.5					
Dodick [21]	2018	Fremanezumab-M	290		3.8			1.4	5.5	2.4							
Dodick [21]	2018	Fremanezumab-Q	291		3.8			0.7	3.8	3.4							
Dodick [21]	2018	Placebo	293		3.1			2.7	5.1	1.4							
Stauffer [32]	2018	Galcanezumab 120 mg	206		7.8			4.6		3.9		2.4					
Stauffer [32]	2018	Galcanezumab 240 mg	220		2.7			3.6		5.9		1.8					
Stauffer [32]	2018	Placebo	432		6.3			3		3.5		1.2					
Vladimir [31]	2018	Galcanezumab 120 mg	226		8.4				5.8			1.3					
Vladimir [31]	2018	Galcanezumab 240 mg	228		7				5.3			4.4					

Vladimir [31]	2018	Placebo	461		8.9				3.5			3						
Reuter [14]	2018	Erenumab 140 mg	119		4				3									
Reuter [14]	2018	Placebo	124		10				0									
Silberstein [25]	2017	Fremanezumab-Q	376		5			3	5									
Silberstein [25]	2017	Fremanezumab-M	379		4			1	4									
Silberstein [25]	2017	Placebo	375		5			3	4									
Tepper [17]	2017	Erenumab 70 mg	190		3				3									
Tepper [17]	2017	Erenumab 140 mg	188		2				3									
Tepper [17]	2017	Placebo	282		6				1									
Goadsby [13]	2017	Erenumab 70 mg	314		9.9			2.2	6.7	1.6		1.3						
Goadsby [13]	2017	Erenumab 140 mg	319		11			3.4	4.7	2.2		2.5						
Goadsby [13]	2017	Placebo	319		10			2.2	5.6	2.2		1.9						
Hong Sun [16]	2016	Erenumab 7 mg	108		9				1			1						
Hong Sun [16]	2016	Erenumab 21 mg	105		5				2			4						
Hong Sun [16]	2016	Erenumab 70 mg	106		6				3			1						
Hong Sun [16]	2016	Placebo	153		8				2			3						
Dodick [28]	2014	Galcanezumab 150 mg	107		4			3	17							2		
Dodick [28]	2014	Placebo	110		7			5	9							4		

Fremanezumab-Q, Fremanezumab quarterly; Fremanezumab-M, Fremanezumab monthly

Table 16: Details for general disorders and site injection administration of system organ class (SOC) (%)

Author	Year	Intervention	Participants	Influenza-like illness	I-S pain	I-S reaction	I-S haemorrhage	Pain	Pain in extremity	I-S rash	I-S paraesthesia	I-S bruising	Infusion-S extravasation	I-S Discolouration	I-S discomfort	I-S induration	I-S warmth	I-S pruritus	I-S Oedema	I-S erythema	I-S swelling	Asthenia	Fatigue	Non-cardiac chest pain	I-S Hypersensitivity	I-S Haematoma
Ashina [34]	2023	Atogepant 60 mg	543																				2.6			
Ashina [34]	2023	Oral standard care	196																				6.1			
HO [26]	2022	GAL 120	261		7.3	3.8									2.3			5		1.9						
HO [26]	2022	PBO	259		6.2	0.4									0			0		0						
Ashina [8]	2022	EPT 100	299																				1			
Ashina [8]	2022	EPT 300	294																				2			
Ashina [8]	2022	PBO	298																				1			
Yu [20]	2022	ERE 70	298						1																	
Yu [20]	2022	PBO	297						0.4																	
Sakai [23]	2021	FRE-M	188		7.4	29.3										17.6		5.3		15.4						
Sakai [23]	2021	FRE-Q	190		12.6	26.8										12.1		1.6		12.1						
Sakai [23]	2021	PBO	191		8.9	25.1										12.6		2.6		11						
Ailani [33]	2021	ATO 10	221																				1.4			
Ailani [33]	2021	ATO 30	228																				3.1			
Ailani [33]	2021	ATO 60	231																				3.9			
Ailani [33]	2021	PBO	222																				1.8			
Sakai [24]	2021	FRE-M	121		9.1	25.6	0.8									14.9		5.8		15.7	3.3					
Sakai [24]	2021	FRE-Q	118		13.6	29.7	3.4									11.9		1.7		11.9	1.7					
Sakai [24]	2021	PBO	117		6	21.4	0.9									10.3		0		12.8	0					

Reuter [15]	2021	ERE 140	388																			9.8			
Reuter [15]	2021	TOP 100	388																			17.3			
Wang [18]	2021	ERE 70	335																1.2						
Wang [18]	2021	ERE 140	224																0.4						
Wang [18]	2021	PBO	335																2.4						
Winner [11]	2021	EPT 100	238									0.8												2.1	
Winner [11]	2021	PBO	242									0.8												0	
Lipton [10]	2020	EPT 100	356																			2.2			
Lipton [10]	2020	EPT 300	350																			1.7			
Lipton [10]	2020	PBO	366																			1.9			
Ashina [7]	2020	EPT 100	223																			3.6			
Ashina [7]	2020	EPT 300	224																			3.6			
Ashina [7]	2020	PBO	222																			<1			
Sakai [30]	2020	GAL 120	115		6.1												8.7		14.8	10.4					
Sakai [30]	2020	GAL 240	114		7												20.2		27.2	10.5					
Sakai [30]	2020	PBO	230		1.3												0		2.2	1.3					
Mulleners [29]	2020	GAL 120	232		6	3					1	2				2		0	0	3	0					
Mulleners [29]	2020	PBO	230		2	0						0						1	1	3			2			0
Ferrari [22]	2019	FRE-Q	276		4				0.5	1	1	0.5				4	0.5	1		7		0.5	3			
Ferrari [22]	2019	FRE-M	285		3				1	1	1	2				5	1	2		6		1	3			
Ferrari [22]	2019	PBO	277		3				1	0.5	1	0.5				4	0	1		5		1	1			

Rothrock [6]	2019	BTA 155 U	220																			0.5			
Rothrock [6]	2019	TOP 100	142																			13			
Detke [27]	2018	GAL 120	273		6	3											0		1			2			
Detke [27]	2018	GAL 240	282		7	5											2		5			2			
Detke [27]	2018	PBO	558		4	2											0		1			2			
Dodick [12]	2018	ERE 70	283		6																	3.5			
Dodick [12]	2018	PBO	289		4.2																	2.1			
Dodick [21]	2018	FRE-M	290		30		1									24			17.9			0.7			
Dodick [21]	2018	FRE-Q	291		29.6		3.1									19			18.9			2.1			
Dodick [21]	2018	PBO	293		25.9		2									15			14			1.4			
Stauffer [32]	2018	GAL 120	206		16	3.4						1						4.4		4.9						
Stauffer [32]	2018	GAL 240	220		20.5	5.5						1.8						4.6		4.1						
Stauffer [32]	2018	PBO	432		17.4	0.9						1.4						0.2		2.6						
Vladimir [31]	2018	GAL 120	226		9.3	3.1												2.7		2.7	2.2		2.7			
Vladimir [31]	2018	GAL 240	228		8.8	7.9												3.1		3.1	0.4		2.2			
Vladimir [31]	2018	PBO	461		8.5	0												0		0.9	0		2.6			
Reuter [14]	2018	ERE 140	119		6															3			3			
Reuter [14]	2018	PBO	124		6															3			2			
Silberstein [25]	2017	FRE-Q	376		30		2									20			21						

Silberstein [25]	2017	FRE-M	379		26		2								24				20					
Silberstein [25]	2017	PBO	375		28		3								18				16					
Tepper [17]	2017	ERE 70	190		4																			
Tepper [17]	2017	ERE 140	188		4																			
Tepper [17]	2017	PBO	282		1																			
Goadsby [13]	2017	ERE 70	314		3.2																	1.9		
Goadsby [13]	2017	ERE 140	319		0.3																	2.2		
Goadsby [13]	2017	PBO	319		0.3																	2.5		
Hong Sun [16]	2016	ERE 7	108																			5		
Hong Sun [16]	2016	ERE 21	105																			2		
Hong Sun [16]	2016	ERE 70	106																			4		
Hong Sun [16]	2016	PBO	153																			2		
Dodick [28]	2014	GAL 150	107		17				4										5					
Dodick [28]	2014	PBO	110		6				5										0					

I-S; Injection Site, GAL 120, Galcanezumab 120 mg; GAL 240, Galcanezumab 240 mg; GAL 150, Galcanezumab 150 mg; PBO, Placebo; EPT 100, Eptinezumab 100 mg; EPT 300, Eptinezumab 300 mg; FRE-M, Fremanezumab monthly; FRE-Q, Fremanezumab quarterly; ATO 10, Atogepant 10 mg; ATO 30, Atogepant 30 mg; ATO 60, Atogepant 60 mg; ERE 140, Erenumab 140 mg; ERE 70, Erenumab 70 mg; ERE 7, Erenumab 7 mg; ERE 21, Erenumab 21 mg; TOP 100, Topiramate 100 mg;; AMI 100, Amitriptyline 100 mg; BTA 150, BTA 150 U; BTA 260, BTA 105 to 260 U.

Table 17: Any adverse events reported from 32 trials

Intervention	Dose	Frequency	Total participants	Participants with AEs (%)*
Erenumab [13-15, 17, 18]	140 mg	Monthly	1238	408 (33)
Rimegepant [35]	75 mg,	Once daily	370	133 (36)
Topiramate [1, 6, 15]	100 mg	Twice daily	707	264 (37)
Eptinezumab [7-11]	100 mg	Single dose on day 0	1238	517 (42)
Erenumab [12, 13, 16-20]	70 mg	Monthly	1637	786 (48)
Erenumab [16]	7 mg	Monthly	108	54 (50)
Erenumab [16]	21 mg	Monthly	105	54 (51)
Eptinezumab [7-11]	300 mg	Single dose on day 0	989	509 (51)
Placebo [3, 7-14, 16-33, 35]	-	Matched with active treatments	7977	4040 (52)
Atogepant [33]	30 mg	Once daily	228	119 (52)
Atogepant [33]	10 mg	Once daily	221	117 (53)
*OnabotulinumtoxinA (*BTA) [3, 6]	150 U	Every 12 weeks	907	534 (59)
Galcanezumab [27] [26, 27, 29-32]	120 mg	Monthly	1313	786 (60)
Fremanezumab [21-25]	Monthly (225 mg)	Monthly	1263	774 (61)
Atogepant [33, 34]	60 mg	Once daily	774	488 (63)
Fremanezumab [21-25]	Quarterly (675 mg)	Single dose on day 0	1251	798 (64)
Galcanezumab [27, 29-32]	240 mg	Monthly	844	566 (67)
Galcanezumab [28]	150 mg	Every 2 weeks	107	77 (72)
Amitriptyline [1]	25 to 100 mg	Twice daily	169	150 (89)

*The treatments are listed in order of increasing AEs percentage.; Abbreviations; mg: milligram.

Table 18: Classification of AEs by SOC

System Organ Class (SOC)	Adverse Events (AEs)
Cardiac disorders	Acute myocardial infarction, atrial fibrillation, syncope
Ear and labyrinth disorders	Labyrinthitis, **sudden hearing loss,** vertigo, **vestibular neuronitis**
Eye disorders	Angle closure glaucoma, diplopia, **optic neuritis,** retinal detachment, rhegmatogenous retinal detachment
Gastrointestinal disorders	Abdominal pain, alcoholic pancreatitis, appendicitis, **diverticulitis,** esophagitis, **gastric ulcer haemorrhage,** gastritis, haemorrhoids, **intestinal haemorrhage,** irritable bowel syndrome, mechanical ileus, obstructive defaecation, pancreatitis, pancreatitis acute, parotitis, small intestinal obstruction, vomiting
General disorders and administration site conditions	**Abdominal adhesions,** asthenia, chest pain, **edema peripheral,** malaise, **nasal septum deviation,** non-cardiac chest pain, tooth impacted, **vocal cord thickening**
Hepatobiliary disorders	Cholecystitis, cholecystitis acute, cholelithiasis, **common bile duct stone,**
Immune system disorders	Anaphylactic reaction, anaphylactic shock, hypersensitivity
Infections and infestations	**Acute pyelonephritis**, bacterial pharyngitis, bacteriuria, **clostridium difficile colitis,** COVID-19 pneumonia, gastroenteritis, gastrointestinal infection, **infected dermal cyst**, influenza, kidney infection, nasopharyngitis, papilloma viral infection, parasitic gastroenteritis, pyelonephritis, pyrexia, sepsis, **tonsillitis,** urinary tract infection, viral gastroenteritis, viral infection
Injury	Accident, ankle fracture, brain contusion, **cartilage injury,** clavicle fracture, concussion, contusion, fall, foot fracture, hand fracture, humerus fracture, injury, ligament rupture, limb injury, lower limb fracture, **meniscus injury**, radius fracture, respiratory fume inhalation, rib fracture, road traffic accident, skin laceration, sternal fracture, tendon injury, **thoracic vertebral fracture**, traumatic orbital fracture, ulna fracture, wrist fracture
Investigations	Alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, weight decreased
Metabolism and nutrition disorders	Decreased appetite, hypokalaemia, hyponatremia
Musculoskeletal and connective tissue disorders	Arthralgia, back pain, Behçet's syndrome, **costochondritis,** flank pain, intervertebral disc protrusion, **osteoarthritis,** periarthritis**, post-traumatic neck syndrome**
Neoplasms benign malignant and unspecified (incl cysts and polyps)	Adenocarcinoma of the cervix, brain neoplasm, breast cancer, colon cancer, **fibroma, gallbladder polyp, ovarian cyst, polycystic ovaries**, rectal polyp**, ruptured ovarian cyst**, **uterine leiomyoma**, **breast neoplasm**, fibroadenoma of breast, malignant melanoma, neoplasm malignant, vulval cancer
Nervous system disorders	Cerebellar syndrome, **cerebral venous thrombosis**, cervical radiculopathy, **hypoaesthesia**, lumbar spinal stenosis, migraine, **migraine aggravated**, migraine with aura, nervous system disorders, **neuropathy**, seizure, speech disorder, transient ischemic attack
Neurological	**Spinal pain**

Poisoning and procedural complications	Overdose, **intentional overdose**
Pregnancy, puerperium and perinatal conditions	Pregnancy
Psychiatric disorders	Confusional state, depression, disorientation, major depression, **psychogenic seizure**, suicidal ideation, suicide attempt
Psychiatry	**Panic attack**
Renal and urinary disorders	Bladder dysfunction, **calculus urinary, nephrolithiasis, renal calculus**, renal colic, urinary incontinence
Reproductive system and breast disorders	Cervical dysplasia, dysmenorrhoea, **endometriosis**, menorrhagia, **menstrual disorder and vaginal haemorrhage**, metrorrhagia, ovarian disorder, **spontaneous abortion, threatened abortion**
Respiratory, thoracic and mediastinal	Asthma, **chronic obstructive pulmonary disease, chronic obstructive pulmonary disease (COPD) and apnoea related to COPD**, dyspnoea, epistaxis, pneumonia, **postsurgical laryngospasm with hypoxic brain injury**
Skin and subcutaneous tissue disorders	**Erythema nodosum**
Vascular disorders	**Hypertensive crisis**, orthostatic hypotension, **peripheral vascular disease**, **pulmonary embolism**

AEs in bold font were not found in the CTCAE Version 5.0, thus the best respective categories were chosen by clinical consensus.

Appendix 5: Further results for serious adverse events (SAEs)

Table 19: Arm level data on any serious adverse events and treatment-related serious adverse events (%)

Author, year	Interventions	Participants	Any SAEs	Treatment-related SAEs	Death
Ailani, 2021 [33]	Atogepant 10 mg	221	0.9	0.5	0
Ailani, 2021 [33]	Atogepant 30 mg	228	0	0	0
Ailani, 2021 [33]	Atogepant 60 mg	231	0	0	0
Ailani, 2021 [33]	Placebo	222	0.9	0	0
Ashina, 2020 [7]	Eptinezumab 100 mg	223	1.79	0	0
Ashina, 2020 [7]	Eptinezumab 300 mg	224	1.34	0	0
Ashina, 2020 [7]	Placebo	222	2.8	0	0
Dodick, 2014 [28]	Galcanezumab 150 mg	107	0	-	0
Dodick, 2014 [28]	Placebo	110	0.91		0
Dodick, 2018 [12]	Erenumab 70 mg	283	1.1	-	0
Dodick, 2018 [12]	Placebo	289	1.7	-	0
Dodick, 2009 [1]	Amitriptyline 100 mg	169	4.7	0.5	0
Dodick, 2009 [1]	Topiramate 100 mg	177	2.3	0	0
Detke, 2018 [27]	Galcanezumab 120 mg	273	0.18	-	0
Detke, 2018 [27]	Galcanezumab 240 mg	282	1.8	-	0
Detke, 2018 [27]	Placebo	558	0.7	-	0
Dodick, 2010 [3]	BTA 150 U	687	4.8	0.1	0
Dodick, 2010 [3]	Placebo	692	2.3	0	0
Dodick, 2018 [21]	Fremanezumab-M	289	1	0	0
Dodick, 2018 [21]	Fremanezumab-Q	291	1	0	0.3
Dodick, 2018 [21]	Placebo	293	2.4	0	0
Dodick, 2019 [9]	Eptinezumab 100 mg	122	3.3	0	0
Dodick, 2019 [9]	Eptinezumab 300 mg	121	5.8	0	0
Dodick, 2019 [9]	Placebo	121	0.8	0	0
Goadsby, 2017 [13]	Erenumab 140 mg	319	2.51	-	0
Goadsby, 2017 [13]	Erenumab 70 mg	314	2.5	-	0
Goadsby, 2017 [13]	Placebo	319	2.2	-	0
Hong Sun, 2016 [16]	Erenumab 21mg	105	1	0	0
Hong Sun, 2016 [16]	Erenumab 7 mg	108	0	0	0
Hong Sun, 2016 [16]	Erenumab 70 mg	106	0	0	0
Hong Sun, 2016 [16]	Placebo	153	1	0	
Lipton, 2020 [10]	Eptinezumab 100 mg	356	0.84	-	0
Lipton, 2020 [10]	Eptinezumab 300 mg	350	1.1	-	0
Lipton, 2020 [10]	Placebo	366	0.81	-	0
Rothrock, 2019 [6]	BTA 150 U	220	2	0	0
Rothrock, 2019 [6]	Topiramate 100 mg	142	4	1	0
Sakai, 2020 [30]	Galcanezumab 120 mg	115	2.6	-	0
Sakai, 2020 [30]	Galcanezumab 240 mg	114	0.9	-	0

Sakai, 2020 [30]	Placebo	230	0	0	0
Sakai, 2021 [24]	Fremanezumab-M	121	0	0	0
Sakai, 2021 [24]	Fremanezumab-Q	118	0	0	0
Sakai, 2021 [24]	Placebo	117	0	0	0
Sakai, 2021 [23]	Fremanezumab-M	188	1.6	0	0
Sakai, 2021 [23]	Fremanezumab-Q	190	0.5	0	0
Sakai, 2021 [23]	Placebo	191	0.5	0	0
Silberstein, 2017 [25]	Fremanezumab-M	379	1.32	0	0
Silberstein, 2017 [25]	Fremanezumab-Q	376	0.8		0.26
Silberstein, 2017 [25]	Placebo	375	1.6	-	0
Stauffer, 2018 [32]	Galcanezumab 120 mg	206	2.91	0	0
Stauffer, 2018 [32]	Galcanezumab 240 mg	220	0	0	0
Stauffer, 2018 [32]	Placebo	432	1.16	0	0
Tepper, 2017 [17]	Erenumab 140 mg	188	1	-	0
Tepper, 2017 [17]	Erenumab 70 mg	190	3	-	0
Tepper, 2017 [17]	Placebo	282	2	-	-
Reuter, 2018 [14]	Erenumab 140 mg	119	1.68	0	0
Reuter, 2018 [14]	Placebo	124	0.8	0	0
Reuter, 2021 [15]	Erenumab 140 mg	388	2.58	0.3	0
Reuter, 2021 [15]	Topiramate 100 mg	388	4.9	0.5	0
Vladimir, 2018 [31]	Galcanezumab 120 mg	226	2.2	-	0
Vladimir, 2018 [31]	Galcanezumab 240 mg	228	3.1	-	0
Vladimir, 2018 [31]	Placebo	461	1.1	-	0
Wang, 2021 [18]	Erenumab 140 mg	224	0	0	0
Wang, 2021 [18]	Erenumab 70 mg	335	2.99	0.3	0
Wang, 2021 [18]	Placebo	335	1.94	0	0
Elkind, 2006 (study 1) [2]	BTA 25 U	101	-	0	0
Elkind, 2006 (study 2) [2]	BTA 25 U	173	-	0	0
Elkind, 2006 (study 3) [2]	BTA 25 U	50	-	0	0
Elkind, 2006 (study 1) [2]	BTA 50 U	106	-	0	0
Elkind, 2006 (study 2) [2]	BTA 50 U	180	-	0	0
Elkind, 2006 (study 3) [2]	BTA 50 U	51	-	0	0
Elkind, 2006 (study 1) [2]	BTA 7 U	105	-	0	0
Elkind, 2006 (study 1) [2]	Placebo	106	-	0	0
Elkind, 2006 (study 3) [2]	Placebo	100	-	0	0
Ferrari, 2019 [22]	Fremanezumab-M	285	3.86	0	0
Ferrari, 2019 [22]	Fremanezumab-Q	276	3.62	0	0
Ferrari, 2019 [22]	Placebo	277	1	0	0
Mulleners, 2020 [29]	Galcanezumab 120 mg	232	1	-	0

Mulleners, 2020 [29]	Placebo	230	1	-	0
Ashina, 2022 [8]	Eptinezumab 100 mg	299	1.67	0	0
Ashina, 2022 [8]	Eptinezumab 300 mg	294	2.38	0.68	
Ashina, 2022 [8]	Placebo	298	1.34	0	0
HO, 2022 [26]	Galcanezumab 120 mg	261	0.76	-	0
HO, 2022 [26]	Placebo	259	1.54	-	0
Winner, 2021 [11]	Eptinezumab 100 mg	238	0	0	0
Winner, 2021 [11]	Placebo	242	0	0	0
Croop, 2020 [35]	Placebo	371	1	0.26	0
Croop, 2020 [35]	Rimegepant 75 mg	370	0.81	0	0
Takeshima, 2021 [19]	Erenumab 70 mg	131	1.5	0	0
Takeshima, 2021 [19]	Placebo	130	1.5	0	0
Shengyuan Yu, 2022 [20]	Erenumab 70 mg	279	2.5	0.4	0
Shengyuan Yu, 2022 [20]	Placebo	278	2.5	0	0
Ashina, 2023 [34]	Atogepant 60 mg	543	4.4		0.4
Ashina, 2023 [34]	Oral standard care	197	3.6		0

Table 20: Details for neoplasms benign malignant and unspecified of system organ class (SOC) (%)

Author, year	Interventions	Participants	Breast cancer	Fibroadenoma of breast	breast neoplasm	polycystic ovaries	Thyroid adenoma	vulval cancer	Benign colonic neoplasm	Anal polyp	Uterine leiomyoma	Gallbladder polyp	Lentigo maligna	Neoplasm malignant	Malignant melanoma in situ	Malignant melanoma	Pelvic pain	Squamous cell carcinoma	Papillary thyroid cancer	ruptured ovarian cyst	Adenocarcinoma of the cervix	Ovarian cyst	Colon cancer	Rectal polyp	Brain neoplasm	Fibroma
Ashina, 2023 [34]	Oral Standard care	196	0.5																				0.5			
Hong Sun, 2016 [16]	Erenumab 70 mg	106																		0						
Hong Sun, 2016 [16]	Erenumab 7 mg	108																		0.1						
Hong Sun, 2016 [16]	Erenumab 21mg	105																		0						
Dodick, 2009 [1]	Amitriptyline 100 mg	169			0.6																				0.6	
Dodick, 2010 [3]	BTA 150 U	687	0.44						0.15		0.3				0.15	0.15		0.15							0.15	
Rothrock, 2019 [6]	BTA 150 U	220	0.45																							
Dodick, 2019 [9]	Eptinezumab 100 mg	122									0.82															
Ashina, 2020 [7]	Eptinezumab 300 mg	224	0.45		0.45																					
Dodick, 2019 [9]	Eptinezumab 300 mg	121									0.83						0.83									
Tepper, 2017 [17]	Erenumab 70 mg	190																								0.53
Goadsby, 2017 [13]	Erenumab 70 mg	314																				0.31				
Ferrari, 2019	Fremanezumab-Q	276						0		0.36	0															
Detke, 2018 [27]	Galcanezumab 120 mg	273																					0.36			

Vladimir, 2018 [31]	Galcanezumab 120 mg	226										0									0.44			0.44		
Croop, 2020 [35]	Rimegepant 75 mg	370														0.27										
Reuter, 2021 [15]	Topiramate 100 mg	388		0.26																						
Rothrock, 2019 [6]	Topiramate 100 mg	142	0.7																							
Sakai, 2021 [23]	Placebo	191	0.5																							
Silberstein, 2017 [25]	Placebo	375									0.26															
Dodick, 2010 [3]	Placebo	692																	0.28							
Ferrari, 2019	Placebo	277	0.36				0.36	0.36			0.36															
Ashina, 2020 [7]	Placebo	222	0.45																							
Dodick, 2018 [12]	Placebo	289									0.3															
Dodick, 2018 [21]	Placebo	293											0.34													
Vladimir, 2018 [31]	Placebo	461										0.2									0			0		

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 21: Details for nervous system disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Migraine with aura	Dizziness	Migraine aggravated	Neuropathy	Hypoesthesia	Intracranial aneurysm	Multiple sclerosis	Optic neuritis	Transient ischemic attack	Tonic-clonic seizure	Nervous system disorders	Cerebellar syndrome	Spinal pain	Speech disorder	Serotonin syndrome	Migraine	Headache	Convulsion	Seizure	Cervical radiculopathy

Hong Sun, 2016 [16]	Erenumab 70 mg	106																0.1				
Dodick, 2009 [1]	Amitriptyline 100 mg	169			0.6																	
Dodick, 2010 [3]	BTA 150 U	687																0.59		0.15		
Dodick, 2019 [9]	Eptinezumab 100 mg	122																	0.82			
Ashina, 2022 [8]	Eptinezumab 100 mg	299																0			0	0.33
Ashina, 2022 [8]	Eptinezumab 300 mg	294																0			0.34	0
Dodick, 2019 [9]	Eptinezumab 300 mg	121															0.83			0.83		
Goadsby, 2017 [13]	Erenumab 140 mg	319													0.26			0				
Reuter, 2018 [14]	Erenumab 140 mg	119																0.84				
Dodick, 2018 [12]	Erenumab 70 mg	283																0.4				
Goadsby, 2017 [13]	Erenumab 70 mg	314													0			0.31				
Dodick, 2018 [21]	Fremanezumab-M	289										0.35										
Ferrari, 2019 [22]	Fremanezumab-M	285					0		0.35	0.35												
Ferrari, 2019 [22]	Fremanezumab-Q	276					0	0.35														
Vladimir, 2018 [31]	Galcanezumab 240 mg	228									0.44							0				
Reuter, 2021 [15]	Topiramate 100 mg	388	0															0.26				
Silberstein, 2017 [25]	Placebo	375																0.26				
Dodick, 2010 [3]	Placebo	692																0.28				
Tepper, 2017 [17]	Placebo	282																0.35				

Ferrari, 2019	placebo	277					0.36											0.36				
Ashina, 2020 [7]	Placebo	222																0.45				
Dodick, 2018 [12]	Placebo	289																0.3				
Dodick, 2018 [21]	Placebo	293		0.34														0.34				
Vladimir, 2018 [31]	Placebo	461									0							0.2				
Wang, 2021 [18]	Placebo	335																0.3				
Ashina, 2022 [8]	Placebo	298																0.34			0	0

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 22: Details for injury, poisoning and procedural complications of system organ class (SOC) (%) – part 1

Author, year	Interventions	Participants	respiratory fume inhalation	Seroma	Incarcerated incisional hernia	Foot Fracture	Clavicle fracture	Accident	Cartilage injury	Wrist fracture	Ulna fracture	thoracic vertebral fracture	lower limb fracture	Injury	Hand fracture	Humours fracture	Ankle fracture	Traumatic orbital fracture	Meniscus injury	Radius fracture	Fall	Tendon injury	Ankle fracture
Rothrock, 2019 [6]	BTA 150 U	220						0.45															
Ashina, 2022 [8]	Eptinezumab 100 mg	299														0.33							
Tepper, 2017 [17]	Erenumab 140 mg	188							0.53														
Goadsby, 2017 [13]	Erenumab 140 mg	319																					0.26
Reuter, 2018 [14]	Erenumab 140 mg	119																0.84					
Reuter, 2021 [15]	Erenumab 140 mg	388																			0.26	0.26	
Silberstein, 2017 [25]	Fremanezumab-M	379									0.26									0.26	0.26		
Ferrari, 2019 [22]	Fremanezumab-M	285	0.35																				
Silberstein, 2017 [25]	Fremanezumab-Q	376								0.26													
Ferrari, 2019 [22]	Fremanezumab-Q	276				0.36	0.36																
Dodick, 2018 [21]	Fremanezumab-Q	291																				0.34	
Sakai, 2020 [30]	Galcanezumab 120 mg	115																	0.9				
Stauffer, 2018 [32]	Galcanezumab 120 mg	206		0.49	0.49																		

Vladimir, 2018 [31]	Galcanezumab 240 mg	228																	0.44				
Dodick, 2009 [1]	Topiramate 100 mg	177												0.5									
Reuter, 2021 [15]	Topiramate 100 mg	388															0.26						
Rothrock, 2019 [6]	Topiramate 100 mg	142						0.7															
Silberstein, 2017 [25]	Placebo	375					0.26	0.26															
Ferrari, 2019 [22]	Placebo	277										0.36						0.35					
Dodick, 2018 [21]	Placebo	293								0.34											0.34		
Goadsby, 2017 [13]	Placebo	319																			0.26		
Vladimir, 2018 [31]	Placebo	461				0.2																	
Mulleners, 2020 [29]	Placebo	230											0.43										
Ashina, 2022 [8]	Placebo	298													0.34	0							

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 23: Details for injury, poisoning and procedural complications of system organ class (SOC) (%) - part 2

Author, year	Interventions	Participants	Ligament rupture	Sternal fracture	Skin laceration	Limb injury	Stomal Hernia	Procedural Pain	Postprocedural Constipation	Postprocedural Complication	Abdominal Wound Dehiscence	Road traffic accident	Head injury	Concussion	Brain contusion	Contusion	Rib Fracture	Radius fracture	Overdose	Intentional overdose
Rothrock, 2019 [6]	BTA 150 U	220												0.45						

Ashina, 2020 [7]	Eptinezumab 100 mg	223						0.45	0.45											
Ashina, 2020 [7]	Eptinezumab 300 mg	224								0.45	0.45									
Dodick, 2019 [9]	Eptinezumab 300 mg	121											0.83	0.83						
Reuter, 2021 [15]	Erenumab 140 mg	388	0.26	0.26	0.26	0.26								0		0.26				
Tepper, 2017 [17]	Erenumab 70 mg	190																0.53		
Sakai, 2021 [23]	Fremanezumab-M	188													0.53					
Ferrari, 2019	Fremanezumab-M	285															0.36			
Silberstein, 2017 [25]	Fremanezumab-Q	376										0.26								
Ferrari, 2019	Fremanezumab-Q	276										0.36					0.35			
Reuter, 2021 [15]	Topiramate 100 mg	388												0.26						
Rothrock, 2019 [6]	Topiramate 100 mg	142												0.7						
Dodick, 2014 [28]	Placebo	110						0.91												
Dodick, 2018 [21]	Placebo	293										0.34								
Goadsby, 2017 [13]	Placebo	319																		0.26
Vladimir, 2018 [31]	Placebo	461										0.2					0.2	0.2		
Croop, 2020 [35]	Placebo	371																	0.27	
Ashina, 2022 [8]	Placebo	298										0.34		0.34						

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 24: Details for respiratory, thoracic and mediastinal disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Pneumonia	Postsurgical laryngospasm with hypoxic brain injury	Chronic obstructive pulmonary disease (COPD) and apnea related to COPD	Chronic obstructive pulmonary disease	Asthma	Respiratory distress	Dyspnoea	Vocal cord thickening	Pulmonary embolism	Pulmonary sarcoidosis	Sleep apnoea syndrome	Hypoxia	Epistaxis
Ailani, 2021 [33]	Atogepant 10 mg	221					0.45								
Dodick, 2010 [3]	BTA 150 U	687	0.44										0.15	0.15	
Rothrock, 2019 [6]	BTA 150 U	220	0.45		0.45										
Dodick, 2019 [9]	Eptinezumab 300 mg	121						0.83							
Sakai, 2021 [23]	Fremanezumab-M	188					0.53								
Ferrari, 2019 [22]	Fremanezumab-M	285								0.35					
Silberstein, 2017 [25]	Fremanezumab-Q	376	0.26			0.26	0		0						
Rothrock, 2019 [6]	Topiramate 100 mg	142	0.7		0.7										
Silberstein, 2017 [25]	Placebo	375	0			0	0.26		0.26						
Dodick, 2010 [3]	Placebo	692	0.28									0.28			
Detke, 2018 [27]	Placebo	558													0.18
Ailani, 2021 [33]	Placebo	222		0.45			0								
Ashina, 2020 [7]	Placebo	222				0.45							0.45		
Stauffer, 2018 [32]	Placebo	432									0.23				
Croop, 2020 [35]	Placebo	371	0.27												

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 25: Details for gastrointestinal disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Mechanical ileus	intestinal haemorrhage	Haemorrhoids	Irritable bowel syndrome	esophagitis	Pancreatitis acute	Pancreatitis acute	Colitis ischaemic	Colitis	Pancreatitis	Gastroesophageal reflux	Inguinal hernia	Parotitis	gastric ulcer haemorrhage	Vomiting	diverticulitis	Abdominal pain	gastritis	Small intestinal obstruction	Obstructive defaecation	alcoholic pancreatitis
Dodick, 2009 [1]	Amitriptyline 100 mg	169					0.6																
Dodick, 2010 [3]	BTA 150 U	687							0.15	0.15	0.15												
Tepper, 2017 [17]	Erenumab 140 mg	188																	0.53				
Reuter, 2021 [15]	Erenumab 140 mg	388	0.26																			0.26	
Sakai, 2021 [23]	Fremanezumab-M	188		0.53																			
Ferrari, 2019 [22]	Fremanezumab-Q	276											0.36	0.36									
Dodick, 2018 [21]	Fremanezumab-Q	291		0.34																			
Mulleners, 2020 [29]	Galcanezumab 120 mg	232			0.43																		
Stauffer, 2018 [32]	Galcanezumab 120 mg	206						0.5													0.5		
Vladimir, 2018 [31]	Galcanezumab 120 mg	226																		0.44			
Detke, 2018 [27]	Galcanezumab 240 mg	282										0.35											
Reuter, 2021 [15]	Topiramate 100 mg	388				0.26														0.26			
Detke, 2018 [27]	Placebo	558																		0.18			0.18
Tepper, 2017 [17]	Placebo	282										0.35			0.35		0.35		0				

Ailani, 2021 [33]	Placebo	222														0.45							
HO, 2022 [26]	Placebo	259			0.38																		

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 26: Details for renal and urinary disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Nephrolithiasis	Urinary incontinence	Kidney injury	Calculus urinary	Renal calculus	Renal colic	Bladder dysfunction
Dodick, 2009 [1]	Amitriptyline 100 mg	169					0.6		
Dodick, 2010 [3]	BTA 150 U	687				0.15			
Silberstein, 2017 [25]	Fremanezumab-M	379				0.26			
Ferrari, 2019 [22]	Fremanezumab-M	285	0.7						
Ferrari, 2019 [22]	Fremanezumab-Q	276						0.35	
Vladimir, 2018 [31]	Galcanezumab 120 mg	226							0.44
Vladimir, 2018 [31]	Galcanezumab 240 mg	228							
Detke, 2018 [27]	Galcanezumab 240 mg	282	0.35					0.35	
Rothrock, 2019 [6]	Topiramate 100 mg	142	0.7						
Silberstein, 2017 [25]	Placebo	375	0.26						

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 27: Details for infections and infestations of system organ class (SOC) (%) - part 1

Author, year	Interventions	Participants	Gastrointestinal infection	Viral infection	Nasopharyngitis	Tonsillitis	Upper respiratory tract infection bacterial	Sepsis	Pyelonephritis	Kidney infection	Vaginal abscess	Viral gastroenteritis	Gastroenteritis	Pharyngitis streptococcal	Infected dermal cyst	Sinusitis
Dodick, 2009 [1]	Amitriptyline 100 mg	169											0.6			
Dodick, 2010 [3]	BTA 150 U	687								0.5						
Dodick, 2019 [9]	Eptinezumab 300 mg	121									0.83	0.83				
Goadsby, 2017 [13]	Erenumab 140 mg	319						0.26	0.26	0.26		0.26				
Wang, 2021 [18]	Erenumab 70 mg	335											0.3			
Mulleners, 2020 [29]	Galcanezumab 120 mg	232				0.43										
HO, 2022 [26]	Galcanezumab 120 mg	261											0.38		0.38	
Croop, 2020 [35]	Rimegepant 75 mg	370											0.27			
Reuter, 2021 [15]	Topiramate 100 mg	388	0.26		0.26				0.26				0.26			
Dodick, 2010 [3]	Placebo	692					0.28	0.28					0.28	0.28		
Ferrari, 2019 [22]	placebo	277														0.35
Reuter, 2018 [14]	Placebo	124	0.8													
Wang, 2021 [18]	Placebo	335		0.3									0.3			

Croop, 2020 [35]	Placebo	371							0.27						

Table 28: Details for infections and infestations of system organ class (SOC) (%) - part 2

Author, year	Interventions	Participants	Peri tonsillitis	Diverticulitis	Dengue fever	Cellulitis	Labyrinthitis	Clostridium difficile colitis	Influenza	Papilloma viral infection	Appendicitis	Parasitic gastroenteritis	Bacteriuria	Pyrexia	Acute pyelonephritis	COVID-19 pneumonia	Urinary tract infection	Bacterial pharyngitis
Ashina, 2022 [8]	Eptinezumab 100 mg	299														0.33		
Ashina, 2022 [8]	Eptinezumab 300 mg	294														0.68		
Goadsby, 2017 [13]	Erenumab 140 mg	319						0.26										
Reuter, 2021 [15]	Erenumab 140 mg	388								0.26								
Tepper,2017 [17]	Erenumab 70 mg	190									0.53							
Dodick, 2018 [12]	Erenumab 70 mg	283															0.4	
Goadsby, 2017 [13]	Erenumab 70 mg	314													0.31			
Wang, 2021 [18]	Erenumab 70 mg	335					0.3											
Dodick, 2018 [21]	Fremanezumab-M	289									0.35							
Sakai, 2021 [23]	Fremanezumab-Q	190							0.5									
Ferrari, 2019 [22]	Fremanezumab-Q	276		0.35														
Vladimir, 2018 [31]	Galcanezumab 120 mg	226																0.44
Vladimir, 2018 [31]	Galcanezumab 240 mg	228							0.44					0.44				

Reuter, 2021 [15]	Topiramate 100 mg	388							0.26		0.26	0.26	0.26					
Tepper, 2017 [17]	Placebo	282															0.35	
Ferrari, 2019 [22]	Placebo	277	0.35		0.35													
Ashina, 2020 [7]	Placebo	222				0.45												
Wang, 2021 [18]	Placebo	335				0.3												
Croop, 2020 [35]	Placebo	371									0.27							

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 29: Details for cardiac disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Atrial fibrillation	Acute coronary syndrome	Tachycardia	Atrial fibrillation	Palpitations	Pericarditis	Syncope	Acute myocardial infarction
Dodick, 2010 [3]	BTA 150 U	687		0.15	0.15			0.15		0.15
Rothrock, 2019 [6]	BTA 150 U	220			0.45				0.45	
Ferrari, 2019 [22]	Fremanezumab-M	285				0.35				
Ferrari, 2019 [22]	Fremanezumab-Q	276	0.36							
Vladimir, 2018 [31]	Galcanezumab 240 mg	228								0.44
Reuter, 2021 [15]	Topiramate 100 mg	388							0.26	
Detke, 2018 [27]	Placebo	558								0.18
Ferrari, 2019 [22]	Placebo	277					0.36			
Ashina, 2020 [7]	Placebo	222							0.45	

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 30: Details for congenital, familial and genetic disorders and reproductive system and breast disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Congenital diaphragmatic hernia	Metrorrhagia	Menometrorrhagia	Ovarian disorder	Abortion threatened	Spontaneous abortion	Uterine Prolapse	Endometriosis	Menstrual disorder and vaginal hemorrhage	Dysmenorrhoea	Menorrhagia	Cervical dysplasia
Dodick, 2009 [1]	Amitriptyline 100 mg	169											0.6	
Dodick, 2010 [3]	BTA 150 U	687						0.15						
Lipton, 2020 [10]	Eptinezumab 300 mg	350					0.38							
Reuter, 2021 [15]	Erenumab 140 mg	388										0.26		0.26
Dodick, 2018 [21]	Fremanezumab-M	289											0.35	
Ferrari, 2019 [22]	Fremanezumab-M	285			0.35					0.35				
Ferrari, 2019 [22]	Fremanezumab-Q	276										0.35	0.35	
Dodick, 2009 [1]	Topiramate 100 mg	177				0.5					0.5		0.5	
Reuter, 2021 [15]	Topiramate 100 mg	388								0.26				
Dodick, 2010 [3]	Placebo	692								0.28				
Lipton, 2020 [10]	Placebo	366			0.27									
Ferrari, 2019 [22]	Placebo	277	0.36	0.36										
Ashina, 2020 [7]	Placebo	222							0.45					

Dodick, 2018 [21]	Placebo	293						0.34						
Goadsby, 2017 [13]	Placebo	319								0.26				
Wang, 2021 [18]	Placebo	335						0.5						

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 31: Details for hepatobiliary disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Cholelithiasis	Hepatic Cholestatic	Cerebral venous thrombosis	Common bile duct stone	Cholecystitis acute
Dodick, 2009 [1]	Amitriptyline 100 mg	169	0.6				
Dodick, 2019 [9]	Eptinezumab 100 mg	122	0.5				
Ashina, 2020 [7]	Eptinezumab 100 mg	223	0.45				
Ashina, 2022 [8]	Eptinezumab 100 mg	299	0.33				
Goadsby, 2017 [13]	Erenumab 140 mg	319	0.63		0.26		
Ferrari, 2019 [22]	Fremanezumab-Q	276	0.36				0.36
Vladimir, 2018 [31]	Galcanezumab 240 mg	228	0.44				
Reuter, 2021 [15]	Topiramate 100 mg	388	0.26				
Dodick, 2010 [3]	Placebo	692	0.28				
Tepper, 2017 [17]	Placebo	282	0.35				
Dodick, 2018 [12]	Placebo	289					0.3
Stauffer, 2018 [32]	Placebo	432	0.5				

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 32: Details for psychiatric disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Major depression	Depression	Stress	Conversion disorder	Suicidal ideation	Suicidal attempt	Confessional state	Disorientation	Substance-induced mood disorders	Panic attack	Menorrhagia	Suicide attempt	Psychogenic seizure
Ashina, 2023 [34]	Atogepant 60 mg	543					0.9	0.4							
Ashina, 2023 [34]	Oral standard care	196					0.5								
Dodick, 2010 [3]	BTA 150 U	687		0.3	0.15	0.15	6.8								
Dodick, 2019 [9]	Eptinezumab 100 mg	122									0.82		0.82		
Ashina, 2020 [7]	Eptinezumab 100 mg	223					0.45					0.45		0.45	
Ashina, 2022 [8]	Eptinezumab 300 mg	294													0.34
Reuter, 2021 [15]	Erenumab 140 mg	388	0.26												
Silberstein, 2017 [25]	Fremanezumab-M	379					0.26								
Vladimir, 2018 [31]	Galcanezumab 240 mg	228								0.44					
Croop, 2020 [35]	Rimegepant 75 mg	370												0.27	
Reuter, 2021 [15]	Topiramate 100 mg	388		0.26											
Vladimir, 2018 [31]	Placebo	461												0.2	
Ashina, 2022 [8]	Placebo	298					0.34								

Fremanezumab-M, Fremanezumab monthly

Table 33: Details for musculoskeletal and connective tissue disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Costochondritis	Tendonitis	Vertebral osteophyte	Rhabdomyolysis	Periarthritis	Post-traumatic neck syndrome	Back pain	Behcets syndrome	Intervertebral disc protrusion	Osteoarthritis	Lumbar spinal stenosis	Arthralgia	Flank pain
Dodick, 2010 [3]	BTA 150 U	687							0.15						
Ashina, 2022 [8]	Eptinezumab 300 mg	294									0.34				
Tepper, 2017 [17]	Erenumab 140 mg	188									0.52				
Reuter, 2021 [15]	Erenumab 140 mg	388									0.26				
Tepper, 2017 [17]	Erenumab 70 mg	190	0.53								0				
Dodick, 2018 [12]	Erenumab 70 mg	283									0.4				
Goadsby, 2017 [13]	Erenumab 70 mg	314						0.31	0.31						
Silberstein, 2017 [25]	Fremanezumab-M	379							0.26						
Ferrari, 2019 [22]	Fremanezumab-Q	276							0.35						
Stauffer, 2018 [32]	Galcanezumab 120 mg	206		0.46											
Reuter, 2021 [15]	Topiramate 100 mg	388											0.26		
Dodick, 2010 [3]	Placebo	692									0.28				
Tepper, 2017 [17]	Placebo	282									0.35				
Ashina, 2020 [7]	Placebo	222									0.45				
Dodick, 2018 [12]	Placebo	289													0.3
Goadsby, 2017 [13]	Placebo	319										0.26		0.26	
Stauffer, 2018 [32]	Placebo	432			0.23										
Mulleners, 2020 [29]	Placebo	230								0.43					
Ashina, 2022 [8]	Placebo	298					0.34								

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 34: Details for investigations of system organ class (SOC) (%)

Author, year	Interventions	Participants	Weight decreased	International normalised ratio abnormal	Blood pressure increased	Hepatic enzyme increased	Aspartate aminotransferase increased	Alanine aminotransferase increased
Ferrari, 2019 [22]	Fremanezumab-Q	276		0.35				
Reuter, 2021 [15]	Topiramate 100 mg	388	0.26					

Fremanezumab-Q, Fremanezumab quarterly

Table 35: Details for metabolism and nutrition disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Hypokalaemia	Hypoglycaemia	Dehydration	Hyponatremia	Decreased appetite	Erythema nodosum
Dodick, 2010 [3]	BTA 150 U	687	0.15					
Detke, 2018	Galcanezumab 240 mg	282	0.35					
Reuter, 2021 [15]	Topiramate 100 mg	388					0.26	
Rothrock, 2019 [6]	Topiramate 100 mg	142			0.7			
Dodick, 2018 [12]	Placebo	289				0.3		
Dodick, 2018 [21]	Placebo	293		0.34				

Table 36: Details for vascular disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Hypertensive crisis	Peripheral arterial occlusive disease	Deep vein thrombosis	Peripheral vascular disease	Pulmonary embolism	Orthostatic hypotension
Dodick, 2010 [3]	BTA 150 U	687	0.15					
Silberstein, 2017 [25]	Fremanezumab-M	379	0.26					
Detke, 2018 [27]	Galcanezumab 240 mg	282					0.35	
Rothrock, 2019 [6]	Topiramate 100 mg	142		0.7	0.7			
Stauffer, 2018 [32]	Placebo	432			0.23			

Fremanezumab-M, Fremanezumab monthly; Fremanezumab-Q, Fremanezumab quarterly

Table 37: Details for general disorders and administration site conditions of system organ class (SOC) (%)

Author, year	Interventions	Participants	Non-cardiac chest pain	Malaise	Nasal septum deviation	Tooth impacted	Chest pain	Abdominal adhesions	Asthenia	Edema peripheral
Dodick, 2010 [3]	BTA 150 U	687	0.15							
Tepper, 2017 [17]	Erenumab 140 mg	188	0					0.53		
Goadsby, 2017 [13]	Erenumab 140 mg	319	0.31							
Tepper, 2017 [17]	Erenumab 70 mg	190	0.53							
Goadsby, 2017 [13]	Erenumab 70 mg	314	0.26							
Wang, 2021 [18]	Erenumab 70 mg	335							0.3	
Sakai, 2020 [30]	Galcanezumab 120 mg	115				0.9				
Sakai, 2020 [30]	Galcanezumab 240 mg	114			0.9					
Silberstein, 2017 [25]	Placebo	375								0.26

Goadsby, 2017 [13]	Placebo	319	0.26							

Table 38: Details for eye disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Diplopia	Retinal tear	Rhegmatogenous retinal detachment	Angle closure glaucoma	Retinal detachment	Optic neuritis
Ailani, 2021 [33]	Atogepant 10 mg	221						0.45
Ashina, 2022 [8]	Eptinezumab 100 mg	299					0.33	
Ferrari, 2019 [22]	Fremanezumab-M	285		0.35				
Reuter, 2021 [15]	Topiramate 100 mg	388			0.26	0.26	0.26	
Silberstein, 2017 [25]	Placebo	375	0.26					

Fremanezumab-M, Fremanezumab monthly

Table 39: Details for ear and labyrinth disorders, immune system disorders, and blood and lymphatic system disorders of system organ class (SOC) (%)

Author, year	Interventions	Participants	Ear and labyrinth disorders			Immune system disorders			Blood and lymphatic system disorders
			Vestibular neuronitis	Sudden hearing loss	Vertigo	Hypersensitivity	Anaphylactic reaction	Anaphylactic shock	Thrombocytopenia
Hong Sun, 2016 [16]	Erenumab 70 mg	106			0.1				
Ashina, 2020 [7]	Eptinezumab 300 mg	224			0.45				
Ashina, 2022 [8]	Eptinezumab 300 mg	294					0.68		
Goadsby, 2017 [13]	Erenumab 140 mg	319	0.26						
Ferrari, 2019 [22]	Fremanezumab-M	285					0.35		
Sakai, 2020 [30]	Galcanezumab 120 mg	115		0.9					
Reuter, 2021 [15]	Topiramate 100 mg	388						0.26	
Silberstein, 2017 [25]	Placebo	375				0.26			
Dodick, 2010 [3]	Placebo	692							0.28
Dodick, 2018 [21]	Placebo	289				0.3			
Dodick, 2018 [21]	Placebo	293				0.3			

Goadsby, 2017 [13]	Placebo	319				0.26			

Fremanezumab-M, Fremanezumab monthly

Table 40: Any serious adverse events reported from 32 trials

Treatments	Doses	Frequency	Total participants (n)	Participants with any SAEs* (%)
Atogepant [33]	30 mg	Once daily	228	0
Erenumab [16]	21 mg	Monthly	105	0
Galcanezumab [28]	150 mg	Every two weeks	107	0
Rimegepant [35]	75 mg	Once daily	370	3 (0.81)
Atogepant [33]	10 mg	Once daily	221	2 (0.9)
Erenumab [16]	7 mg	Monthly	108	1 (0.93)
Fremanezumab [21-25]	Quarterly, 625 mg	Single dose on day 0	1251	15 (1.2)
Eptinezumab [7-11]	100 mg	Single dose on day 0	1238	16 (1.29)
Galcanezumab [27, 30-32]	240 mg	Monthly	844	12 (1.42)
Placebo [3, 7-14, 17-33, 35, 36]	-	Matched with active treatments	7979	120 (1.5)
Galcanezumab [26, 27, 29-32]	120 mg	Monthly	1313	20 (1.52)
Fremanezumab [21-25]	Monthly, 225 mg	Monthly	1262	22 (1.74)
Erenumab [13-15, 17, 18]	140 mg	Monthly	1238	22 (1.78)
Eptinezumab [7-10]	300 mg	Single dose on day 0	989	21 (2.12)
Erenumab [12, 13, 17-20]	70 mg	Monthly	1555	39 (2.5)
Atogepant [33, 34]	60 mg	Once daily	774	30 (3.87)
BTA [3, 6]	150 U	Every 12 weeks	907	37 (4.08)
Topiramate [1, 6, 15]	100 mg	Twice daily	707	29 (4.1)
Amitriptyline [1]	25 to 100 mg	Twice daily	169	8 (4.73)

*Treatments are listed in order of increasing SAEs percentage.

Table 41: Classification of SAEs by SOC

System Organ Class (SOC)	Serious Adverse Events (SAEs)
Cardiac disorders	Acute myocardial infarction, atrial fibrillation, syncope
Ear and labyrinth disorders	Labyrinthitis, **sudden hearing loss,** vertigo, **vestibular neuronitis**
Eye disorders	Angle closure glaucoma, diplopia, **optic neuritis,** retinal detachment, rhegmatogenous retinal detachment
Gastrointestinal disorders	Abdominal pain, alcoholic pancreatitis, appendicitis, **diverticulitis,** esophagitis, **gastric ulcer haemorrhage,** gastritis, haemorrhoids, **intestinal haemorrhage,** irritable bowel syndrome, mechanical ileus, obstructive defaecation, pancreatitis, pancreatitis acute, parotitis, small intestinal obstruction, vomiting
General disorders and administration site conditions	**Abdominal adhesions,** asthenia, chest pain, **edema peripheral,** malaise, **nasal septum deviation,** non-cardiac chest pain, tooth impacted, **vocal cord thickening**
Hepatobiliary disorders	Cholecystitis, cholecystitis acute, cholelithiasis, **common bile duct stone,**
Immune system disorders	Anaphylactic reaction, anaphylactic shock, hypersensitivity
Infections and infestations	**Acute pyelonephritis**, bacterial pharyngitis, bacteriuria, **clostridium difficile colitis,** COVID-19 pneumonia, gastroenteritis, gastrointestinal infection, **infected dermal cyst**, influenza, kidney infection, nasopharyngitis, papilloma viral infection, parasitic gastroenteritis, pyelonephritis, pyrexia, sepsis, **tonsillitis,** urinary tract infection, viral gastroenteritis, viral infection
Injury	Accident, ankle fracture, brain contusion, **cartilage injury,** clavicle fracture, concussion, contusion, fall, foot fracture, hand fracture, humerus fracture, injury, ligament rupture, limb injury, lower limb fracture, **meniscus injury**, radius fracture, respiratory fume inhalation, rib fracture, road traffic accident, skin laceration, sternal fracture, tendon injury, **thoracic vertebral fracture**, traumatic orbital fracture, ulna fracture, wrist fracture
Investigations	Alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, weight decreased
Metabolism and nutrition disorders	Decreased appetite, hypokalaemia, hyponatremia
Musculoskeletal and connective tissue disorders	Arthralgia, back pain, Behçet's syndrome, **costochondritis,** flank pain, intervertebral disc protrusion, **osteoarthritis,** periarthritis**, post-traumatic neck syndrome**
Neoplasms benign malignant and unspecified (incl cysts and polyps)	Adenocarcinoma of the cervix, brain neoplasm, breast cancer, colon cancer, **fibroma, gallbladder polyp, ovarian cyst, polycystic ovaries**, rectal polyp**, ruptured ovarian cyst**, **uterine leiomyoma**, **breast neoplasm**, fibroadenoma of breast, malignant melanoma, neoplasm malignant, vulval cancer
Nervous system disorders	Cerebellar syndrome, **cerebral venous thrombosis**, cervical radiculopathy, **hypoaesthesia**, lumbar spinal stenosis, migraine, **migraine aggravated**, migraine with aura, nervous system disorders, **neuropathy**, seizure, speech disorder, transient ischemic attack

Neurological	**Spinal pain**
Poisoning and procedural complications	Overdose, **intentional overdose**
Pregnancy, puerperium and perinatal conditions	Pregnancy
Psychiatric disorders	Confusional state, depression, disorientation, major depression, **psychogenic seizure**, suicidal ideation, suicide attempt
Psychiatry	**Panic attack**
Renal and urinary disorders	Bladder dysfunction, **calculus urinary, nephrolithiasis, renal calculus**, renal colic, urinary incontinence
Reproductive system and breast disorders	Cervical dysplasia, dysmenorrhoea, **endometriosis**, menorrhagia, **menstrual disorder and vaginal haemorrhage**, metrorrhagia, ovarian disorder, **spontaneous abortion, threatened abortion**
Respiratory, thoracic and mediastinal	Asthma, **chronic obstructive pulmonary disease, chronic obstructive pulmonary disease (COPD) and apnoea related to COPD**, dyspnoea, epistaxis, pneumonia, **postsurgical laryngospasm with hypoxic brain injury**
Skin and subcutaneous tissue disorders	**Erythema nodosum**
Vascular disorders	**Hypertensive crisis**, orthostatic hypotension, **peripheral vascular disease**, **pulmonary embolism**

SAEs in bold font were not found in the CTCAE Version 5.0, and thus were categorised by our clinical team.

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