Erenumab and galcanezumab for prophylaxis of migraine

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Summary

- Migraine is a common disorder which can be associated with considerable impact on quality of life and lost productivity. It can be classified as episodic (occurring on <15 days per month on average) or chronic (≥15 days per month).
- A new class of monoclonal antibodies specific for CGRP (a neuropeptide involved in pain signalling) has been developed for the prophylaxis of migraine. One of these (erenumab) has been launched while a second (galcanezumab) has been given a positive opinion by the CHMP of the EMA. Two more (fremanezumab and eptinezumab) are expected to launch in the next 1-3 years.
- Erenumab is licensed for prophylaxis in people with ≥4 migraine days per month. The bulk of the clinical data are from phase III trials in patients with episodic migraine treated for 12-24 weeks. Pooled data from these trials found that erenumab was associated with a larger reduction in mean migraine days than placebo (2 vs. 3 days per month, treatment difference -1.2 days, 95% CI -1.5 to 0.8, p<0.001).
- These trials had extensive limitations, e.g. more than half of participants had never tried any other prophylactic medicines, so the efficacy of erenumab in patients with previous treatment failure is unclear. This gap in the evidence has been partially addressed by the LIBERTY trial, which found a benefit of erenumab 140 mg over placebo in patients with episodic migraine and prior failure of 2-4 preventive drugs (treatment response in 30% vs. 14%, odds ratio 2.7,p=0.002). The trial was limited to 12 weeks duration, and does not provide any information on patients with previous failure of Botox therapy.
- In patients with chronic migraine, a phase II RCT found that erenumab 70 mg & 140 mg was associated with a reduction in monthly migraine days versus placebo (-6.6 vs. -4.2 days, treatment difference -2.5 days, 95% CI -3.5 to -1.4). The reduction in monthly migraine days was identical for both doses.
- Most adverse events were of mild-moderate severity, and there were few differences between placebo and active treatment groups. Some evidence suggests that erenumab may lead to increases in systolic and diastolic blood pressure, but the overall cardiovascular safety profile is not clear. The EMA has requested additional studies.
- Galcanezumab is also licensed for prophylaxis of migraine in people with ≥4 migraine days per month, but there are no published data for people with chronic migraine (≥15 headache days per month). Two 6 month trials in people with episodic migraine found that galcanezumab reduced the mean number of migraine days by roughly 5 days, compared to roughly 3 days for placebo. The treatment effect was similar irrespective of galcanezumab dose. Limitations were similar to those highlighted for erenumab.
- Adverse event rates were similar between galcanezumab and placebo, with the main difference being injection site reactions. There was no difference in serious adverse events.
- Erenumab costs £386.50 per 70 mg dose, equating to £5,025-£10,049 per patient per year depending on dose and exclusive of VAT. Results from one economic study suggest that this could result in an ICER of £54,000-£109,000 per QALY in the UK. It is not yet known whether any commercial arrangements will be offered. The price for galcanezumab is not yet available.

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Introduction and background

Migraine is a primary headache disorder, characterised by episodic headaches accompanied by other symptoms such as photophobia, phonophobia, nausea and vomiting. Migraine can occur with or without aura, which commonly features positive or negative visual phenomena, sensory symptoms or speech/language symptoms. Migraine is relatively common, with a prevalence of around 18% in women and 6% in men.[1,2] The disease burden is therefore also relatively high, with millions of work days lost to migraine in the UK each year.[3] The impact on quality of life can be substantial, and patients with chronic migraine may also have a high degree of co-morbid disease and high utilisation of emergency healthcare.

Migraine can be described as episodic or chronic, although the distinction is somewhat arbitrary. Episodic migraine is defined by the presence of headache on fewer than 15 days each month. Chronic migraine sufferers experience 15 or more headache days each month, of which at least 8 are migraine days. Around 2.5% of patients with episodic migraine progress to chronic migraine over the course of a year. Similarly, chronic migraine remits to episodic migraine at a rate of 26% over the course of 2 years. Symptoms and clinical imaging are similar in episodic and chronic migraine, so they are thought to share a common pathophysiology.[4]

Treatment of migraine involves pharmacological intervention plus lifestyle advice. Known triggers should be avoided, but it is acknowledged that for many patients triggers are not identifiable or avoidable. Acute treatment with an oral triptan plus an NSAID or paracetamol should be the first choice of treatment, although a triptan, NSAID, or aspirin 900mg can be offered if the patient prefers monotherapy. Consideration should be given to adding an anti-emetic, even in the absence of nausea and vomiting. Preventive treatment can be considered if migraines are causing frequent disability, in patients at risk of medication overuse headache, when standard analgesia are not effective or are contraindicated, or for uncommon types of migraine (e.g. hemiplegic migraine). Options for migraine prophylaxis are discussed below.

Several monoclonal antibodies are currently in development for prophylaxis of migraine:

- Erenumab (Aimovig®▼, Novartis) – launched in the UK in September 2018.[5]
- Galcanezumab (Emgality®, Eli Lilly) – received a positive opinion from the EMA in September 2018. Marketing authorisation is expected in 2-3 months, with launch to follow.[6]
- Fremanezumab (Ajovy®, Teva) – an application for marketing authorisation was filed in the EU in February 2018.[7] Licence and launch are expected in 2019. Fremanezumab was licensed in the USA in September 2018.[8]
- Eptinezumab (Alder Bio) – currently in phase III trials. Launch is predicted for 2021.[9]

Erenumab is a fully human antibody specific for calcitonin gene-related peptide (CGRP) receptor. CGRP is a neuropeptide involved in pain signalling, and which also promotes vasodilation and inflammation. Erenumab competes with CGRP for binding of its receptor, and thereby interrupts the signalling pathway. It is thought to target smooth muscle cells in blood vessels, as well as neurons and glial cells outside the blood-brain barrier.[4,10]

Erenumab is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month. It is the first drug in its class to launch in the EU although, as detailed above, several other drugs are in development. Detailed information is not yet available for galcanezumab, but the mechanism of action is likely to be similar.

This document will review the evidence for the safety, effectiveness and cost-effectiveness of erenumab and galcanezumab for the prophylaxis of migraine.

Guidance and related advice

NICE technology appraisals of erenumab and fremanezumab are planned, but the expected publication dates are not yet available. Galcanezumab and eptinezumab were not in the NICE workplan at time of writing.

A NICE clinical guideline makes the following recommendations for patients with migraine who require prophylactic treatment:[11]

- Discuss the benefits and risks of prophylaxis.
- Offer topiramate or propranolol according to the person's preference, comorbidities and risk of adverse events.
- Consider amitriptyline, according to the person's preference, comorbidities and risk of adverse events Evidence suggests efficacy is similar to propranolol, but as a tricyclic antidepressant amitriptyline is not suitable for all patients.[2]
- Do not offer gabapentin
- If both topiramate and propranolol are unsuitable or ineffective, consider a course of up to 10 sessions of acupuncture over 5–8 weeks according to the person's preference, comorbidities and risk of adverse events.
- For people who are already having treatment with another form of prophylaxis and whose migraine is well controlled, continue the current treatment as required.
- Review the need for continuing migraine prophylaxis 6 months after the start of prophylactic treatment.
- Advise people with migraine that riboflavin (400 mg once a day) may be effective in reducing migraine frequency and intensity for some people.

In addition, NICE CKS acknowledges that other treatments are in use but not recommended, largely due to lack of evidence. All options are unlicensed unless specified otherwise:[2]

- Pizotifen (licensed) – limited evidence of effectiveness, and associated with unwanted adverse effects which limit use.
- Venlafaxine
- Lisinopril
- Sodium valproate
- Losartan
- Candesartan
- Magnesium citrate (some RCT evidence for reduced frequency)
- Coenzyme Q10 – RCTs show potential benefit, but more evidence is needed before recommendations can be made.

Finally, botulinum toxin A (Botox®, Allergan) is licensed for prophylaxis in adults with chronic migraine.[12] No other brands are licensed in this indication. NICE recommends use in patients with ≥15 headache days per month, of which at least 8 are migraine days. Treatment should be stopped in patients who do not achieve at least a 30% reduction in headache days per month after two cycles, or whose condition reverts to episodic migraine (<15 headache days/month) for three consecutive months.[13]

Guidance on trial endpoints

The EMA has published guidance on the evaluation of medicinal products for migraine prophylaxis.[14] The recommended primary endpoint in clinical trials is the number of migraine attacks during a pre-specified period, for example the mean frequency of attacks during a 4 week period or during the final 4 weeks of a 12 week trial. Suggested secondary endpoints include the number of days with migraine per 4 weeks, responder rate (where responder is defined as patients with ≥50% in attack frequency), and use of drugs for acute treatment of migraine. Tools measuring health-related quality of life are not recommended for use unless fully clinically validated. This guidance is currently under review.

Quality of life measures

In the erenumab trials quality of life was measured using the Migraine Physical Function Impact Diary (MPFID) score. This is a set of 13 questions comprising a physical impairment domain, an impact on everyday activities domain, and a single global impact question (overall difficulty doing everyday activities). See appendix 1 for full list of questions. Each question is scored from 1-5, with lower scores indicating greater impairment. The Physical Impairment domain produces a possible score of 5-25, while the Everyday Activities domain is scored from 7-35; higher scores represent greater disability.[15] The clinical relevance of changes in this scale is not clear. One study published in abstract suggests that a change of 4-5 points in the everyday activities domain, or of 3-5 points in the physical impairment domain, may be clinically meaningful.[16] In contrast a clinical expert involved in the FDA review of erenumab considered changes of 8-9 points for everyday activities and 6-7 points for physical impairment likely to be clinically important.[15] The MPFID has not been independently validated.

Three scales were used in the galcanezumab trials:

- Patient Global Impression of Severity (PGI-S). A single question, which asks the patient how their condition is now. It is rated on a scale of 1 (least severe) to 4 (most severe). No literature was found validating this scale in migraine, or establishing a minimal clinically important difference (MCID).
- Migraine-Specific Quality of Life Questionnaire Role Function-Restrictive domain (MSQ-R-FR). The MSQ consists of 14 questions, each of which is scored from 1 (none of the time) to 6 (all of the time). Seven of these questions are considered to comprise the role function-restrictive domain. Higher scores indicate greater impact. See appendix 2 for more details. The MSQ has been validated for use in both episodic and chronic migraine, but opinions on what constitutes the MCID for differ from 3.2 to 5 points for the R-DR domain.[4,17-19]

- Migraine Disability Assessment (MIDAS). The MIDAS consists of 5 questions, each of which asks how many days a specific activity was affected by migraine in the prior 3 months. The total number of days from each question is then added up to produce a score, with higher scores indicating greater disability.[20] See appendix 3 for more details. No information was found on the MCID for the MIDAS scale.

Clinical efficacy – erenumab

STRIVE trial – episodic migraine

STRIVE was a randomised, double-blind, placebo-controlled, 28 week trial in people with episodic migraine.[21] The EMA considered it to be a pivotal trial for licensing purposes.[4] Patients (n=955) were adults aged 18-65 with a history of migraine (with or without aura) for at least 12 months prior to screening. Exclusion criteria were extensive:

- Age >50 at migraine onset
- History of hemiplegic migraine or cluster headache
- Use of botulinum toxin during the 4 months prior to the baseline period
- Use of ergotamine derivatives, steroids or triptans for migraine prophylaxis in the 2 months prior to the baseline period
- Use of any device or procedure for migraine prevention within 2 months of baseline period
- History of lack of therapeutic response to 3 or more classes of migraine-preventative drugs (including valproate-containing medicines, topiramate, beta blockers, tricyclic antidepressants, SNRIs, flunarazine or verapamil, and lisinopril; or candesartan.
- Patients using two or more specified drugs for migraine prevention during the 2 months prior to the baseline period (incl. anti-convulsants, beta blockers, antidepressants, calcium channel blockers, lisinopril, candesartan, clonidine, guanfacine, cyproheptadine, methysergide, pizotifen, herbal remedies, magnesium ≥600 mg/day, riboflavin ≥100 mg/day).

Notably, patients using any preventive medicines were completely excluded for part of the enrolment period. This was changed during enrolment to allow inclusion of patients taking one medicine for migraine prophylaxis, as long as the dose had been stable for at least 2 months. As a result only 2.8% of enrolled patients were current users of any prophylactic medicines, 40.6% had tried 1 or 2 prophylactic medicines but were not current users, and 56.5% had never tried any medicines for migraine prophylaxis. Otherwise, patients were largely female (85%) with a mean age of 41 years and a 20 year history of migraine. At baseline, enrolled patients experienced a mean of around 8 migraine days, 9 headache days and 5 migraine attacks per month.

Enrolled patients were randomised to receive erenumab 70 mg, erenumab 140 mg, or placebo. Erenumab is supplied in pens or syringes containing 70 mg, so to maintain blinding all patients received 2 injections:

- Erenumab 70 mg + erenumab 70 mg
- Erenumab 70 mg + placebo
- Placebo + placebo

All treatments were administered once every four weeks, and patients received a total of six doses during the trial's 28 week double-blind phase. The primary outcome was change in mean number of migraine days between baseline and weeks 13-28 of the double-blind treatment phase. Migraine days were measured using an electronic headache diary, which patients were asked to complete every day. A migraine day was any day with a migraine lasting at least 30 minutes and involving at least two pain features or one non-pain feature. Any day where a patient took acute treatment for migraine was counted as a migraine day.

Trial outcomes are summarised in table 1 below. Erenumab was generally superior to placebo, but the clinical importance of these outcomes is not clear. The two doses of erenumab were not compared.

Table 1. Outcomes of the STRIVE trial, weeks 13-28 (erenumab for episodic migraine)

	Placebo (n=316)	**Erenumab 70 mg (n=312)**	**Erenumab 140 mg (n=318)**
Mean monthly migraine days (primary outcome)	-1.8	-3.2 TD -1.4 (-1.9 to -0.9)	-3.7 TD -1.9 (-2.3 to -1.4)
≥50% reduction in migraine days per month	84 (26.6%)	135 (43.3%) OR 2.13 (1.52 to 2.98)	159 (50.0%) OR 2.81 (2.01 to 3.94)
Days per month with use of acute migraine-specific medication	-0.2	-1.1 TD -0.9 (-1.2 to -0.6)	-1.6 TD -1.4 (-1.7 to -1.1)
Monthly MPFID everyday-activities score	-3.3	-5.5 TD-2.2 (-3.3 to -1.2)	-5.9 TD -2.6 (-3.6 to -1.5)
Monthly MPFID physical-impairment score	-2.4	-4.2 TD -1.9 (-3.0 to -0.8)	-4.8 TD -2.4 (-3.5 to -1.4)

OR – odds ratio. TD – treatment difference. All comparisons are erenumab vs. placebo; erenumab doses were not compared.

ARISE trial – episodic migraine

ARISE was a randomised, double-blind, placebo-controlled phase 3 trial in people with episodic migraine. The design was very similar to that described above for the STRIVE trial, with the exception that this was a two-arm trial comparing erenumab 70 mg to placebo.

In addition to the exclusion criteria detailed above, patients were excluded from ARISE if they had a history of major psychiatric disorder or current evidence of depression, history of a seizure disorder, malignancy in the prior 5 years, or history of HIV, major cardiovascular events, hepatic disease, or any other significant medical condition, clinical sign or laboratory finding.

As with STRIVE, patients using prophylactic medicines were only permitted during part of the enrolment period. As a result 51% of participants had never used any prophylactic medicines, 43% had tried 1 or 2 but were not current users, and only 6% were current users. Otherwise patients were largely female (85%), Caucasian (90%), had a mean age of 42 years and a 20+ year history of migraine. At baseline,

enrolled patients experienced a mean of around 8 migraine days, 9 headache days and 5 migraine attacks per month.

Outcomes are summarised in table 2. As with the STRIVE trial erenumab was generally superior to placebo, but the clinical importance of the difference is not clear.

Table 2. Outcomes of the ARISE trial (erenumab for episodic migraine)

	Placebo (n=288)	**Erenumab 70 mg (n=282)**	**Difference vs. placebo (95% CI)**
Mean monthly migraine days (primary outcome)	-1.8	-2.9	TD -1.0 (-1.6 to -0.5), p<0.001
≥50% reduction in migraine days per month	85 (29.5%)	112 (39.7%)	OR 1.59 (1.12 to 2.27), p=0.01
Days per month with use of acute migraine-specific medication	-0.6	-1.2	TD -0.6 (-1.0 to -0.2), p=0.002
≥5 point reduction in MPFID everyday-activities score	103 (35.8%)	114 (40.4%)	OR 1.22 (0.87 to 1.71), p=0.3
≥5 point reduction in MPFID physical impact score	78 (27.1%)	93 (33%)	OR 1.33 (0.92 to 1.90), p=0.1

TD – treatment difference; OR – odds ratio.

Limitations

The exclusion criteria for these trials mean the results may not be generalizable to the UK population. The low numbers of patients with current or previous use of prophylactic medicines is of particular concern. Patients were also excluded from STRIVE if they did not show at least 80% adherence to reporting with the electronic diary during the baseline phase, which may have introduced a selection bias. The lack of an active comparator and relatively short treatment duration in both trials is also of concern.

EMA guidance for clinical trials in migraine prophylaxis recommends that the number of migraine attacks in a 4 week period should be used as the primary outcome.[14] The erenumab trials instead used mean number of migraine days, which the EMA suggest may be used as a secondary endpoint. The trial sponsor in this case contended that number of migraine days is easier to measure and more sensitive, and this was accepted by the EMA.[4]

Pooled data – episodic migraine

An analysis of pooled data from the STRIVE and ARISE trials, plus an additional phase 2 trial in patients with episodic migraine, is presented in the European Public Assessment Report for erenumab.[4] As expected, pooled outcomes are very similar to the individual trials (see Table 3 below). At baseline patients reported a mean of around 8.3 migraine days per month.

Table 3. Pooled data: 12 weeks treatment with erenumab for episodic migraine

	Placebo (n=756)	Erenumab 70 mg (n=699)	Difference vs. placebo (95% CI)
Change from baseline in mean monthly migraine days	-1.9	-3.06	TD -1.16 (-1.5 to -0.8), p<0.001
≥50% reduction in migraine days per month	28.3%	40.6%	OR 1.74 (1.4 to 2.2), p<0.001
Days per month with use of acute migraine-specific medication	-0.5	-1.24	TD -0.74 (-1.0 to -0.5), p<0.001
Change from baseline in MPFID everyday-activities score	-3.39	-4.94	TD -1.56 (-2.4 to -0.8), p<0.001
Change from baseline in MPFID physical impairment score	-2.18	-3.7	TD -1.51 (-2.3 to -0.7), p<0.001

TD – treatment difference; OR – odds ratio.

LIBERTY trial – episodic migraine

LIBERTY was a 12 week phase 3 RCT in people with episodic migraine who had had previous unsuccessful treatment with 2-4 previous preventive treatments.[22] LIBERTY was published in October 2018, and was not included in the EU regulatory submission for erenumab. Treatment failure could be due to tolerability or efficacy, or both. Patients were otherwise similar to those recruited to the trials discussed above; they were adults aged 18-65 with a ≥12 month history of migraine on 4-14 days per month. Trial exclusion criteria were similar to those discussed above, including use of Botox in the prior 4 months. Patients were required to demonstrate ≥80% compliance with an electronic headache diary during the baseline phase.

Patients were required to have been treated unsuccessfully with 2-4 of: propranolol or metoprolol, topiramate, flunarizine, valproate, amitriptyline, venlafaxine, lisinopril, candesartan, or other locally approved preventives (including pizotifen in the UK). They were also required to have been treated unsuccessfully with, or deemed unsuitable for, at least one of propranolol, metoprolol, topiramate, flunarizine or valproate. Unsuitability was defined as any circumstance leading to lack of eligibility, including contraindications, cautions, national guidelines or any other locally binding arrangements. Failure due to lack of efficacy was defined as a lack of any meaningful reduction in migraine after treatment at accepted doses lasting 2-3 months in the preceding 5 years. Failure due to tolerability was defined as documented discontinuation due to adverse effects at any time.

Patients (n=246) were randomised to receive erenumab 140 mg or placebo, each delivered as two injections. The primary endpoint was the proportion of patients achieving at least 50% reduction in mean monthly migraine days during weeks 9-12 of this 12 week trial. This endpoint was used as a secondary outcome in the trials discussed above.

Patients were largely female (81%) and white (92%). A total of 39% had received unsuccessful treatment with two prior therapies, 38% had had three prior therapies, and the remaining 23% had failed treatment with four therapies. The most common preventive therapies used were topiramate (85%), amitriptyline (46%) and propranolol (45%). The trial publication does not report what population of patients

had previously tried therapy with Botox. The mean number of monthly headache days at baseline was 10. Around 30% of patients reported 4-7 monthly migraine days at baseline, while 70% reported 8-14 migraine days.

Erenumab was superior to placebo for all of the assessed outcomes (see table 4 below). However, treatment effects appear to be smaller than in the trials discussed above despite use of the higher licensed dose.

Table 4. Outcomes of the LIBERTY trial at weeks 9-12 (erenumab for episodic migraine)

	Placebo (n=119)	Erenumab 140 mg (n=124)	Difference vs. placebo (95% CI)
≥50% reduction in migraine days per month (primary outcome)	17 (14%)	36 (30%)	OR 2.7 (1.4 to 5.2), p=0.002
≥75% reduction in migraine days per month	5 (4%)	14 (12%)	OR 3.2 (1.1 to 9.0), p=0.025
100% reduction in migraine days per month	0	7 (6%)	Not calculable
Change from baseline in mean monthly migraine days	-0.2	-1.8	TD -1.6 (-2.7 to -0.5), p=0.004
Days per month with use of acute migraine-specific medication	0.5	-1.3	TD -1.7 (-2.4 to -1.0), p<0.001
Change from baseline in MPFID physical impairment score	1.6	-1.9	TD -3.5 (-5.7 to -1.2), p=0.003
Change from baseline in MPFID everyday-activities score	0.6	-3.4	-3.9 (-6.1 to -1.7), p<0.001

TD – treatment difference; OR – odds ratio.

The LIBERTY trial addresses the gap in the evidence created by the small number of patients in the published trials who have previous experience of prophylactic medicines. However it is limited by the short duration of double-blinded treatment, and exclusion of patients with chronic migraine. The trial did not include a 70 mg treatment arm, so it is not clear whether there is any benefit to use of this dose in patients with prior treatment failures. Additionally, the trial publication does not provide information on patients who have failed treatment with 5 or more preventive medicines. It is not clear if this would constitute a large group, or whether these patients are likely to be substantially different from people who have failed 2-4 treatments. Finally, the LIBERTY trial excluded patients who had received Botox in the preceding three months, and did not report what proportion of participants (if any) had ever tried Botox. Efficacy in this patient group therefore remains unclear.

Phase II trial – chronic migraine

The efficacy of erenumab for prophylaxis of chronic migraine has been assessed in a phase II placebo-controlled, double blind RCT.[23] The EMA considered this to be a pivotal trial for licensing purposes.[4] Participants (n=667) were adults aged 18-65 with a history of chronic migraine. Patients with ≥80% compliance to use of an electronic

headache diary were randomised 3:2:2 to placebo, erenumab 70 mg or erenumab 140 mg once every 4 weeks for a total of 12 weeks. Other prophylactic drugs were prohibited during the study and patients were excluded if they had used botulinum toxin in the preceding 4 months.

The primary outcome was the mean change in monthly migraine days between baseline and the final 4 weeks of the trial. At baseline participants had around 18 migraine days and 215-235 headache hours per month. See table 5 below for a summary of trial outcomes.

This trial has a 256 week open-label extension which is currently ongoing.[4]

Table 5: efficacy of erenumab in the treatment of chronic migraine (phase II)

	Placebo (n=281)	**Erenumab 70 mg (n=188)**	**Erenumab 140 mg (n=187)**
Mean monthly migraine days (primary outcome)	-4.2	-6.6, TD -2.5 (-3.5 to -1.4), p<0.0001	-6.6, TD -2.5 (-3.5 to -1.4), p<0.0001
≥50% reduction in migraine days per month	66 (23%)	75 (40%), OR 2.2 (1.5 to 3.3), p=0.0001)	77 (41%), OR 2.3 (1.6 to 3.5), p<0.0001
Days with use of acute migraine-specific medication per month	-1.6	-3.5, TD -1.9 (-2.6 to -1.1), p<0.0001	-4.1, TD -2.6 (-3.3 to -1.8), p<0.0001
Cumulative monthly headache hours	-55.2	-64.8, TD -9.5 (-27 to 7.9), p=0.28	-74.5, TD -19.3 (-36.7 to -1.9), p=0.03

TD – treatment difference; OR – odds ratio.

Safety – erenumab

An analysis of pooled data from the clinical trial programme is presented in the European Public Assessment Report for erenumab.[4] Several pools were analysed, differing in the dose of erenumab given and duration of exposure. Most adverse events (AEs) were mild to moderate in severity.

- In a pool comprising data from patients receiving double blind treatment for 12 weeks, overall rates of AEs, treatment-emergent AEs, AEs leading to discontinuation, and serious AEs were similar between placebo and erenumab treatment arms. Events which were slightly more common with erenumab included constipation, injection site pain or erythema, bronchitis, muscle spasms and generalised pruritus. None of these exceeded an incidence of 4% in any treatment arm.
- In a pool comprising data from 24 weeks of exposure, overall AE rates were again similar. Events which were more common with erenumab treatment were similar to those outlined above.
- In a pool including longer term data from double-blind trials plus open-label extensions, the most commonly reported AEs were: upper respiratory tract infection, sinusitis, back pain, arthralgia, nausea, UTI, fatigue, injection site pain, migraine, dizziness and bronchitis. Rates of all of these events were broadly similar across treatment arms, including placebo.

The EMA highlighted that there is a theoretical concern that molecules antagonising CGRP may exacerbate ischaemic events such as stroke, transient ischaemic attack or myocardial infarction. Rates of these events were very low in the studied populations and did not appear to differ between treatment groups, but no conclusions can yet be drawn. Additionally, patients treated with erenumab appeared to be slightly more likely to develop a systolic blood pressure >160 mmHg, or diastolic blood pressure >100 mmHg. Patients with existing major cardiovascular disease were excluded from the trials, so safety in these patients is not known.

The EMA requested additional studies to assess long-term safety, cardiovascular outcomes in patients with pre-existing conditions, and use in pregnant women. These studies are all either planned or ongoing.[4]

Clinical efficacy – galcanezumab

Episodic migraine

Two RCTs have been completed and published, with broadly similar designs to those conducted for erenumab.[24,25] EVOLVE-1 and EVOLVE-2 enrolled adults aged 18-65 with at least a one year history of migraine, including 4-14 migraine days per month and at least 2 migraine episodes in the 30-40 days prior to randomised treatment. Patients were required to demonstrate at least 80% compliance with an electronic headache diary.

Patients were excluded if they had failed treatment with ≥3 drugs for migraine prevention, had used botulinum toxin in the head or neck in the prior 4 months, used opioids or barbiturates more than twice per month or had used any therapeutic antibody in the prior 12 months. In addition, patients were excluded from EVOLVE-1 if they were currently using any drug for migraine prevention or had serious cardiovascular risk or recent history of a cardiovascular event. Patients were excluded from EVOLVE-2 if they had “any medical or psychiatric illness that would preclude participation”. This was not further clarified.

Patients in both trials were randomised to receive placebo, galcanezumab 120 mg or galcanezumab 240 mg. Patients in the 120 mg arm received a 240 mg loading dose. Galcanezumab is supplied in pre-filled devices containing a single 120 mg dose. To preserve blinding all patients received 2 injections at each study visit, similar to the process described for erenumab above. All patients received 6 doses of study medication, and were followed up for 5 months after the final dose was administered.

Participants in EVOLVE-1 (n=862) were predominantly female (83%) and white (80%), with a mean age of around 40 years and a 20 year history of migraine. Around two-thirds had tried a prior preventive treatment, and 19% had failed treatment with ≥1 preventive treatment. They had around 9 migraine days and 6 migraine attacks per month. Participants in EVOLVE-2 (n=922) were broadly similar.

The primary outcome measure in both trials was change from baseline in number of migraine days during the 6 month active treatment phase. Secondary outcomes included the number of responders (patients with ≥50%, ≥75% or 100% reduction in migraine days), days with acute migraine medication use, and quality of life measures.

Galcanezumab was superior to placebo for all outcomes (see table 6 below). The two doses of galcanezumab were not compared, but outcomes did not appear to differ with increasing dose.

Table 6. Outcomes of the EVOLVE trials of galcanezumab for episodic migraine

EVOLVE-1	**Placebo**	**Galcanezumab 120 mg**	**Galcanezumab 240 mg**
	n=433	**n=213**	**n=212**
Mean monthly migraine days (primary outcome)	-2.8	-4.7, TD -1.9 (-2.5 to -1.4), p<0.001	-4.6, TD -1.8 (-2.3 to -1.2), p<0.001
Days with use of acute migraine medication per month	-2.2	-4.0, TD -1.8 (-2.3 to -1.3), p<0.001	-3.8, TD -1.6 (-2.1 to -1.1), p<0.001
≥50% reduction in migraine days per month	38.6%	62.3%, OR 2.6 (2.0 to 3.4), p<0.001	60.9%, OR 2.5 (1.9 to 3.2), p<0.001
≥75% reduction in migraine days per month	19.3%	38.8%, OR 2.7 (2.0 to 3.5), p<0.001	38.5%, OR 2.6 (2.0 to 3.4), p<0.001
100% reduction in migraine days per month	6.2%	15.6%, OR 2.8 (2.0 to 4.0), p<0.001	14.6%, OR 2.6 (1.8 to 3.7), p<0.001
Change in MSQ-R-FR score	24.7	32.4, TD 7.7 (5.2 to 10.3), p<0.001	32.1, TD 7.4 (4.8 to 10.0), p<0.001
Change in PGI-5 score	-1.3	-1.6, TD -0.3 (-0.5 to -0.1), p=0.002	-1.6, TD -0.3 (-0.5 to -0.1), p=0.008
EVOLVE-2*	**Placebo**	**Galcanezumab 120 mg**	**Galcanezumab 240 mg**
	n=461	**n=231**	**n=223**
Mean monthly migraine days (primary outcome)	-2.3	-4.3, TD -2.0 (-2.7 to -1.3), p<0.001	-4.2, TD -1.9 (-2.6 to -1.2), p<0.001
Days with use of acute migraine medication per month	-1.9	-3.7, TD -1.8 (-2.4 to -1.3), p<0.001	-3.6, TD -1.7 (-2.3 to -1.2), p<0.001
≥50% reduction in migraine days per month	36%	56.3%, OR 2.6 (1.9 to 3.6), p<0.001	56.5%, OR 2.3 (1.7 to 3.2), p<0.001
≥75% reduction in migraine days per month	17.8%	33.5%, OR 2.3 (1.6 to 3.3), p<0.001)	34.3%, OR 2.4 (1.7 to 3.4), p<0.001
100% reduction in migraine days per month	5.7%	11.5%, OR 2.2 (1.3 to 3.9), p<0.001	13.8%, OR 2.7 (1.6 to 4.7), p<0.001
Change in MSQ-R-FR score	19.65	28.5, p<0.001	27.0, p<0.001
Change in PGI-5 score	-0.9	-1.2, p=0.002	-1.2, p=0.01
Change in MIDAS score	-12.0	-21.2, p<0.001	-20.2, p<0.001

All comparisons are galcanezumab vs. placebo. The two galcanezumab doses were not compared. TD – treatment difference; OR – odds ratio

* Treatment differences and odds ratios for EVOLVE-2 were estimated from data presented in the trial publication

Limitations

As in the erenumab trials the results may not be generalizable to patients with extensive treatment history with other migraine preventive medicines.

Chronic migraine

The efficacy of galcanezumab in chronic migraine has been assessed in a large phase 3 RCT, of which the assessment of the primary endpoint has been completed but not published.[26,27] Headline results are available from a press release, but the trial could not be fully critically appraised.

Patients (n=1,113) were adults with ≥15 headache days per month, of which at least 8 were migraine days. They were randomised to receive galcanezumab 120 mg or 240 mg, or placebo. The primary outcome was mean change in monthly migraine days during the three month double-blind treatment phase. At baseline, participants had a mean of 19.4 migraine days per month.

Patients receiving galcanezumab 240 mg achieved a larger reduction in monthly migraine days than the placebo group (4.3 days vs. 2.2 days, p<0.001). Outcomes for the galcanezumab 120 mg arm were not reported. Galcanezumab-treated patients were more likely to achieve ≥50% reduction in monthly migraine days (27.6% for 120 mg and 27.5% for 240 mg compared to 15.4% for placebo, p<0.001 for both dosing groups).[27]

The trial had a 9 month open-label extension phase, results of which are not yet available.

Safety – galcanezumab

The incidence of adverse events was generally similar across treatment groups. In EVOLVE-2 there were no significant differences between galcanezumab and placebo, except that injection site reactions were more common in the active treatment arms. The same was true in EVOLVE-1, except that pruritus was also more common with galcanezumab 240 mg than placebo.

The most common AEs in both trials were similar, and included events such as injection site pain, nasopharyngitis, upper respiratory tract infections, dizziness, and influenza.[24,25] There were no significant differences between groups in the incidence of these AEs. Patients in the active treatment arms were more likely to develop anti-drug antibodies, but the authors of EVOLVE-2 reported that these had no effect on safety or efficacy.

See table 7 below for a summary of the safety profiles from the two trials, with a focus on events which differed in incidence between placebo and active treatment arms.

Table 7: Adverse events reported in EVOLVE-1 and EVOLVE-2

	EVOLVE-1			EVOLVE-2		
	Placebo	**Galc. 120 mg**	**Galc. 240 mg**	**Placebo**	**Galc 120 mg**	**Galc 240 mg**
Any treatment-emergent AE	60.4%	65.5%	67.7%	62.3%	65%	71.5%
Serious AE	1.2%	2.9%	0	1.1%	2.2%	3.1%
Discontinuation due to AE	2.3%	4.2%	3.3%	1.7%	2.2%	4.0%
Injection site reaction	0.9%	3.4% (p<0.05)	5.5% (p<0.05)	0	3.1% (p<0.001)	7.9% (p<0.001)
Injection site pruritus	0.2%	4.4% (p<0.05)	4.6% (p<0.05)	0	2.7% (p=0.001)	3.1% (p<0.001)
Injection site swelling	NR	NR	NR	0	2.2% (p=0.04)	0.4% (p=0.3)
Pruritus	0.2%	1.0%	2.7% (p<0.05)	NR	NR	NR
Anti-drug antibodies at baseline	5.9%	8.9%	10.8%	8.4%	8.1%	11.2%
Treatment-emergent anti-drug antibodies	1.7%	3.5%	5.2%	0.5%	8.6% (p<0.001)	5.1% (p<0.001)

All p values represent comparison with placebo. Where p values are not shown, differences were not statistically significant. NR = not reported.

Network meta-analysis

There are no direct comparisons available for the anti-CGRP antibodies. A network meta-analysis has been conducted and includes data for erenumab, galcanezumab, fremanezumab, botulinum toxin, topiramate, amitriptyline and placebo.[28] The analysis included all studies in adults with chronic or episodic migraine who were eligible for preventive therapy. The results are presented in tables 8 & 9 below. As with any indirect comparison, these figures should be interpreted with caution.

The authors considered the evidence for anti-CGRP antibodies in patients with episodic or chronic migraine to be insufficient compared to oral agents or botulinum toxin.

The treatment effect in patients who had failed treatment with at least one other preventive drug was also examined. However, these data were confidential and will not be made public until December 2018. Instead the authors give the following headline statements:

- the evidence in episodic migraine was promising but inconclusive compared to no treatment
- the evidence in chronic migraine was comparable to or better than no treatment

Table 8: network meta-analysis in patients with episodic migraine. Figures are mean difference vs. placebo

	Monthly migraine days (95% CrI)	Days with acute medicine (95% CrI)	50% responders (OR, 95% CrI)
Erenumab 70 mg monthly	**-1.3 (-1.8 to -0.8)**	**-0.9 (-1.4 to -0.4)**	**1.9 (1.4 to 2.5)**
Erenumab 140 mg monthly	**-1.9 (-2.7 to -1.2)**	**-1.6 (-2.4 to -0.9)**	**2.2 (1.4 to 3.3)**
Fremanezumab 675 mg quarterly	**-1.2 (-2.2 to -0.3)**	**-1.1 (-2.0 to -0.3)**	**1.7 (1.1 to 2.7)**
Fremanezumab 225 mg monthly	**-1.6 (-2.5 to -0.8)**	**-1.2 (-2.0 to -0.4)**	**1.9 (1.4 to 2.9)**
Galcanezumab 120 mg monthly	-1.8 (-2.4 to -1.2)	-1.8 (-2.4 to -1.2)	2.5 (1.9 to 3.3)
Galcanezumab 240 mg monthly	**-1.8 (-2.5 to -1.2)**	**-1.7 (-2.3 to -1.1)**	**2.4 (1.7 to 3.2)**
Topiramate 50 mg/day	-0.2 (-1.0 to 0.6)	-0.4 (-1.3 to 0.4)	**1.6 (1.1 to 2.3)**
Topiramate 100 mg/day	**-1.2 (-1.7 to -0.7)**	**-1.0 (-1.4 to -0.5)**	**2.7 (2.1 to 3.5)**
Topiramate 200 mg/day	**-1.0 (-1.5 to -0.4)**	**-0.7 (-1.3 to -0.2)**	**2.3 (1.7 to 3.1)**
Amitriptyline 25-100 mg/day	-1.1 (-2.2 to 0.1)	-1.2 (-2.4 to 0.1)	**2.0 (1.2 to 3.2)**
Propranolol 160 mg/day	**-1.2 (-2.0 to -0.4)**	**-1.1 (-1.9 to -0.3)**	**2.7 (1.7 to 4.1)**

CrI – credible interval. Bold entries indicate statistical significance.

Table 9: network meta-analysis in patients with chronic migraine. Figures are mean difference vs. placebo

	Monthly migraine days (95% CrI)	Days with acute medicine (95% CrI)	Monthly headache days
Erenumab 70 mg monthly	**-2.4 (-4.8 to 0.0)**	-1.9 (-4.3 to 0.6)	n/a
Erenumab 140 mg monthly	**-2.4 (-4.8 to 0.0)**	**-2.5 (-4.9 to 0.0)**	n/a
Fremanezumab 675 mg quarterly	-1.3 (-3.5 to 0.9)	-1.4 (-3.8 to 1.0)	-1.5 (-3.7 to 0.8)
Fremanezumab 675/225 mg monthly	-1.7 (-3.5 to 0.1)	**-2.2 (-4.1 to -1.3)**	**-1.8 (-3.6 to -0.1)**
Onabotulinum toxin A 155U quarterly	**-2.0 (-3.6 to -0.3)**	n/a	**-2.1 (-3.5 to -0.6)**
Topiramate 100 mg/day	-1.7 (-4.2 to 0.8)	-1.3 (-3.5 to 0.7)	-1.1 (-3.6 to 1.4)

CrI – credible interval. Bold entries indicate statistical significance.

Dosage and administration

Erenumab is licensed for use in adults with at least 4 migraine days per month, at a dose of 70 mg once every 4 weeks, administered as single subcutaneous injection. It is supplied in pre-filled pens and syringes, each containing a single 70 mg dose. The SPC states that some patients may benefit from a dose of 140 mg every 4 weeks, but does not offer guidance on selecting this population.[10] This dose would

be administered as two 70 mg injections. Most patients who respond to therapy will see improvements after 3 months of treatment. Discontinuation of therapy should be considered in patients who have not responded after 3 months of use.

Erenumab is supplied in a single-use pre-filled syringe and is intended for self-administration, following appropriate training. The injection may be given in the abdomen, thigh or upper arm, although the arm should only be used if the injection is given by someone other than the patient. Injection sites should be rotated.

The SPC for galcanezumab is not yet available. The Committee for Medicinal Products for Human Use gave a positive opinion in September 2018, recommending a marketing authorisation be granted for galcanezumab 120 mg for use as prophylaxis of migraine in adults who have at least 4 migraine days per month.[6] The dose is presumed to be a single subcutaneous injection of 120 mg once every 4 weeks, as was used in the clinical trials. It is not clear as yet whether the higher dose has been recommended for marketing authorisation.

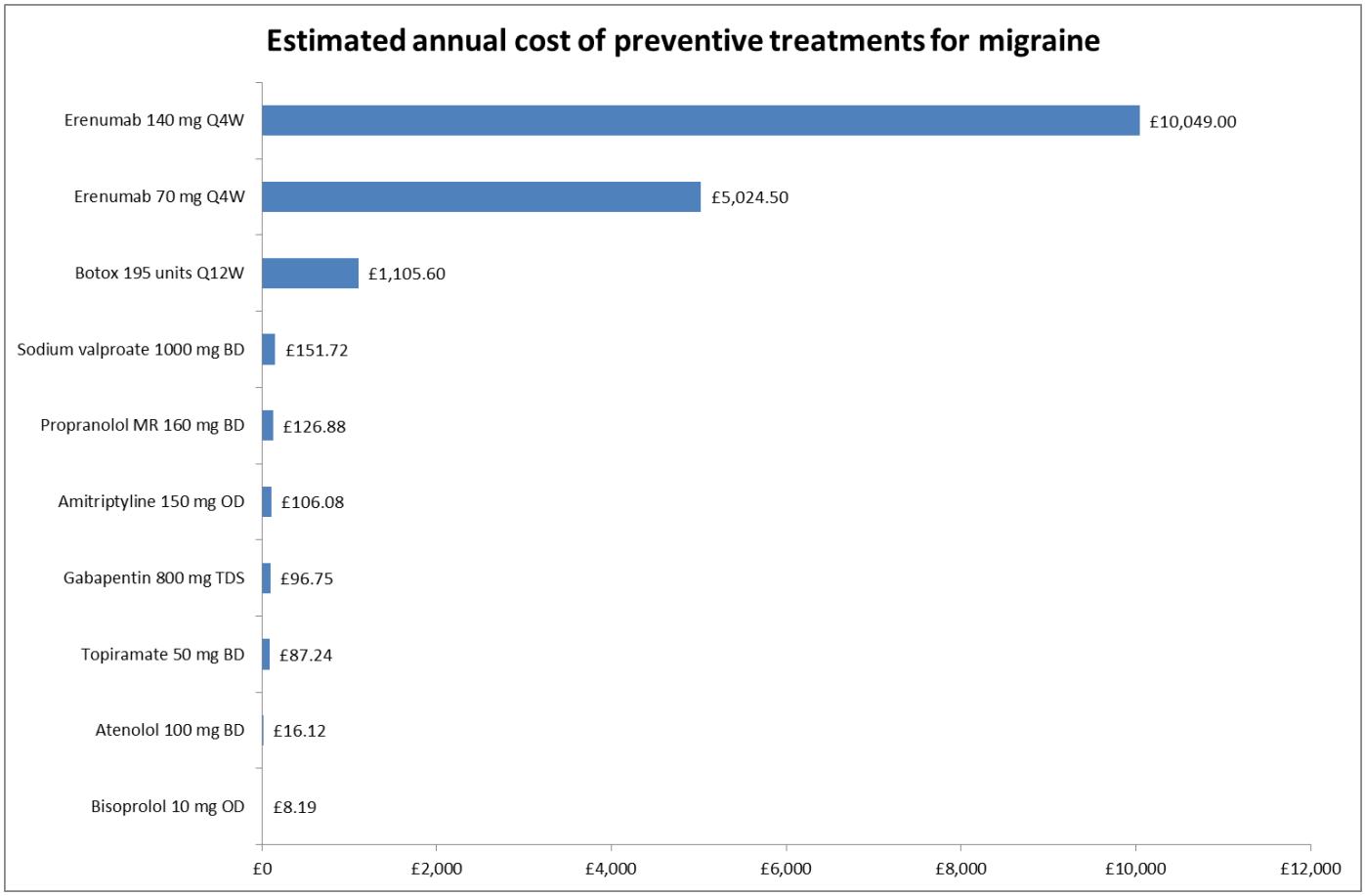
Cost analysis

Price

All prices exclude VAT, unless otherwise specified. The NHS list price of erenumab is £386.50 for one pre-filled pen, each containing a single 70 mg dose.[5] The total annual cost would therefore be £5,024.50 per patient (70 mg Q4W) or £10,049 (140 mg Q4W). It is not known whether any commercial agreements are planned to reduce the cost. Erenumab is intended for self-administration. The price for galcanezumab is not yet available but is expected to be similar.

For comparison, the most costly option for prophylaxis currently in routine use is Botox, which is licensed in chronic migraine only. Treatment is required once every 3 months, at a dose of around 155-195 units per administration.[13] Botox 200 units costs £276.40 per vial (totalling £1,106 per year) and is not tariff excluded in this indication.[5,29] The cost of an outpatient neurology attendance is estimated at £116-135 (2018/19 National Tariff, non-mandatory price for outpatient attendance with single or multiple professionals). One visit will be required for each administration.

Since the anti-CGRP antibodies have not been extensively trialled in patients currently using prophylactic treatments, it is not clear to what degree their use would allow discontinuation of preventive treatments. For illustrative purposes, costs of other preventive medicines are shown in the chart below.



NB: costs are for general comparison only and do not imply therapeutic equivalence. List is not exhaustive.

Pharmacoeconomic studies

Two pharmacoeconomic studies were located, both for the use of erenumab. Both were conducted using data from the USA

The first study estimated the incremental costs and quality-adjusted life-years (QALYs) associated with erenumab 140 mg from a US societal perspective and with a time horizon of 10 years.[30] The population was adults with episodic or chronic migraine who had previously failed treatment with at least one preventive therapy. It was assumed that, due to discontinuation, the mean duration of treatment was 2 years. The chosen comparator was acute migraine treatment only, since it was considered that patients starting erenumab were likely to have exhausted other options for migraine prevention. The study found that after 10 years erenumab 140 mg was associated with a gain of 0.185 QALYs and with 144 fewer migraine days compared to acute treatment alone.[30]

In the UK 2 years of erenumab treatment will cost £10,049-£20,098, depending on dose. Based on data from this study the incremental cost-effectiveness ratio for the UK is therefore an estimated £54,348 to £108,697 per QALY gained. This estimate is highly dependent on the NHS price of erenumab, and does not take into account any discounts or patient access schemes, reductions in use of other healthcare resources (e.g. acute treatments, emergency care, etc.), or losses due to reduced productivity associated with migraine. The ICER compared to continuing prophylactic treatment is likely to be higher, but can't be quantified.

The second economic analysis had a two year time horizon and took a US third-party payer perspective.[28] Separate models were produced for episodic and chronic migraine. The details of the base case (costs, migraine-free days and QALYs gained) are redacted, and the ICERs are rounded to the nearest $10,000. See table 10 below for ICERs. It should be noted that inputs to this model were heavily redacted in the published report, and it is not clear whether the assumed cost of care is comparable to that in the UK.

Table 10: Cost per QALY gained with treatment with erenumab 140 mg monthly (US setting)

	Episodic migraine	Chronic migraine
vs. placebo	$150,000	$90,000
vs. other preventive treatments	$395,000	$345,000
vs. other preventive treatments (incl. impact on productivity)	$110,000	$50,000

Points to consider

The likely target population for CGRP-specific antibodies is patients with significant disease burden despite standard care with the currently-available options. Current management of these patients will vary depending on their migraine subtype:

- Episodic migraine: oral preventive medicines, with or without acute treatments
- Chronic migraine: Botox every 12 weeks, with or without oral preventives and acute treatments.

Due to the design of the clinical trials it is not clear to what degree these existing treatments would be displaced if anti-CGRP antibodies were to be introduced.

The bulk of the clinical trial data comes from studies with low proportions of patients with previous use of preventive medicines. Patients with recent use of Botox were excluded entirely. The LIBERTY trial compared erenumab 140 mg to placebo in patients with previous failure of 2-4 prophylactic treatments. It showed a treatment effect, but a smaller proportion of patients achieved ≥50% reduction in migraine days than in the ARISE & STRIVE trials. This implies that patients with previous treatment failures may require the higher licensed dose of 140 mg every four weeks to receive benefit from treatment.

Erenumab may be more acceptable to patients than Botox, since it can be self-administered as a single injection each 4 weeks. By contrast Botox requires attendance at clinic every 3 months, and each treatment consists of multiple injections.

The SPC for erenumab states that consideration should be given to discontinuing treatment in patients who have shown no response after 3 months of treatment.[10] However, no definition of a clinical response is given. If the definition from the clinical trials is applied (≥50% reduction in monthly migraine days) then around 40% of patients are expected to respond.

The trial data on impact on quality of life are useful, but do not capture all of the relevant information. For example, it is not clear whether a patient with no reduction in number of migraine days or attacks may yet derive benefit in terms of reduced severity of symptoms. Data on headache intensity were collected as an exploratory endpoint in the erenumab trials, but not presented in any publication.[4]

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Appendix 1: Migraine Physical Function Impact Diary (MPFID)

Patients are asked to answer each question on a scale of 1 (without any difficulty) to 5 (unable to do).[15]

Impact on Everyday Activities domain

1. In the past 24 hours, were you able to do your usual household chores?
2. In the past 24 hours, were you able to do your usual activities outside your home? (For example, shopping or doing errands)
3. In the past 24 hours, were you able to keep to your daily routine or schedule?
4. In the past 24 hours, were you able to do activities that required you to concentrate?
5. In the past 24 hours, were you able to get yourself ready for the day?
6. In the past 24 hours, how much of the time did you avoid interacting with other people?
7. In the past 24 hours, how much of the time did you need to rest or lie down during your normal waking hours?

Physical Impairment domain

8. In the past 24 hours, overall, how difficult was it to do your usual activities?
9. In the past 24 hours, how much of the time did you have difficulty moving your head?
10. In the past 24 hours, how much of the time did you have difficulty moving your body?
11. In the past 24 hours, were you able to get out of bed?
12. In the past 24 hours, were you able to bend over?
13. In the past 24 hours, were you able to do your usual activities that required physical effort?

Appendix 2: Migraine-Specific Quality of Life Questionnaire Role Function-Restrictive domain (MSQ-R-FR)

Patients are asked to answer each question on a scale of 1 (none of the time) to 6 (all of the time).[31] Questions highlighted with bold text comprise the role function restrictive domain, which was used as a secondary outcome in the trials of galcanezumab.

1. **In the past 4 weeks, how often have migraines interfered with how well you dealt with family, friends and others who are close to you?**
2. **In the past 4 weeks, how often have migraines interfered with your leisure time activities, such as reading or exercising?**
3. **In the past 4 weeks, how often have you had difficulty in performing work or daily activities because of migraine symptoms?**
4. **In the past 4 weeks, how often did migraines keep you from getting as much done at work or at home?**
5. **In the past 4 weeks, how often did migraines limit your ability to concentrate on work or daily activities?**
6. **In the past 4 weeks, how often have migraines left you too tired to do work or daily activities?**
7. **In the past 4 weeks, how often have migraines limited the number of days you have felt energetic?**
8. In the past 4 weeks, how often have you had to cancel work or daily activities because you had a migraine?
9. In the past 4 weeks, how often did you need help in handling routine tasks such as every day household chores, doing necessary business, shopping, or caring for others, when you had a migraine?
10. In the past 4 weeks, how often did you have to stop work or daily activities to deal with migraine symptoms?
11. In the past 4 weeks, how often were you not able to go to social activities such as parties, dinner with friends, because you had a migraine?
12. In the past 4 weeks, how often have you felt fed up or frustrated because of your migraines?
13. In the past 4 weeks, how often have you felt like you were a burden on others because of your migraines?
14. In the past 4 weeks, how often have you been afraid of letting others down because of your migraines?

Appendix 3: Migraine Disability Assessment (MIDAS)

Patients are asked to provide an answer to each of the questions 1-5.[32] These answers are then summed to produce a score.

Scores indicate:

- 0-5 - little to no disability
- 6-10 - mild disability
- 11-20 - moderate disability
- ≥21 - severe disability.

Patients are also asked to answer questions A and B.

1. On how many days in the last 3 months did you miss work or school because of your headaches?
2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school.)
3. On how many days in the last 3 months did you not do household work (such as housework, home repairs and maintenance, shopping, caring for children and relatives) because of your headaches?
4. How many days in the last 3 months was your productivity in household work reduced by half of more because of your headaches? (Do not include days you counted in question 3 where you did not do household work.)
5. On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?

A. On how many days in the last 3 months did you have a headache? (If a headache lasted more than 1 day, count each day.)
B. On a scale of 0 - 10, on average how painful were these headaches? (where 0=no pain at all, and 10=pain as bad as it can be.)