Erenumab in the treatment of migraine

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Practice points

- Erenumab is a novel migraine preventive therapy that does not require office visits and can be self administered by the patient in the comfort of their homes.
- The manufacturer of the drug can provide supplementary at-home training to the patients on how to use the self injector for drug administration.
- It is an ideal migraine therapy for patients with multiple comorbidities with documented evidence of cardiovascular safety and minimal gastrointestinal side effects.
- No initial blood work or lab tests are needed prior to the initiation of the therapy.
- In patients with severe refractory migraine, provider may start the patient on initial dose of 140 mg erenumab.
- Clinically, erenumab can be used as a first-line drug for migraine prophylaxis and does not require failure of prior migraine therapies.
- Providers must keep in mind that erenumab is a migraine preventive therapy, and patients may still require prescribed migraine abortive medications.
- Erenumab has no known drug–drug interactions and can safely be prescribed to patients on multiple medications.

Migraine is a highly prevalent neurological pain syndrome, and its management is limited due to side effects posed by current preventive therapies. Calcitonin gene-related peptide (CGRP) plays a crucial role in the pathogenesis of migraine. In recent years, research has been dedicated to the development of monoclonal antibodies against CGRP and CGRP receptors for the treatment of migraine. This review will focus on the first US FDA-approved CGRP-receptor monoclonal antibody developed for the prevention of migraine: erenumab. Two Phase II trials (one for episodic migraine and one for chronic migraine) and two Phase III trials for episodic migraine have been published demonstrating the efficacy and safety of erenumab in the prevention of migraine.

First draft submitted: 29 May 2018; Accepted for publication: 10 August 2018; Published online: 21 September 2018

Keywords: Aimovig™ • AMG 334 • CGRP • CGRP monoclonal antibody • CGRP receptor • erenumab • FDA-approved migraine treatment • migraine • migraine prophylaxis • new migraine treatment

Headache disorders are among the most prevalent neurologic disorders worldwide. Approximately 30% of adults in the age group 18–65 suffer from headache disorders and about 30% of these individuals have migraine [1]. In the USA, over 15% of adults aged 18 years and over suffer from migraine [2]. Migraine is usually described as recurrent headache disorder, with each pain episode lasting 4–72 h. The pain is typically described as pulsating, moderate to severe and unilateral in location. It is often accompanied by nausea and/or vomiting, photophobia and phonophobia [3]. Based on the chronicity and frequency of headache attacks, migraine may be classified into episodic and chronic migraine. Episodic migraine is defined as headache attacks for <15 days per month. Episodic migraine may progress to chronic migraine if the frequency of headache attacks increases to ≥15 days per month for 3 consecutive months [4].

In the Global Burden of Disease study 2016, migraine was reported to be the second highest cause of years lived with disability in the world [5]. Migraine accounted for 0.5% of all ambulatory care visits in 2010 across the USA and hence poses a significant economic impact [6]. Projected health-related burden in the USA was estimated to be US$11 billion in the year 2004 [7]. Annual health expenditure in 2010 was roughly US$1500 (episodic migraine treatment) and US$4100 (chronic migraine treatment) per person in the USA. In Europe, the reported
health expenditure was €500–1100 and €1600–3700 per person for episodic and chronic migraine treatment, respectively [8,9].

Considering the huge economic burden and disability that migraine poses, substantial resources are being devoted to the development of new migraine drug therapies. Depending on whether these medications are used as needed or daily, they may be categorized into abortive (rescue) and preventive (prophylactic) medications, respectively. Headache frequency primarily determines the strategy of treatment; low frequency headaches may be managed by abortive medications (e.g., triptans, analgesics, NSAIDS), while higher frequency headaches require the addition of preventive medications to decrease headache burden and to prevent conversion to chronic headaches [10,11]. A preventive medication regimen also helps to reduce the frequent use or overuse of abortive medications. To date, many drugs borrowed from different classes are used for the preventive treatment of migraine, such as β-blockers (e.g., propranolol), antiepileptics (e.g., valproate), tricyclic antidepressants (e.g., amitriptyline) and others [11]. However, because most of these drugs were originally designed for other clinical indications and have variable drug interactions, they may have side effects with prolonged use [12]. Therefore, there is a need for migraine-specific preventive drug therapies with minimal adverse effects and drug–drug interactions. Recent evidence suggests the involvement of calcitonin gene-related peptide (CGRP) in the pathogenesis of migraine [13–16]. Hence in the recent years research has been focused on developing CGRP targeting antibodies. This review will discuss the monoclonal antibody ‘erenumab (AMG 334)’: its development, mechanism of action, pharmacodynamics and pharmacokinetics.

Calcitonin gene-related peptide, its receptor & role in migraine

CGRP is a 37-amino acid peptide discovered as a consequence of alternative RNA processing of the calcitonin gene in 1982 by Amara et al. [17] Realization that CGRP was located in the neuronal tissue, especially in C sensory fibers, led to several studies with capsaicin to illustrate the role of CGRP in pain and inflammation [18,19]. CGRP exists in two forms, α-CGRP and β-CGRP, also known as CGRP I and II, respectively. α-CGRP is predominantly expressed in the CNS and peripheral nervous system, whereas β-CGRP is found mainly in the enteric nervous system [15,20]. The structure of human CGRP consists of four domains: the first seven residues of the NH2 terminus form the first domain in a ring like structure; the second domain consists of an α helix formed by residues 8–18; the third domain of CGRP is either a β or γ twist formed by residues 19–27; and the fourth and last domain is formed by the COOH terminus and remaining residues from 28 to 37 [21–23].

CGRP receptor

In humans, the CGRP receptor complex is composed of three subunits. The functional CGRP receptor subunit is called calcitonin receptor-like protein or CLR, which was first described in the early 1990’s [24,25]. CLR alone was found to be unresponsive to CGRP until co-expressed with a protein called receptor activity-modifying protein or RAMP [26]. Three RAMPs are now known: RAMP1, RAMP2 and RAMP3. The affinity to CGRP is determined by which RAMP is co-expressed with CLR [27]. Dimerization of CLR and RAMP1 creates a receptor with high affinity for CGRP, while CLR and RAMP2 create a receptor for adrenomedullin (AM1 receptor). RAMP3 with CLR forms another adrenomedullin receptor (AM2) with some affinity for CGRP [28,29]. CLR is a widely expressed protein and hence CGRP bioactivity in various tissues is determined by expression of RAMP [30]. An additional third protein has been described for optimal functioning of the CGRP receptor, called receptor component protein. Although receptor component protein does not affect CGRP binding to its receptor, it is essential in optimum signal transduction and cAMP generation [31–34].

CGRP & migraine

The pathophysiology of migraine is complex and has been debated for years. The prevailing theory for many years was that migraine is primarily a vascular disorder, and the dilation of cerebral and meningeal arteries caused the associated pain [35]. Initially the role of CGRP in migraine was attributed to its vasodilating action at the level of intracranial arteries [15]. This theory was further supported by the fact that the human dural and cerebral arteries express relatively high levels of CGRP and CGRP receptors [36–38]. However, in recent years, the trigeminovascular pathway has been implicated in the pathogenesis of migraine [39,40]. CGRP is the most abundant neuropeptide in the trigeminal nerve [41,42]. CGRP is thought to be involved in the transmission of nociceptive information from the trigeminal ganglion to the brainstem and then to higher order regions involved in pain processing [43]. CGRP has been implicated in both peripheral and central sensitization of migraine [44,45]. Glial cells surrounding
the trigeminal ganglia are thought to contribute to peripheral sensitization of migraine [46]. CGRP contributes to neuronal sensitization via nitric oxide and proinflammatory cytokine release from these glial cells [46,47]. In the dura, CGRP may also contribute to neurogenic inflammation by causing vasodilation, plasma protein leakage from blood vessels, and secretion of histamine and proinflammatory cytokines from mast cells [48,49].

The role of CGRP in migraine has further been supported by several physiological studies. Intravenous infusion of CGRP has been shown to induce migraine-like attacks in migraine patients [50,51]. Increased CGRP serum levels have been found interictally in patients with episodic and chronic migraine [52,53]. Triptans and botulinum toxin have been shown to decrease serum CGRP levels during and in between migraine attacks [54,55]. Elevated salivary levels of CGRP during migraine attacks have been observed, and their reduction with botulinum toxin and triptan administration has also been demonstrated [56,57]. Based on these findings, CGRP was made the focus for new migraine treatment and preventive therapies.

**CGRP receptor antagonists (gepants) as migraine therapy**

Multiple attempts have been made in the past by pharmaceutical companies to develop a suitable CGRP receptor antagonist for the treatment of migraine. Boehringer Ingelheim developed the first selective nonpeptide CGRP receptor antagonist, BIBN4096BS (olcegepant) for the treatment of migraine [58]. In a Phase II study published in 2004, the response rate of olcegepant was found to be 66 versus 27% for placebo (p = 0.001) [59]. Even though the compound was potent in the treatment of migraine, it could only be administered by intravenous infusion due to its large molecular weight and low bioavailability [59,60]. Due to this limitation and the unpredictable nature of migraine, it was a neither a practical nor a commercially viable option for migraine treatment. Merck & Co. developed an orally bioavailable drug referred to as Compound 2, which displayed modest affinity for the human CGRP receptor (Ki = 4.8 μM) [61]. With further optimization a more potent molecule, telcagepant (MK-0974), was developed with a higher affinity of Ki = 0.8 nM. This became the first orally bioavailable drug to be tested clinically [62,63]. It was tested in a large randomized, placebo-controlled, double-blind trial of 1380 patients receiving telcagepant. The 300 mg dosage of telcagepant was found to be more effective than placebo for the treatment of acute migraine, and had fewer side effects compared with zolmitriptan [64]. Telcagepant was tested in other randomized, double-blind, placebo-controlled trials and was found to be more effective than placebo in treatment of acute migraine even at lower dosages [65,66]. A clinical trial (NCT00797667) where 140 or 280 mg telcagepant was administered twice daily for 3 months for migraine prophylaxis was terminated early secondary to two patients having symptomatic elevation of transaminase levels. In 2011, Merck stopped development of telcagepant secondary to concerns about liver toxicity with the drug [67]. Merck developed another orally bioavailable drug, MK-3207, which was found to be more potent than telcagepant for the treatment of acute migraine [68]. This drug was tested in a multicenter, double-blind, randomized, placebo-controlled study, which showed superior 2 h pain freedom in migraine patients when compared with placebo [69]. However, secondary to concerns for liver toxicity, Merck discontinued development of MK-3207. Bristol-Myers Squibb started developing BMS-694153, a drug that demonstrated high affinity for the human CGRP receptor and a favorable predictive toxicology profile. However, no clinical data have been published so far for this drug [70]. Ubrogepant (MK-1602) is another orally available small molecule antagonist of the CGRP receptor for the treatment of acute migraine. A Phase IIb, multicenter, randomized, double-blind, placebo-controlled trial demonstrated a positive dose response for 2 h pain freedom, and when compared with placebo, the 100 mg dose demonstrated increased pain freedom (25.5% for ubrogepant and 8.9% for placebo) [71]. Results of the Phase III, multicenter, randomized, double-blind, placebo-controlled trial, (NCT02828020; ACHIEVE I), were presented at the 70th American Academy of Neurology annual meeting in Los Angeles. Sixteen hundred and seventy-two adult patients with a history of migraine (with or without aura) were randomized in a 1:1:1 ratio to placebo, ubrogepant 50 mg or ubrogepant 100 mg. At 2 h post initial dose, the percentage of ubrogepant-treated patients achieving pain freedom was significantly greater than those treated with placebo (50 mg: 19.2%, p = 0.0023; 100 mg: 21.2%, p = 0.0003; placebo: 11.8%) [72]. Rimegepant (BMS-927711) is another CGRP receptor antagonist that remains in clinical development for the treatment of acute migraine. A single double-blind, randomized, placebo-controlled, dose-ranging trial has been reported exploring rimegepant at 10, 25, 75, 150, 300 and 600 mg or sumatriptan at 100 mg [73]. The primary end point of the study was achieving pain freedom 2 h after the migraine attack. Patients receiving sumatriptan (35%) and those in the rimegepant 150 mg group (32.9%) showed the maximal efficacy in achieving the primary end point when compared with placebo (15.3%). Patients receiving rimegepant 75 (31.4%) and 300 mg (29.7%) also had significantly increased pain freedom at 2 h; however, the higher dose of 600 mg had no significant effect (~25%). Even though both
ubrogepant and rimegepant are promising CGRP receptor antagonists for treatment of acute migraine, they have not been clinically tested as a migraine preventive therapy. Erenumab/AMG 334 is the first drug of its class to be the US FDA approved for the prevention of migraine and is the focus of this review.

**Erenumab**

**Development, pharmacodynamics & pharmacokinetics**

Effective CGRP receptor blockade by an antibody requires it to successfully span the distance between CLR-RAMP1 receptor subunits on the CGRP receptor complex [74]. An antibody must have a long half-life and must be highly selective for the CGRP receptor. Erenumab is such an antibody with a favorable pharmacokinetic/pharmacodynamic profile. Shi et al. first described the development and pharmacological characteristics of AMG 334 [75]. Xenomice were immunized with purified soluble CGRP receptor protein as antigen, and human CLR and RAMP1 receptor polypeptides were generated by transiently cotransfecting 293 6E cells. After hybridomas were generated using sera titer of mice, AMG 334 was identified through screening assays looking at binding competition data, functional blocking and receptor selectivity against the human CGRP receptor. [125I]-CGRP radio ligand was used to study the binding affinity of AMG 334. Agonist and antagonistic activities of AMG 334 were measured using functional cAMP accumulation and SK-N-MC (human neuroblastoma) cells, which endogenously express CGRP receptors [76]. Receptor specificity of AMG 334 was studied using human embryonic kidney cells, Chinese hamster ovary cells and human MCF-7 epithelial cells, which stably express human adrenomedullin-1, adrenomedullin-2 and amylin receptors, respectively.

AMG 334 was found to be highly selective for the human CGRP receptor [75]. It inhibited binding of [125I]-CGRP to human CGRP receptors expressed on SK-N-MC cells with Ki (the concentration of the inhibitor required to produce half maximum inhibition) of 0.02 nM and inhibited CGRP-induced cAMP accumulation with an IC$_{50}$ (concentration of inhibitor required to decrease agonist binding by half) of 2.3 nM. No agonist or antagonist activity was seen at the human adrenomedullin, calcitonin and amylin receptors even at the highest concentration tested (10 µM). Efficacy of AMG 334 was assessed using capsaicin-induced dermal blood flow (CIDBF): dose-response study design where the lowest dose to produce statistically significant effect was found to be 0.3 mg/kg on day 2 (p = 0.05) but not day 4 (p = 0.17). 3 mg/kg produced maximal response on day 2 (p = 0.0098) and on day 4 (p = 0.012). ED$_{50}$ ('median effective dose' producing quantal effect in 50% of the population) for erenumab was estimated to be 0.15 and 0.25 mg/kg at days 2 and 4, respectively, with a 95% CI.

AMG 334 is not eliminated via hepatic, renal or biliary processes, which reduces the burden of drug–drug interactions by not competing with the other drugs using these elimination pathways [77,78]. Xu et al. first demonstrated this by studying the interaction between erenumab and oral contraceptives [79]. A total of 22 study subjects received norgestimate/ethinyl estradiol containing oral contraceptives over three 28-day cycles. The subjects received a single 140 mg subcutaneous (sc.) dose of erenumab on day 10 of cycle three. 24-h pharmacokinetic profiles (peak plasma concentration and area under the concentration–time curve) of norgestimate metabolites and ethinyl estradiol were compared on day 21 of cycles two and three, and were found to be similar. Luteinizing hormone, follicular-stimulating hormone and progesterone concentrations were also measured and found to be similar.

Vu et al. published one of the first Phase I studies for erenumab characterizing its pharmacokinetics and inhibitory effects [80]. CIDBF data pooled from the single- and multiple-dose study in healthy and migraine subjects were used as a biomarker. Both single ascending dose and multiple ascending dose studies were double-blind, placebo-controlled studies enrolling 60 and 48 subjects, respectively. A population analysis was conducted using a nonlinear mixed-effects modeling approach. The mean sc. absorption time was approximately 2 days. The estimated absorption half-life was 1.6 days, and the estimated sc. bioavailability for erenumab was 74% (95% CI: 66–85%). Erenumab exhibited target-mediated drug disposition behavior with a slow nonspecific elimination pathway through the hepatic reticuloendothelial system (i.e., linear clearance) and a rapid saturable elimination pathway (i.e., nonlinear clearance) mediated by degradation or internalization of the erenumab-receptor complex. A population estimate of linear clearance remained approximately 0.214 l/day (95% CI: 0.191–0.243) and was independent of erenumab concentration. Nonlinear clearance was dependent on erenumab concentration. Erenumab was highly potent in inhibiting CIDBF with an IC$_{50}$ of 255 ng/ml or 1.7 nm (95% CI: 115–395 ng/ml). Maximal CIDBF inhibition estimated by modeling was 89% (95% CI: 87.3–91.4). It was concluded that erenumab potently inhibited CIDBF in both healthy and migraine subjects, and its pharmacokinetics was favorable for erenumab to serve as a migraine preventive therapy. De Hoon et al. published results from two Phase I studies assessing safety, pharmacokinetics and pharmacodynamics of erenumab [81]. Erenumab underwent...
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Drug Evaluation

Table 1. Erenumab in migraine: Phase II studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion criteria</th>
<th>Dose, administration, frequency</th>
<th>Primary end point</th>
<th>Results active/placebo</th>
<th>Common adverse events</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun et al.</td>
<td>Episodic migraine</td>
<td>7, 21, 70 mg sc. once/month</td>
<td>Week 9–12 vs baseline change in MMD</td>
<td>70 mg vs placebo</td>
<td>Nasopharyngitis, fatigue and headache</td>
<td>[82]</td>
</tr>
<tr>
<td>Tepper et al.</td>
<td>Chronic migraine</td>
<td>70 and 140 mg sc. once/month</td>
<td>Week 9–12 vs baseline change in MMD</td>
<td>70 mg, 140 mg vs placebo</td>
<td>Injection site pain, upper respiratory tract infection and nausea</td>
<td>[83]</td>
</tr>
</tbody>
</table>

MMD: Monthly migraine days; sc.: Subcutaneous.

Table 2. Erenumab in migraine: Phase III studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion criteria</th>
<th>Dose, administration, frequency</th>
<th>Primary end point</th>
<th>Results active/placebo</th>
<th>Common adverse events</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goadsby et al.</td>
<td>Episodic migraine</td>
<td>70 and 140 mg sc. once/month × 6 months</td>
<td>Month 4–6 vs baseline change in MMD</td>
<td>70 mg, 140 mg vs placebo</td>
<td>Nasopharyngitis, upper respiratory tract infection, sinusitis</td>
<td>[84]</td>
</tr>
<tr>
<td>Dodick et al.</td>
<td>Episodic migraine</td>
<td>70 mg sc. once/month</td>
<td>Week 9–12 vs baseline change in MMD</td>
<td>70 mg vs placebo</td>
<td>Upper respiratory tract infection, injection site pain, influenza, fatigue, nausea, migraine</td>
<td>[85]</td>
</tr>
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</table>

MMD: Monthly migraine days; sc.: Subcutaneous.

nonlinear clearance for doses ranging from 1 to 70 mg and linear clearance for doses ranging from 70 to 210 mg. Single erenumab doses resulted in >75% inhibition of CIDBF, with no apparent dose dependency for subjects receiving erenumab doses ≥21 mg. De Hoon et al. concluded that erenumab had an acceptable efficacy and safety profile to be a potential drug for migraine prevention.

Efficacy & safety profile

Several Phases II (Table 1) and III studies (Table 2) have been published assessing the efficacy and safety profile of erenumab in migraine. Sun et al. reported the results from one of the first multicenter, randomized, double-blind, placebo-controlled, Phase II clinical trials (NCT01952574) [82]. The study included 483 patients with episodic migraine, ages 18–60 years, who experienced 4–14 migraine days per month. They were randomly assigned in a 3:2:2:2 ratio to monthly sc. placebo (160), 7 mg (108), 21 mg (108) and 70 mg (107) erenumab, respectively. The primary end point was mean change in monthly migraine days (MMD) from baseline to the last 4 weeks of the 12-week double-blind treatment phase. These results were compared with the placebo response. A difference of -1.1 days in the MMD was found between placebo and 70 mg erenumab (-2.3 ± 0.3 vs -3.4 ± 0.4 days, respectively [95% CI: -2.1 to -0.2], p = 0.021). However, the 7 and 21 mg erenumab doses produced mean changes of -2.2 ± 0.4 and -2.4 ± 0.4 in MMD, which was comparable to placebo. The most frequently reported adverse events were nasopharyngitis, fatigue and headache. In the 7-mg group, one patient reported a ruptured ovarian cyst. One patient in the 70-mg group reported having migraine and vertigo. All of these adverse events were found to be unrelated to the active drug. The 70-mg dose of erenumab was found to be an effective therapy for the prevention of episodic migraine, since, erenumab was found to be comparable to placebo at dosages 7 and 21 mg.

Interim results of an ongoing open-label extension of the Phase II clinical trial (NCT01952574) were published reporting efficacy of erenumab in episodic migraine [86]. 383 of the 472 patients that were enrolled in the 12-week, double-blind, placebo-controlled treatment phase of the parent clinical trial continued in an open-label extension receiving erenumab 70 mg sc. every 4 weeks for up to 5 years. The analysis examined the reported answers from the headache impact test (HIT-6), migraine-specific quality of life and migraine disability assessment. Mean (standard deviation) MMDs were 8.8 (2.6), 6.3 (4.2) and 3.7 (4.0) at baseline, 12-week and 64 weeks, respectively. Erenumab 70 mg showed efficacy in reducing MMDs over time in the study subjects. The mean (standard deviation) HIT-6 total score reduction was 8.5 (60.2 [6.3] at baseline vs 51.7[9.2]) at 64 weeks. Migraine-specific quality of life and migraine disability assessment improvements were maintained from baseline through week 64. A single event of arteriosclerosis and myocardial ischemia was reported in the open-label extension study and was determined to
be unrelated to erenumab treatment. CGRP is known to decrease mean-arterial pressure, and CGRP antagonists can result in hypertension, theoretically putting patients at risk for cardiovascular events [87]. De hoon et al. presented another Phase I study at the 69th American Academy of Neurology meeting in Boston as an abstract. They demonstrated that concomitant administration of intravenous erenumab 140 mg with sc. sumatriptan had no effect on baseline blood pressure compared with sc. sumatriptan alone [88]. Deppe et al. published the results of a randomized, double-blind, placebo-controlled study in 80 patients to demonstrate the effects of erenumab on exercise time during a treadmill test in patients with stable angina [89]. In this study an exercise treadmill test was conducted following single intravenous infusion of erenumab 140 mg or placebo and a safety follow-up was conducted after 12 weeks. The primary end point of the study was the change from baseline in exercise duration as measured by total exercise time. Total exercise time change from baseline in the erenumab group was found to be noninferior to the placebo group. No significant difference was found between erenumab and placebo groups when evaluated for time to exercise-induced angina and time to onset of ≥1 mm ST-segment depression. Deppe et al. concluded that erenumab did not adversely affect exercise time in a high cardiovascular risk population of patients. This study reinforced the cardiovascular safety profile of erenumab.

Tepper et al. published the Phase II randomized, double-blind, placebo-controlled, multicenter study (NCT02066415) demonstrating the effectiveness of erenumab in 667 patients with chronic migraine [83]. In this study, patients were randomly assigned to receive either sc. placebo (n = 286), 70 mg erenumab (n = 191) or 140 mg erenumab (n = 190) given every 4 weeks for 12 weeks. The change in MMDs from the baseline to the last 4 weeks of the 12-week period (weeks 9–12) was the primary end point. Patients that received 70 or 140 mg of erenumab demonstrated a significant reduction in MMDs in comparison to placebo (both doses -6.6 days vs placebo -4.2 days; difference -2.5, 95% CI: -3.5 to -1.4; p < 0.0001). The most frequent adverse events reported were injection site pain, upper respiratory tract infection and nausea. The incidence of adverse events was similar in all three groups. Tepper et al. concluded that erenumab 70 and 140 mg could be a potential therapy for migraine prevention. Ashina et al. presented the subgroup analysis of this trial as an abstract at the International Headache Society meeting held in 2017. The changes in MMDs, acute migraine-specific medication days (MSMD) and proportion of patients achieving ≥50% reduction in MMDs were analyzed in chronic migraine (CM) patients with and without aura. Erenumab was found to work with similar efficacy in chronic migraine patients with and without aura [90]. The efficacy of erenumab in chronic migraine patients with medication overuse was demonstrated in another subgroup analysis of the clinical trial (NCT02066415) [91]. Compared with placebo, erenumab 70 and 140 mg groups had a greater reduction in MMDs at week 12 (least-squares [LS] mean standard error [SE]): -3.5 [0.6] vs -6.6 [0.7] and -6.6 [0.7]; p < 0.001 for both) and a greater reduction in acute migraine-specific medication days (LS mean [SE]: -2.1 [0.5] vs -5.4 [0.6] and -4.9 [0.5]; p < 0.001 for both doses).

Reuter et al. then conducted a subgroup analysis of the Phase II clinical trial (NCT02066415) to evaluate the efficacy of erenumab prior to week 4 [92]. A ≥50% reduction in weekly migraine days was observed in both 70 and 140 mg dosage groups by week 1 (26% patients for both doses vs 16% for placebo; p ≤ 0.011), increasing in week 2 to 31, 41 and 21% in the 70 mg, 140 mg and placebo groups, respectively (p < 0.011). Reductions in weekly migraine days from baseline were observed in weeks 1–4 in both treatment groups, 70 mg (-1.5 to -0.9 days [4.5 at baseline]) and 140 mg (-0.8 to -0.5 days [4.5 days at baseline]) versus placebo (-0.8 to -0.5 days [4.6 days at baseline]); week 1: 70 mg, p = 0.047, 140 mg, p = 0.18; weeks 2–4: p ≤ 0.002 for both doses versus placebo.

Goadsby et al. reported the results of the pivotal STRIVE “The study to evaluate the efficacy and safety of erenumab in migraine prevention’ study (NCT02456740), an international, Phase III, multicenter, randomized, double-blind, placebo-controlled, 24-week study that evaluated the safety and efficacy of erenumab in the prevention of episodic migraine [94]. 955 patients were randomized in 1:1:1 ratio to receive once monthly sc. placebo (n = 319), sc. 70 mg erenumab (n = 317) or sc. 140 mg erenumab (n = 319) for 6 months. Key inclusion criteria included a history of migraine, with 4–14 migraine days per month and <15 headache days per month. Key exclusion criteria included the failure of more than two migraine preventive medications from different categories due to lack of efficacy. The primary end point was change in mean MMDs from baseline to months 4 through 6. Secondary end points were ≥50% reduction in mean MMDs, change in number of days of use of acute migraine-specific medications (AMSM), and change in scores on the physical-impairment and everyday activities domains of the migraine physical function impact diary (MPFID). Erenumab was superior to placebo in achieving the primary end point. The baseline MMD for all three groups was 8.3; reduction in mean MMDs with 70 mg erenumab versus placebo (-3.2 ± 0.2 vs -1.8 ± 0.2 days, respectively [95% CI: -1.9 to -0.9], p < 0.001), and with 140 mg erenumab versus placebo (-3.7 ± 0.2 vs -1.8 ± 0.2 days, respectively [95% CI: -2.3 to -1.4], p < 0.001).
also showed superiority over placebo in achieving all secondary end points; a ≥50% reduction in mean MMDs for 70 and 140 mg erenumab was seen in 43.3 and 50% patients, respectively, versus 26.6% in the placebo group (p < 0.001 for each dose vs placebo). The changes in AMSM days from baseline were -1.1 ± 0.1 and -1.6 ± 0.1 for 70 and 140 mg dose, respectively, versus -0.2 ± 0.1 for placebo (p < 0.001 for both doses vs placebo). Patients reported improved outcomes on MPFID physical-impairment (PI) score and MPFID everyday activities (EA) score. Reductions of 5.5 (70 mg) and 5.9 days (140 mg) were reported in MPFID-EA scores versus 3.3 days in the placebo group. Reductions of 4.2 (70 mg) and 4.8 days (140 mg) were reported in MPFID-PI scores versus 2.4 days in the placebo group (p < 0.001). The most frequently reported adverse events during the study were nasopharyngitis, upper respiratory tract infections and sinusitis. The safety profile of erenumab was found to be similar to placebo.

Dodick et al. reported results of the 12-week ARISE (a Phase III, randomized, double-blind, placebo-controlled, study to evaluate the efficacy and safety of erenumab in migraine prevention) study (NCT02483585) of 577 patients evaluating the efficacy of 70 mg erenumab versus placebo in episodic migraine (NCT02483585) of 577 patients evaluating the efficacy of 70 mg erenumab versus placebo in episodic migraine [85]. Key inclusion criteria included a history of migraine (with or without aura) for at least 12 months, with 4 to 14 migraine days per month and <15 headache days per month. Key exclusion criteria included patients with a history of cluster headache or hemiplegic migraine and the failure of more than two migraine preventive medications from different categories due to lack of efficacy. Five hundred and seventy patients were included in the efficacy analysis, and the primary end point was change in MMDs. Secondary end points were ≥50% reduction in mean MMDs, change in number of days of use of AMSM, and ≥5-point reduction in MPFID-PI and MPFID-EA scores. Reduction in mean MMDs in placebo versus 70 mg erenumab was -1.8 ± 0.2 versus -2.9 ± 0.2, respectively (p < 0.001). Erenumab was found to be superior to placebo in reducing AMSM days and achieving a ≥50% reduction in mean MMDs; however, patient reported outcomes including MPFID-PI and MPFID-EA between erenumab and placebo were not statistically different. Change in AMSM days from baseline in placebo versus erenumab was -0.6 ± 0.1 versus -1.2 ± 0.1 days, respectively (p = 0.002). A ≥50% reduction in mean MMDs was reported in 29.5 and 39.7% patients, respectively, in the placebo and the erenumab groups (p = 0.01). The most common adverse events reported during the study were found to be similar in both groups, and included upper respiratory tract infection, injection site pain, influenza, fatigue, nausea and migraine.

Another 12-week randomized, double-blind, placebo-controlled, multicenter, Phase III clinical trial (NCT03096834/CAMG334A2301/LIBERTY trial) was recently completed (18 January 2018) by Novartis Pharmaceuticals with an enrollment of 246 episodic migraine patients [93]. Key inclusion criteria were 4–14 migraine days per month, documented history of episodic migraine in the 12 months prior to screening, and failure of two to four migraine preventive therapeutics. Key exclusion criteria included a history of cluster headache or hemiplegic migraine, an active chronic pain syndrome, and evidence of seizure or psychiatric disorders. The primary end point of the study was ≥50% reduction in mean MMDs in weeks 9–12 from baseline. Secondary end points included change in mean MMDs, change in number of days of use of AMSM, change in scores on the physical-impairment and everyday activities domains of the MPFID, percentage of patients with ≥75 and 100% response (assessed via patient reported data collected in the headache e-diary) from baseline to weeks 9–12 of treatment. Results of the LIBERTY trial were presented at the 70th American Academy of Neurology annual meeting, 2018 in Los Angeles, CA, USA. At baseline, 38.6% patients had failed two, 37.8% patients failed three and 22.8% patients had failed four prior migraine therapies. These patients were randomized into two groups in a 1:1 ratio (140 mg erenumab vs placebo). At week 12, the proportion of patients achieving ≥50% reduction in MMDs was higher in the 140 mg erenumab group (30.3% [erenumab 140 mg] vs 13.7% [placebo]; p = 0.002). Also, erenumab 140 mg group showed greater reductions in MMDs and MSMDs when compared with the placebo group (mean difference [95% CI] in MMD: -1.61 [-2.70, -0.52]; p = 0.004; mean difference [95% CI] in MSMD: -1.73 [-2.46, -1.01]; p < 0.001). Adverse events reported in the erenumab group were similar to placebo [94].

**Conclusion, FDA approval & post-approval marketing**

Erenumab is currently the only available FDA-approved CGRP receptor antagonist and has proven to be an effective preventive therapy for both episodic and chronic migraine. It has been shown to have a superior pharmacokinetic and pharmacodynamic profile compared with the small molecule gepants, which makes it a desirable migraine preventive medication. Administering this drug once monthly makes compliance among migraineurs easy, a challenge faced by other migraine preventive drugs. It has no hepatotoxic side effects as were seen with the older gepants. In all of the Phases II and III trials conducted so far, the safety profile of erenumab was found to be
similar to placebo. The efficacy of erenumab in prevention of episodic and chronic migraine has been sufficiently demonstrated in Phases II and III clinical trials. However, there is a paucity of data for its use in patients with comorbidities, including chronic painful syndromes such as fibromyalgia.

There is a need for Phase IV trials to assess the effectiveness of erenumab as a treatment option for patients with chronic migraine who also experience chronic painful syndromes. Moving forward, it is also important to understand any long-term or rare side effects that the drug may have.

Erenumab received approval from the FDA on 17th May 2018 to be marketed as a migraine preventive therapy. This was a landmark step in migraine management, as erenumab became the first monoclonal antibody drug to be specifically approved for migraine prevention. The drug is currently co-marketed by Amgen and Novartis in the USA and will be available under the brand name Aimovig (Erenumab/AMG 334) by the end of May 2018. Aimovig 70 or 140 mg is self-administered sc., once monthly via Amgen's device, the SureClick® autoinjector. The US list price of Aimovig is US$575 for once monthly 70 or 140 mg single-use prefilled SureClick autoinjector(s), or US$6900 annually [95]. Erenumab is a novel migraine preventive medication and is the first new therapy made available to migraineurs in over a decade. It has shown tremendous potential in preventing migraine attacks and can significantly reduce global healthcare expenditure and headache-related disability.

Financial & competing interest disclosure
No funding was received for the preparation of this review. H Yuan has received honoraria from Supernus Pharmaceuticals; N Spare has received honoraria from Supernus Pharmaceuticals and Amgen; S D Silberstein has received honoraria from Alder Biopharmaceuticals; Allergan, Inc.; Amgen; Avanir Pharmaceuticals, Inc.; Curelator, Inc.; Depomed; Dr. Reddy's Laboratories; eNeura Inc.; electroCore Medical, LLC; IpsenBiopharmaceuticals; Lilly USA, LLC; Medscape, LLC; Medtronic, Inc.; Mitsubishi Tanabe Pharma America, Inc.; NINDS; St. Jude Medical; Supernus Pharmaceuticals, Inc.; Teva Pharmaceuticals; and Trigemina, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Company review
In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the author at their discretion and based on scientific or editorial merit only. The author maintained full control over the manuscript, including content, wording and conclusions.

References
Papers of special note have been highlighted as: ● of interest; ●● of considerable interest


- Provides an eloquent review of mechanism of calcitonin gene-related peptide in migraine and helps in better understanding on how calcitonin gene-related peptide receptor antagonist would help in migraine treatment.


62. Salvatore CA, HERSHEY JC, Corcoran HA et al. Pharmacological characterization of MK-0974 [N-[3R)-6,6-(2,3-difluorophenyl)-2-oxo-1-(2,2,2-trifluoroethyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide], a potent and powerful CGRP receptor antagonist for the acute treatment of migraine.

Erenumab in the treatment of migraine

Drugs Evaluation


