


Erenumab: A First-in-Class Monoclonal Antibody for Migraine Prevention

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Abstract

Objective: To review the pharmacology, efficacy, and safety of the calcitonin gene-related peptide (CGRP) inhibitor erenumab for migraine preventive therapy. **Data Sources:** A MEDLINE/PubMed search (January 2000 to January 2019) was conducted using the keywords *erenumab-aooe*, *erenumab*, *migraine*, *migraine prophylaxis*, *migraine prevention*, and *chronic migraine*. Additional articles were identified by hand from references. **Study Selection and Data Extraction:** We included English-language articles (excluding poster presentations) evaluating erenumab pharmacology, efficacy, or safety in humans for migraine prevention. **Data Synthesis:** Erenumab is a CGRP inhibitor that inhibits vasodilation in response to acute migraines, which decreases pain perception during the migraine. Erenumab efficacy and safety has only been compared with placebo, but its reduction in monthly migraine days (MMDs) and medication response ($\geq 50\%$ reduction in MMDs) are comparable to current recommended off-label therapies for migraine prevention in short-term treatment studies. Additionally, erenumab is associated with low adverse event burden with no difference found compared with placebo per published clinical trials. **Relevance to Patient Care and Clinical Practice:** Erenumab is the first medication approved in the United States for the prevention of migraines in adults. No head-to-head data are available, but existing data suggest that erenumab is at least as effective as current off-label products and with reduced adverse effects. **Conclusion:** Erenumab is an effective once-monthly injectable agent for migraine prevention in patients with chronic or episodic migraine. It is also effective for patients who have previously failed migraine preventive therapy. Erenumab has a favorable adverse effect profile, which may improve patient adherence.

Keywords

erenumab-aooe, erenumab, migraine, migraine prophylaxis, migraine prevention, chronic migraine

Introduction

Migraines and severe headaches affect roughly 10% of men and 20% of women in the United States.¹ Patients with episodic migraines (EMs), defined as ≥ 4 to < 15 monthly migraine days (MMDs), or chronic migraines, defined as ≥ 15 MMDs, have significant disease burden that negatively affects quality of life and work productivity.^{2–5} Several migraine prophylaxis therapies are used clinically to reduce the frequency of migraines,⁶ but most were developed to treat other conditions. Current migraine prophylaxis therapies, including β -blockers, anticonvulsants, and antidepressants, among others, are somewhat effective, but many patients discontinue therapy because of poor medication tolerability.⁷

Erenumab (Aimovig) is a first-in-class calcitonin gene-related peptide (CGRP) inhibitor that was Food and Drug Administration (FDA) approved for the preventive treatment of migraine in adults in May 2018.⁸ The CGRP inhibitors are a novel class of medications designed specifically

for migraine prophylaxis, and erenumab is the first of 3 agents currently on the market.⁹ The purpose of this article is to review erenumab's pharmacology, clinical trial efficacy, and safety data and assess its place in migraine prophylaxis therapy.

Data Selection

We performed a systematic review of all relevant articles indexed in the MEDLINE and PubMed databases and the

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Table 1. Pharmacokinetic Parameters for Erenumab.⁸

Parameter	Erenumab 70 mg	Erenumab 140 mg
Absorption		
C_{\max} mean	6.1 µg/mL	15.8 µg/mL
AUC_{last} mean	159 day·µg/mL	505 day·µg/mL
C_{\min} mean		
Episodic migraine	5.7 µg/mL	12.8 µg/mL
Chronic migraine	6.2 µg/mL	14.9 µg/mL
Distribution (V_d)	3.86 L	
Metabolism	Proteolysis ^b	
Excretion	Nonspecific elimination of amino acids	
Half-life	~28 Days	

Abbreviations: AUC_{last} , area under the curve after last dose in trial; C_{\min} , trough concentration prior to next dose; C_{\max} , peak concentration.

^aVolume of distribution (V_d) during the terminal phase after a single 140-mg intravenous dose (not subcutaneous).

^bErenumab is a protein that is broken down by proteases into peptides and single amino acids. The peptides and amino acids utilized are either excreted or incorporated into new proteins. Erenumab does not have active metabolites.

National Institutes of Health Clinical Trials Registry (<http://www.clinicaltrials.gov>) between January 1, 1990, and January 20, 2018. Search terms included *erenumab-aooe*, *erenumab*, *migraine*, *migraine prophylaxis*, *migraine prevention*, and *chronic migraine*. Only English-language articles were included, and abstracts and poster presentations were excluded from the search. References of identified articles were searched for additional relevant citations.

Pharmacology

Erenumab is a human monoclonal antibody that binds and inhibits CGRP receptor function. Release of CGRP is increased during acute migraine attacks, and it activates receptors in the trigeminal ganglion outside the blood-brain barrier, which are thought to be involved in pain perception.⁹ The trigeminal ganglion is also part of the trigeminovascular reflex, a series of reactions that prevent vasoconstriction during migraines and induces pain perception.¹⁰

Selected pharmacokinetic parameters for erenumab are summarized in Table 1.⁸ With monthly administration, peak serum concentrations of erenumab occur at day 6 after administration, and trough concentrations approach steady state by 3 months. The effective half-life of erenumab is 28 days. Despite the long half-life, erenumab trough concentrations at steady state are 2 times less than the trough of the initial dose, indicating the lack of erenumab accumulation in the body. Erenumab has a low volume of distribution (3.86 L) and is unlikely to accumulate in overweight patients. It is metabolized via proteolysis into amino acids; thus, its elimination should not be affected by hepatic or renal impairment, but specific studies in these populations are lacking. Currently, there are no known drug interactions. Additionally,

there are no animal or human data available for the pregnant population.

Clinical Trials

The FDA approved erenumab for migraine prevention based on 2 phase II trials and 2 phase III trials (ARISE and STRIVE). The LIBERTY trial was published after erenumab's indication approval and evaluated erenumab in patients who had previously failed preventive migraine therapy (divalproex sodium, sodium valproate, topiramate, β -blockers, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, flunarizine, verapamil, lisinopril, candesartan). Extended safety data from ARISE and STRIVE are complete but not published as of December 2018. The ARISE and STRIVE trials enrolled patients with EM defined as ≥ 4 days and < 15 migraine days per month and < 15 headache days per month.⁵ The following section will review the ARISE and STRIVE trials in detail. Efficacy results for the trials are presented in Tables 2 and 3.

The STRIVE and ARISE trials used similar inclusion and exclusion criteria and primary/secondary outcomes.^{11,12} For both trials, eligible patients included adults aged 18 to 65 years with a history of EM with or without aura for at least 12 months prior to enrollment.^{11,12} Major exclusion criteria were migraine onset began after 50 years of age, history of hemiplegic migraine or cluster headaches, or prior treatment failure with ≥ 2 migraine preventive treatments as listed previously. In the original trial protocols, eligible patients who were utilizing migraine preventive therapy at enrollment were required to have a washout period of ≥ 2 months prior to randomization. However, the inclusion criteria were later amended to include patients taking 1 concomitant migraine prophylaxis treatment without a washout period to capture a broader patient population.

The primary outcome for both trials was change in MMDs, though the duration of treatment varied between the ARISE and STRIVE trials. Key secondary outcomes were $\geq 50\%$ reduction in MMDs, change in acute migraine-specific medication days per month (MSMD), and point reduction in both the Migraine Physical Function Impact Diary Physical Impairment (MPFID-PI) and Migraine Physical Function Impact Diary Everyday Activities (MPFID-EA) quality-of-life scales. The MPFID-PI is a patient-reported 5-item survey completed every 24 hours, with scores ranging from 5 to 25, and the MPFID-EA is a 7-item survey with scores ranging from 7 to 35. For both scales, higher scores indicate greater impairment.¹¹⁻¹⁴

STRIVE

The STRIVE trial was a phase III randomized, double-blind placebo controlled trial that evaluated the efficacy of erenumab 70 and 140 mg on prevention of migraines.¹¹ Patients

Table 2. Summary of Primary End Point Results in Erenumab Phase III Trials.

Trial	Interventions	Primary End Point	Results ^a
STRIVE ¹¹	<ul style="list-style-type: none"> Erenumab 70 mg subQ monthly (n = 318) Erenumab 140 mg subQ monthly (n = 312) Placebo (n = 316) 	MMDs change from baseline to mean of final 3 months of therapy	Erenumab 70 mg vs placebo <ul style="list-style-type: none"> • -3.2 vs -1.8 MMDs • Difference = -1.4 MMDs (95% CI = -1.9 to -0.9) Erenumab 140 mg vs placebo: <ul style="list-style-type: none"> • -3.7 vs -1.8 MMDs • Difference = -1.9 MMDs (95% CI = -2.3 to -1.4)
ARISE ¹²	<ul style="list-style-type: none"> Erenumab 70 mg subQ monthly (n = 282) Placebo (n = 288) 	MMDs change from baseline to 12 weeks	Erenumab 70 mg vs placebo <ul style="list-style-type: none"> • -2.9 vs -1.8 MMDs • Difference = -1.0 MMD (95% CI = -1.6 to -0.5)
LIBERTY ¹⁵	<ul style="list-style-type: none"> Erenumab 140 mg subQ monthly (n = 121) Placebo (n = 125) 	Proportion of patients who achieved $\geq 50\%$ reduction in baseline MMDs during month 3 of treatment	Erenumab 140 mg vs placebo <ul style="list-style-type: none"> • 23% vs 5% • OR = 2.7 (95% CI = 1.4 to 5.2)

^aNegative signs in this column represent reductions in the end point (end of therapy minus baseline). Abbreviations: MMDs, mean monthly migraine days; OR, odds ratio; subQ, subcutaneous.

were randomly allocated 1:1:1 to receive monthly subcutaneous injections of erenumab 70 mg (n = 317), erenumab 140 mg (n = 319), or placebo (n = 319). The trial included a 3-week screening phase to assess symptom-reporting compliance, a 4-week baseline phase to establish migraine frequency and severity, followed by a 28-week treatment phase. The primary outcome was change in MMDs from baseline to months 4 through 6.

Notable baseline characteristics were the following: the average age was 41 years; approximately 85% were female; approximately 60% had current use of acute migraine-specific medication; and 40% had previous failure with migraine preventive treatment. Only 27 total patients (0.03% of the study population) were taking concomitant migraine preventive treatment at trial completion. Baseline mean \pm SD MMDs were 8.2 ± 2.5 for placebo and 8.3 ± 2.5 MMDs for both erenumab groups. There was no difference between groups.

Change in MMDs at months 4 through 6 (the primary outcome) was -1.8 MMDs for placebo, -3.2 MMDs for erenumab 70 mg (difference vs placebo = -1.4; 95% CI = -1.9 to -0.9), and -3.7 MMDs for erenumab 140 mg (difference vs placebo = -1.9; 95% CI = -2.3 to -1.4). CIs overlapped between erenumab doses, suggesting no difference between them. The greater MMDs reduction with erenumab occurred for both doses as early as month 1 and persisted through month 6; the peak effect of both doses of erenumab occurred at roughly month 3. The percentage of patients who achieved $\geq 50\%$ reduction in MMDs was also significantly greater for both erenumab doses (70 mg = 43.3%; 140 mg = 50%) compared with placebo (26.6%; erenumab 70 mg vs placebo: odds ratio (OR) = 2.13, 95% CI = 1.52 to 2.98; erenumab 140 mg vs placebo: OR =

2.81, 95% CI = 2.01 to 3.94). Additionally, improvements in both the MPFID-IP and MPFID-EA scores were reported in both erenumab dose groups compared with placebo. Patient-reported outcomes were not significantly different between erenumab doses. Specific values are presented in Tables 2 and 3.

ARISE

The ARISE trial was a phase III, randomized, double-blind placebo-controlled trial that evaluated erenumab efficacy in patients with EMs.¹² Patients were randomly allocated 1:1 to erenumab 70 mg subcutaneous monthly (n = 291) or matching placebo injection (n = 286) for a 12-week treatment phase. The trial had a 3-week screening phase and a 4-week baseline phase where patients were evaluated on electronic health reporting compliance before starting the treatment phase. The primary end point was change in MMDs from baseline to week 12 of treatment.

Significant baseline characteristics included an average baseline age of 42 years, 85% female, and 60% with acute migraine specific medication use. Additionally, 39.5% of placebo- and 40.9% of erenumab-treated patients had failed previous migraine preventive treatment. Only 16 patients (5.5%) in the placebo group and 19 patients (6.6%) in the erenumab group were taking concomitant migraine preventive treatment at enrollment. The baseline MMDs were 8.4 ± 2.6 and 8.1 ± 2.7 for placebo and erenumab groups, respectively.

Change in MMDs from baseline to week 12 was -2.9 for the erenumab group compared with -1.8 MMDs for the placebo group (difference = -1.0; 95% CI = -1.6 to -0.5).

Table 3. Summary of Secondary End Point Results From STRIVE and ARISE.

Secondary End Point	Treatment Group		
	Placebo (n = 316)	Erenumab 70 mg (n = 312)	Erenumab 140 mg (n = 318)
STRIVE Trial¹¹			
≥50% Reduction from baseline MMDs			
n (%)	84 (26.6%)	135 (43.3%)	159 (50%)
Odds ratio (95% CI)	Reference	2.13 (1.52 to 2.98)	2.81 (2.01 to 3.94)
Number needed to treat	Reference	5.99	4.27
MSMD change from baseline			
Change, mean ± SD	−0.2 ± 0.1	−1.1 ± 0.1	−1.6 ± 0.1
Difference vs placebo (95% CI)	Reference	−0.9 (−1.2 to −0.6)	−1.4 (−1.7 to −1.1)
MPFID-EA ^a change from baseline			
Change, mean ± SD	−3.3 ± 0.4	−5.5 ± 0.4	−5.9 ± 0.4
Difference vs placebo (95% CI)	Reference	−2.2 (−3.3 to −1.2)	−2.4 (−3.6 to −1.5)
MPFID-PI ^b change from baseline			
Change, mean ± SD	−2.4 ± 0.4	−4.2 ± 0.4	−4.8 ± 0.4
Difference vs placebo (95% CI)	Reference	−1.9 (−3.0 to −0.8)	−2.4 (−3.5 to −1.4)
ARISE Trial¹²			
Placebo (n = 288)		Erenumab 70 mg (n = 282)	
≥50% Reduction from baseline MMDs			
n (%)	85 (29.5%)	112 (39.7%)	
Odds ratio (95% CI)	Reference	1.59 (1.12 to 2.27)	
Number needed to treat	Reference	9.80	
MSMD change from baseline			
Change, mean ± SD	−0.6 ± 0.1	−1.2 ± 0.1	
Difference vs placebo (95% CI)	Reference	−0.6 (−1.0 to −0.2)	
≥5-Point reduction from baseline in MPFID-EA			
n (%)	103 (35.8%)	114 (40.4%)	
Odds ratio (95% CI)	Reference	1.22 (0.87 to 1.71)	
≥5-Point reduction from baseline in MPFID-PI			
n (%)	78 (27.1%)	93 (33%)	
Odds ratio (95% CI)	Reference	1.33 (0.92 to 1.90)	

Abbreviations: MMDs, monthly migraine days; MPFID-EA, Migraine Physical Function Impact Diary Everyday Activities; MPFID-PI, Migraine Physical Function Impact Diary Physical Impairment; MSMD, migraine-specific medication days per month.

^aMPFID-EA is a 7-item survey with scores ranging from 7 to 35; higher scores indicate greater impairment.

^bMPFID-PI is a 5-item survey with scores ranging from 5 to 25; higher scores indicate greater impairment.

Notably, significant reduction in MMDs from baseline occurred, starting at week 4, and continued to improve through week 12 for both placebo- and erenumab-treated patients. However, the difference in MMDs reduction between erenumab and placebo groups was stable from week 4 (statistical difference, $P < 0.001$) to week 12. Regarding secondary outcomes, the proportion of patients who achieved ≥50% reduction in MMDs was greater in the erenumab group compared with the placebo group (39.7% vs 29.5%; OR = 1.59; 95% CI, 1.12 to 2.27). The reduction from baseline in MSMD was also greater with erenumab (−1.2 MSMD) compared with placebo (−0.6 MSMD), with a difference of −0.6 MSMD (95% CI = −1.0 to −0.2). Conversely, no difference was observed in the proportion of patients achieving a ≥5-point reduction in MPFID-EA and MPFID-PI (Tables 2 and 3).

Erenumab Efficacy in Patients With Prior Treatment Failure

The LIBERTY trial compared erenumab 140 mg monthly (n = 121) with placebo (n = 125) in patients who had previously experienced treatment failure with 2 to 4 previous migraine preventive therapies.¹⁵ Previous migraine preventive therapies include those mentioned above and, more specifically, propranolol, metoprolol, amitriptyline, or venlafaxine. The primary outcome was ≥50% reduction in MMDs from baseline to 12 weeks of therapy. Significant baseline characteristics included an average baseline age of 44 years, approximately 80% female, and approximately 85% with acute migraine-specific medication use. At baseline, approximately 39% of patients had 2 unsuccessful migraine preventive treatments, 38% had 3 unsuccessful treatments, and 23% had 4 unsuccessful treatments. As

regards baseline MMDs, it was reported that 30% of patients had 4 to 7 baseline MMDs and 70% had 8 to 14 baseline MMDs in both placebo and erenumab groups.

A significantly higher proportion of patients in the erenumab group achieved the primary outcome compared with placebo (30% vs 14%; OR = 2.7; 95% CI = 1.4 to 5.2). These findings support prior subgroup post hoc analyses from phase 2 trials that suggested erenumab efficacy in patients with ≥ 1 prior treatment failure.¹⁶

Safety

Erenumab appears to have a fairly benign safety profile from the short-duration clinical trials available. No adverse effects reported in clinical trials were significantly different from placebo with any dose of erenumab.^{11,12,17-19} An initial concern with erenumab was the possibility of increased blood pressure because of its mechanism of action. However, clinical trial data to date have suggested no clinically significant change in blood pressure or incidence of hypertension.^{11,12,17-19} Additionally, existing safety data suggest that erenumab 140 mg does not worsen myocardial ischemia during exercise, a concern considering its effect on reducing dermal blood flow.²⁰ In the STRIVE and ARISE trials, numerically more injection-site pain cases were reported in the erenumab 70-mg groups than in the placebo or erenumab 140-mg groups, but the overall prevalence was relatively low ($\leq 6.0\%$ of patients), suggesting that the pain is unrelated to the medication. Drop-out rates for erenumab resulting from adverse effects (eg, irritable bowel syndrome, fatigue, mechanical urticaria) were similar to those for placebo in all trials ($\leq 3\%$ of patients).^{11,12,18,19}

Access and Financial Considerations

The annual price of erenumab 70 mg monthly is estimated to be \$6900.⁸ Currently, AMGEN, the manufacturer of Aimovig, is offering a patient assistance program in the form of an Aimovig Ally program (<http://www.aimovig.com>). Patients with private insurance are eligible for either a \$5 copay or a no cost prescription of Aimovig for up to 12 months if their private insurance does not cover Aimovig. However, the annual cost of erenumab is considerable compared with current non-FDA-approved migraine prevention medications, most of which are available in generic form and could be considered first in treatment-naïve patients. Nevertheless, pharmacoeconomic modeling suggests that erenumab treatment would reduce migraine-related direct and indirect costs and increase quality-adjusted life-years, compared with only supportive care.²¹ Over 10 years, increased work productivity is estimated to offset erenumab drug costs by approximately \$8000.²² Whether a similarly positive impact would be realized in comparing erenumab versus currently available therapy is not known.

Dosage and Administration

Erenumab is available in 70-mg doses, administered subcutaneously via the single-use Aimovig SureClick autoinjector.⁸ The recommended dose is 70 mg monthly, with the package insert caveat that some patients may benefit from 140 mg monthly (requires 2 autoinjectors per dose). Patients should be instructed to administer injections subcutaneously in the abdomen, thigh, or upper arm. Consecutive 70-mg doses (ie, 140-mg dose) may be administered in the same location, just not the exact same spot. Erenumab must be refrigerated for storage. The product should be discarded if left at room temperature for more than 7 days.

Relevance to Patient Care and Clinical Practice

Prior trials have traditionally used treatment response, defined as $\geq 50\%$ reduction in MMDs, as the primary outcome used to assess efficacy of migraine prevention.²³ Both STRIVE and ARISE include this measurement as a secondary outcome. Current off-label migraine prophylaxis treatments generally result in 25% (absolute difference) more patients achieving treatment response compared with placebo.²⁴ However, whether erenumab offers a significant increase in percentage of responders (approximately $\geq 40\%$ achieving response with erenumab in both trials) is difficult to ascertain in the context of differing patient populations and trials. Unfortunately, direct comparisons have not been performed. Propranolol, metoprolol, valproate, and topiramate have been shown in randomized clinical trials to reduce migraine frequency. These preventive medications have demonstrated reductions in MMDs similar to erenumab's reduction of 1 to 2 MMDs.²⁵⁻²⁸ Erenumab's maximum effect on MMDs seems to take place after 3 to 4 months of therapy, suggesting that this time frame should be the maximal amount of time needed to assess adequacy of therapy. However, achievement of $\geq 50\%$ reduction in MMDs can be seen as early as after the first week of treatment with erenumab.²⁹ Onset of efficacy for off-label migraine prophylaxis treatments have been reported at 1 month; earlier effects are likely, but data are limited.^{6,24}

Erenumab also appears to be effective for patients who have failed 2 or more prior migraine preventive therapies because of lack of efficacy or intolerable adverse effects.¹⁵ Subgroup analysis of a phase 2 trial suggests that erenumab 140 mg monthly may improve treatment response compared with 70 mg monthly in patients with ≥ 1 treatment failure. However, differences between erenumab doses were not reported in the STRIVE trial, and the LIBERTY trial only treated patients with erenumab 140 mg monthly.^{11,15,16} Because the erenumab 140-mg monthly dose has not proven its benefit compared with the 70-mg monthly dose and is also double the cost, erenumab 70 mg

is a reasonable strength to start at this time. Cost restrictions and limited evidence as a first-line agent will likely limit erenumab's use as an initial agent for migraine prevention.

Erenumab phase III trials used the MPFID-EA and MPFID-PI, which are recently validated patient-reported outcome scales.^{13,14} Conversely, MPFID-EA and MPFID-PI scales have not been used in trials of other migraine preventive therapies, which makes comparison with current off-label therapies difficult. Unfortunately, clinically meaningful reductions in the MPFID-EA or MPFID-PI scales are not well established. Nevertheless, erenumab failed to achieve the specified secondary outcome of a ≥ 5 -point reduction in both the MPFID-EA and MPFID-PI scales in the ARISE trial. However, post hoc analyses in the STRIVE trial suggested clinically meaningful improvements in health-related quality of life with erenumab, using previously established questionnaires.⁴

Although comparative trials are lacking, the significant advantage of erenumab over other migraine prophylaxis treatments is likely medication tolerability, which is relatively low for most current off-label migraine prevention therapies.⁷ For example, adherence rates to existing oral migraine-preventive medications are about 25% at 6 months and 20% at 12 months of therapy.³⁰ In contrast, drop-out rates for erenumab ($\leq 3\%$ per treatment group for all causes) were similar to those for placebo in phase III trials.^{11,12} These data suggest that adherence rates under real-world use may be greater with erenumab than with conventional therapy, at least in the short term, but empirical data are, thus far, lacking.

Finally, it is unknown whether erenumab maintains MMD reductions during long-term therapy. Both the ARISE and STRIVE phase III trials have 28-week extensions (yet to be published), but even with these studies, data beyond 1 year of therapy are nonexistent.^{11,12}

Conclusion

Erenumab is a first-in-class monoclonal antibody that inhibits CGRP, which is believed to be involved in pain perception and acute migraine attacks. Erenumab, administered at a dose of 70 or 140 mg subcutaneously once monthly, appears to have efficacy at least comparable to those of other treatments, with a significantly improved adverse event profile and patient tolerability. However, no head-to-head comparison trials with erenumab and other migraine prophylaxis therapies have been completed. Erenumab is also effective for patients who have failed prior migraine preventive treatment. Cost is a concern with erenumab, and the extent to which commercial insurers cover erenumab and other CGRP inhibitors is not known. Additional research is needed to understand efficacy and safety in real-world treatment scenarios (eg, in patients with multiple

comorbidities) and to ensure the same risks versus benefits with long-term treatment.


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