Erenumab for the Prevention of Migraine, Including the Rationale, Findings and Clinical Implications of the LIBERTY Study

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Many migraine sufferers require preventative treatment to reduce the frequency of acute attacks; however, current therapeutic options for migraine prophylaxis are associated with low efficacy and/or tolerability. Monoclonal antibodies to the calcitonin gene-related peptide (CGRP) receptor, including erenumab, fremanezumab, galcanezumab and eptinezumab, have emerged as effective treatments for migraine prevention. Fremanezumab, galcanezumab and eptinezumab target the CGRP protein, while erenumab targets the canonical receptor. A growing body of clinical data supports their efficacy and safety. While long-term data are needed, these are the first preventative drugs based on the pathophysiology of migraine, and represent a major therapeutic advance.

Keywords

Calcitonin gene-related peptide, erenumab, migraine, monoclonal antibody

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Migraine is the most common neurological disorder and one of the most disabling health disorders worldwide, often occurring in working age, and in young adult and middle-aged women.[1] It is a debilitating condition that is hard to treat, can last anywhere from 4 hours to 3 days and has a substantial negative impact on quality of life.[2] Some patients treat their migraine attacks with drugs to relieve pain but, in some patients, the frequency, severity and impact on quality of life necessitates the use of preventive treatment to reduce the occurrence of acute attacks. However, in contrast to acute treatment, there are no specific treatments for migraine prophylaxis to date. A number of drugs are available, but all have been developed for other conditions, such as hypertension, depression or epilepsy. Currently available preventive therapies are associated with low adherence rates due to lack of efficacy and/or poor tolerability.[3]

Erenumab (Aimovig®, Novartis Pharma GmbH, Nuremberg, Germany) is a first-in-class human monoclonal antibody to the calcitonin gene-related peptide (CGRP) receptor, which is important in the pathophysiology of migraine.[4] It is highly selective and has a high biological half-life, requiring monthly subcutaneous injection, and no drug titration. The clinical development of erenumab involved a number of clinical trials. A phase II study and two phase III studies showed efficacy and safety in patients with episodic migraine,[5–7] and a randomised phase II trial showed efficacy and safety in patients with in chronic migraine (*Table 1*).[8] The effective reduction of monthly headache or migraine days due to treatment could be observed very early, after less than 1 month from the first dose. The 12-week, double-blind, phase IIIb LIBERTY study aimed to answer the question of where to fit erenumab into the treatment paradigm.[9] LIBERTY recruited patients who had failed 2–4 previous migraine therapies and were therefore considered difficult to treat. These represent the majority of migraine patients seen by neurologists in clinical practice, but who are often excluded from clinical studies.

A total of 246 patients were randomly assigned (1:1) to erenumab (140 mg, administered by subcutaneous injection) or placebo. At baseline, 39% of participants had previously unsuccessfully tried two preventive drugs, 93 (38%) had tried three and 56 (23%) had tried four. The primary endpoint was the proportion of patients achieving a reduction of at least 50% from baseline in monthly migraine days (MMDs) during weeks 9–12. At week 12, the proportion of patients achieving a reduction of at least 50% in MMDs in the erenumab group was almost three times that in the placebo group (30.3% versus 13.7%; odds ratio [OR] 2.7; p=0.002). A larger proportion of patients in the active treatment group than in the placebo group achieved a ≥75% rate (11.8% versus 4.0%; OR 3.2). A 100% response rate was seen in 5.9% of the treatment group compared with none in the placebo group. The safety and tolerability of erenumab were comparable to placebo. The safety profiles of erenumab and placebo were similar. The most frequent treatment-emergent adverse event was injection-site pain, which occurred in seven (6%) participants in both groups.[9] The tolerability of erenumab is good, which is reflected by low dropout rates in all erenumab clinical trials. As a result of these findings, erenumab received approval from the European Medicines Agency (EMA) in May 2019.

Table 1: Results of studies investigating the efficacy and safety of anti-CGRP antibodies

	Study type	Patient population	Efficacy findings	Safety findings
Erenumab	Phase II, n=483[7]	Aged 18–60 years with episodic migraine (4–14 MMDs)	Mean change in MMDs at week 12 was -3.4 (SE 0.4) days with erenumab 70 mg versus -2.3 (0.3) days with placebo (difference -1.1 days [95% CI -2.1 to -0.2], p=0.021). The mean reductions in MMDs with the 7 mg (-2.2 [SE 0.4]) and the 21 mg (-2.4 [0.4]) doses were not significantly different from that with placebo	AEs in 54% patients in placebo group, 50% patients in 7-mg group, 51% patients in the 21-mg group, and 54% in the 70-mg group. Most frequently reported AEs were nasopharyngitis, fatigue, and headache. Serious AEs in two patients, both unrelated to treatment. 3% had neutralising antibodies. No unusual vital signs, laboratory, or electrocardiogram findings
Erenumab	Phase II, n=667[8]	Aged 18–65 years with chronic migraine, defined as ≥15 headache days per month, of which ≥8 were migraine days	Erenumab 70 mg and 140 mg reduced MMDs versus placebo (both doses -6.6 days versus placebo -4.2 days; difference -2.5, 95% CI -3.5 to -1.4, p<0.0001)	AEs in 39%, 44% and 47% of placebo, 70-mg, and 140-mg groups, respectively. Most frequent were injection-site pain, upper respiratory tract infection, and nausea. Serious AEs in 2%, 3%, and 1%, none led to discontinuation. No clinically significant abnormalities in vital signs, laboratory results, or electrocardiogram findings were identified
Erenumab	Phase III, ARISE trial, n=570[6]	Aged 18–65 years with episodic migraine	Erenumab resulted in -2.9 days change in MMDs, compared with -1.8 days for placebo, ≥50% reduction in MMDs in 39.7% (erenumab) and 29.5% (placebo) of patients (OR 1.59; 95% CI 1.12, 2.27; p=0.010). Migraine-specific medication treatment days were reduced by -1.2 (erenumab) and -0.6 (placebo) days	Safety and adverse event profiles of erenumab were similar to placebo. Most frequent adverse events were upper respiratory tract infection, injection-site pain, and nasopharyngitis
Erenumab	Phase III, n=955[5]	Aged 18–65 years with episodic migraine	Number of MMDs was reduced by 3.2 in the 70-mg erenumab group and by 3.7 in the 140-mg erenumab group, compared with 1.8 days in the placebo group (p<0.001 for each dose versus placebo). ≥50% reduction in MMDs from baseline to weeks 13–24 in 43.3% of patients in the 70-mg erenumab group and 50.0% of patients in the 140-mg erenumab group, versus 26.6% in the placebo group (p<0.001 for each dose versus placebo)	Rates of adverse events were similar between erenumab and placebo. Constipation and muscle spasm were more frequent in the 140-mg group
Erenumab	Phase IIIb, LIBERTY trial, n=246[9]	Aged 18–65 years with episodic migraine and in whom previous treatment with 2–4 migraine preventives had been unsuccessful	At week 12, 30% patients in the erenumab group had a ≥50% reduction in MMDs, compared with 14% in the placebo group (OR 2.7; 95% CI 1.4–5.2; p=0.002)	Tolerability and safety profiles of erenumab and placebo were similar. Most frequent TEAE was injection-site pain, which occurred in seven (6%) participants in both groups
Eptinezumab	Phase II, n=174[19]	Aged 18–55 years with episodic migraine (5–14 migraine days per 28-day period)	Mean change in migraine days between baseline and weeks 5–8 was -5.6 (SD 3.0) for treatment group compared with -4.6 (SD 3.6) for the placebo group (difference -1.0; 95% CI -2.0 to 0.1; one-sided p=0.0306)	AEs in 57% of treatment group and 52% of placebo group. Most frequent AEs were upper respiratory tract infection (placebo 7% patients versus treatment 9%), urinary tract infection (5% versus 1%), fatigue (4% versus 4%), back pain (5% versus 4%), arthralgia (5% versus 1%), and nausea and vomiting (2% versus 4%). Six serious AEs unrelated to study drug. No differences in vital signs or laboratory safety data between the two treatment groups
Fremanezumab	Phase III, n=1,130[11]	Aged 18–70 years with chronic migraine, defined as headache of any duration or severity on ≥15 days per month and migraine on ≥8 days per month	Reduction in the average number of MMDs was 4.3 ± 0.3 with fremanezumab quarterly, 4.6 ± 0.3 with fremanezumab monthly, and 2.5 ± 0.3 with placebo (p<0.001 for both comparisons with placebo). ≥50% reduction in MMDs in 38% of the fremanezumab-quarterly group, 41% of the fremanezumab-monthly group, and 18% of the placebo group (p<0.001 for both comparisons with placebo)	Abnormalities of hepatic function in five patients in each fremanezumab group (1%) and three patients in the placebo group (<1%)

Table 1: Cont.

Fremanezumab	Phase III, n=875[13]	Aged 18–70 years with episodic migraine (6–14 headache days, with at least 4 migraine days, during 28-day pre-treatment period)	At 12 weeks, mean migraine days per month decreased from 8.9 to 4.9 days in the fremanezumab monthly dosing group, from 9.2 to 5.3 days in the fremanezumab single-higher-dose group, and from 9.1 to 6.5 days in the placebo group	Most common AEs that led to discontinuation were injection-site erythema (n=3), injection-site induration (n=2), diarrhoea (n=2), anxiety (n=2), and depression (n=2)
Fremanezumab	Phase IIIb FOCUS trial, n=838[12]	Aged 18–70 years with episodic or chronic migraine who had documented failure to 2–4 classes of migraine preventive medications in the past 10 years	Reductions in MMDs over 12 weeks versus placebo were -0.6 with quarterly fremanezumab and -4.1 with monthly fremanezumab (p<0.0001)	AEs were similar for placebo and fremanezumab. Serious AEs in 1% of 277 participants on placebo, <1% of 276 with quarterly fremanezumab, and 1% of 285 with monthly fremanezumab
Galcanezumab	Phase III, EVOLVE-1 trial, n=1,671[14]	Aged 18–65 years with episodic migraine, at least a 1-year history of migraine, 4–14 MMDs and a mean of at least 2 migraine attacks per month within the past 3 months	Treatment with galcanezumab significantly reduced MMDs (both doses p<0.001) by 4.7 days (120 mg) and 4.6 days (240 mg) compared with placebo (2.8 days) per 4 weeks over the entire 6-month trial period	No significant difference between treatment and placebo groups, discontinuation owing to AEs was <5% across all treatment groups
Galcanezumab	Phase III, n=410[15]	Aged 18–65 years with episodic migraine, 4–14 MMDs	Galcanezumab 120 mg significantly reduced MMDs compared with placebo (99.6% posterior probability -4.8 days; 90% BCI, -5.4 to -4.2 days versus 95% superiority threshold -3.7 days; 90% BCI, -4.1 to -3.2 days)	AEs reported by ≥5% of patients in at least one galcanezumab-dose group and more frequently than placebo, included injection-site pain, upper respiratory tract infection, nasopharyngitis, dysmenorrhoea, and nausea
Galcanezumab	Phase III, EVOLVE-2 trial, n=915[16]	Aged 18–65 years with episodic migraine	MMDs were reduced by 4.3 and 4.2 days by galcanezumab 120 and 240 mg, respectively, and 2.3 days by placebo	Both galcanezumab doses had significantly more injection-site reactions and injection-site pruritus, and the 240-mg group had significantly more injection-site erythema versus placebo
Galcanezumab	Phase III, REGAIN trial, n=1,113[17]	Aged 18–65 years with episodic migraine	Both galcanezumab dose groups significantly reduced MMDs compared with placebo (placebo -2.7, galcanezumab 120 mg -4.8, galcanezumab 240 mg -4.6; p<0.001 for each dose compared with placebo)	No clinically meaningful differences between galcanezumab doses and placebo except for a higher incidence of treatment-emergent injection-site reaction (p<0.01), injection-site erythema (p<0.001), injection-site pruritus (p<0.01), and sinusitis (p<0.05) in the galcanezumab 240-mg group relative to placebo

AEs = adverse events; BCI = Bayesian credible intervals; CGRP = calcitonin gene-related peptide; CI = confidence interval; MMDs = monthly migraine days; OR = odds ratio; SD = standard deviation; SE = standard error; TEAE = treatment-emergent adverse event.

The implications of these findings are important for clinical practice as, for the first time, clinicians and patients have the option of a drug based on the pathophysiology of migraine. Erenumab shows a low risk for drug–drug interactions and hepatotoxicity since it is metabolised by degradation into peptides and single amino acids,[10] an important consideration for patients using multiple medications.

Since the approval of erenumab, two other anti-CGRP monoclonal antibodies, fremanezumab (Ajovy®, Teva, Petah Tikva, Israel)[11–13] and galcanezumab (Emgality™, Eli Lilly, Indianapolis, IN, USA),[14–18] have received European Medicines Agency approval for migraine prevention, with a fourth agent, eptinezumab, in clinical development (*Table 1*).[19] The most important difference between the drugs is that fremanezumab, galcanezumab and eptinezumab target the CGRP protein, while erenumab targets the canonical receptor. The implications of this difference in terms efficacy and safety are not yet known. Importantly, to date, the LIBERTY,[9] FOCUS (fremanezumab)[12] and recent CONQUER (galcanezumab) trials[16] have included patients treated unsuccessfully with between two and four preventive treatments (*Table 1*). The efficacy of eptinezumab remains untested for patients with severe, treatment-resistant migraine.

There are potential limitations to the use of anti-CGRP antibodies. The duration of trials, to date, is not sufficient to determine the long-term effects of continuingly blocking CGRP or its receptor. CGRP is an ubiquitous peptide that is not only involved in migraine, but also in several other physiological processes.[20] Since this is a new drug class, continued monitoring of efficacy and safety, including production of toxic metabolites, and the production neutralizing antibodies, is important.[21] In the cardiovascular system, CGRP is present in nerve fibres that innervate blood vessels and the heart and are involved in the regulation of blood pressure.[22,23] Patients with cardiovascular and cerebrovascular disease were, therefore, excluded from clinical trials. Although no increased incidence of cardiovascular events was reported in the clinical

trial, further studies should examine the cardiovascular effects of the long-term, continuous blockade of the CGRP pathway.

One potential barrier to the widespread use of these agents is cost; the price of the drugs has to be taken into consideration when deciding whether to use CGRP antibodies as a prophylactic treatment and which patient groups to treat. The Institute for Clinical and Economic Review concluded that CGRP inhibitors are cost-effective in the long-term but could potentially have a significant impact on short-term health budgets.[24] The LIBERTY study has identified an important subgroup of migraine sufferers who will derive benefit from treatment, increasing its cost-effectiveness.

In summary, on the basis of current evidence, anti-CGRP antibodies have the potential to improve the lives of millions of people suffering from frequent migraines. Erenumab appears to be a particularly attractive option for patients with difficult-to-treat migraine who have high unmet needs and few treatment options. ❑

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