

## ORIGINAL ARTICLE

# A Controlled Trial of Erenumab for Episodic Migraine

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## ABSTRACT

**BACKGROUND**

We tested erenumab, a fully human monoclonal antibody that inhibits the calcitonin gene–related peptide receptor, for the prevention of episodic migraine.

**METHODS**

We randomly assigned patients to receive a subcutaneous injection of either erenumab, at a dose of 70 mg or 140 mg, or placebo monthly for 6 months. The primary end point was the change from baseline to months 4 through 6 in the mean number of migraine days per month. Secondary end points were a 50% or greater reduction in mean migraine days per month, change in the number of days of use of acute migraine–specific medication, and change in scores on the physical-impairment and everyday-activities domains of the Migraine Physical Function Impact Diary (scale transformed to 0 to 100, with higher scores representing greater migraine burden on functioning).

**RESULTS**

A total of 955 patients underwent randomization: 317 were assigned to the 70-mg erenumab group, 319 to the 140-mg erenumab group, and 319 to the placebo group. The mean number of migraine days per month at baseline was 8.3 in the overall population; by months 4 through 6, the number of days was reduced by 3.2 in the 70-mg erenumab group and by 3.7 in the 140-mg erenumab group, as compared with 1.8 days in the placebo group ( $P < 0.001$  for each dose vs. placebo). A 50% or greater reduction in the mean number of migraine days per month was achieved for 43.3% of patients in the 70-mg erenumab group and 50.0% of patients in the 140-mg erenumab group, as compared with 26.6% in the placebo group ( $P < 0.001$  for each dose vs. placebo), and the number of days of use of acute migraine–specific medication was reduced by 1.1 days in the 70-mg erenumab group and by 1.6 days in the 140-mg erenumab group, as compared with 0.2 days in the placebo group ( $P < 0.001$  for each dose vs. placebo). Physical-impairment scores improved by 4.2 and 4.8 points in the 70-mg and 140-mg erenumab groups, respectively, as compared with 2.4 points in the placebo group ( $P < 0.001$  for each dose vs. placebo), and everyday-activities scores improved by 5.5 and 5.9 points in the 70-mg and 140-mg erenumab groups, respectively, as compared with 3.3 points in the placebo group ( $P < 0.001$  for each dose vs. placebo). The rates of adverse events were similar between erenumab and placebo.

**CONCLUSIONS**

Erenumab administered subcutaneously at a monthly dose of 70 mg or 140 mg significantly reduced migraine frequency, the effects of migraines on daily activities, and the use of acute migraine–specific medication over a period of 6 months. The long-term safety and durability of the effect of erenumab require further study. (Funded by Amgen and Novartis; STRIVE ClinicalTrials.gov number, NCT02456740.)

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**M**IGRAINE CAN BE BROADLY CLASSIFIED as either episodic or chronic on the basis of the number of migraine days and headache days per month.<sup>1</sup> Episodic migraine is defined as fewer than 15 migraine days or headache days per month, with or without aura, and accounts for more than 90% of persons with migraine,<sup>2</sup> whereas chronic migraine, defined as at least 15 headache days per month (of which  $\geq 8$  are migraine days with or without aura), affects approximately 5% to 8% of persons with migraine.<sup>3</sup>

Acute migraine-specific medications, such as the serotonin 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptor agonists (triptans),<sup>4</sup> are used to abort a migraine attack, whereas preventive treatments aim to reduce the frequency and severity of migraine.<sup>5</sup> Patients who have sufficient migraine attacks to be disabled by the condition are candidates for preventive therapy.<sup>6</sup> Commonly used migraine-preventive therapies, such as topiramate, propranolol, and amitriptyline, may not be entirely effective<sup>5</sup> or may have unacceptable side effects, leading to poor adherence.<sup>7</sup> The currently used preventive medications were developed for other indications rather than for a target that is part of the specific pathophysiological processes involved in migraine.<sup>8</sup>

Calcitonin gene-related peptide (CGRP) is involved in the pathophysiological mechanisms underlying migraine through nociceptive mechanisms in the trigeminovascular system.<sup>9-12</sup> The role of CGRP in migraine was shown in phase 2 and phase 3 clinical trials of small-molecule CGRP-receptor antagonists<sup>13-18</sup> in acute migraine and is further supported by phase 2 and phase 3 trials of monoclonal antibodies targeting the CGRP pathway,<sup>19-22</sup> which suggests that the pathway could be a target for preventive migraine treatment. Erenumab is a fully human monoclonal antibody that selectively and potently binds to the canonical CGRP receptor.<sup>23</sup> In phase 2 trials, erenumab was found to significantly reduce the number of migraine days per month in patients with episodic migraine at a monthly dose of 70 mg<sup>22</sup> and in patients with chronic migraine at doses of 70 mg and 140 mg in the last month of a 3-month double-blind treatment phase.<sup>24</sup> Here we report the results of STRIVE (Study to Evaluate the Efficacy and Safety of Erenumab in Migraine Prevention), a phase 3 trial of erenumab at doses of 70 mg and 140 mg in patients with episodic migraine.

## METHODS

### TRIAL POPULATION

Adults 18 to 65 years of age who had had a history of migraine with or without aura for at least 12 months before screening were eligible for participation in the trial. Migraine was defined in accordance with the International Classification of Headache Disorders, 3rd edition (beta version).<sup>1</sup> Patients had to have at least 4 and fewer than 15 migraine days per month and fewer than 15 headache days per month on average during the 3-month period before screening (as reported by the patients) and during a 4-week baseline phase that was assessed with the use of a handheld electronic diary (ERT) completed daily by the patient and had to demonstrate at least 80% adherence to reporting with the electronic diary during the baseline phase. Patients were excluded if they were older than 50 years of age at migraine onset, had a history of hemiplegic migraine or cluster headache, had received botulinum toxin within 4 months before or during the baseline phase, used devices or procedures for migraine prevention within 2 months before the baseline phase, or had had no therapeutic response to more than two migraine-preventive treatment categories (additional inclusion and exclusion criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org). The original protocol did not permit inclusion of patients who were receiving migraine-preventive medication; in order to evaluate the effect of erenumab in a broader patient population, a protocol amendment that was implemented during the enrollment period allowed the enrollment of patients with concomitant use of one migraine-preventive medication taken at a stable dose (i.e., with no changes to the dose within 2 months before the baseline phase or at any time during the trial) (see the Supplementary Appendix).

### TRIAL OVERSIGHT

The trial protocol was approved by the independent ethics committee at each trial center and is available at NEJM.org. Patients provided written informed consent. Amgen and Novartis, the developers of erenumab, funded this trial. Amgen provided the trial drug and conducted the data analyses. A medical writer, funded by Amgen, wrote the first draft of the manuscript under the direction of the authors. All the authors interpret-

ed the data, contributed to the preparation of the manuscript, made the final decision to submit the manuscript for publication, and attest to the accuracy and completeness of the data and adverse-events reporting and to the fidelity of the trial to the protocol.

#### TRIAL DESIGN

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial conducted at 121 sites across North America, Europe, and Turkey from July 2015 (when the first patients underwent randomization) until September 5, 2016 (primary completion date). The trial had four phases: screening ( $\leq 3$  weeks of initial screening and a 4-week baseline phase); the double-blind treatment phase (24 weeks); the active-treatment phase, in which patients underwent repeat randomization and were assigned to receive 70 mg or 140 mg of erenumab (28 weeks); and a safety follow-up phase (12 weeks). The results from the baseline and double-blind treatment phases are reported here. Results from the active-treatment and safety follow-up phases have not yet been analyzed. Safety follow-up data for patients who did not enter the active-treatment phase are included in this report.

At the end of the 4-week baseline phase, eligible patients were randomly assigned in a 1:1:1 ratio to receive monthly subcutaneous injections of 70 mg of erenumab, 140 mg of erenumab, or placebo at day 1 and weeks 4, 8, 12, 16, and 20, administered by trained staff at the trial sites. Randomization was based on a schedule that had been generated by the sponsor before initiation of the trial and was centrally executed with the use of an interactive voice or Web response system. Randomization was stratified according to region (North America vs. other) and according to the use of migraine-preventive medication (current use, previous use only, or no previous or current use). The patients, site personnel, and trial-sponsor personnel were not aware of the trial-group assignments.

#### TRIAL ASSESSMENTS AND SAFETY EVALUATIONS

During the baseline and double-blind treatment phases, patients completed an electronic diary daily with information about their migraine and nonmigraine headaches, including the date and time of onset and resolution, pain severity and features, associated symptoms, and the use of mi-

graine-specific abortive therapies and analgesic medications. Patients also completed the Migraine Physical Function Impact Diary (MPFID), a 13-item self-administered instrument measuring physical functioning in the past 24 hours, on migraine and nonmigraine days using the electronic diary. The MPFID contains a 7-item everyday-activities domain (MPFID-EA; scores range from 7 to 35, with higher scores indicating greater interference of migraine with everyday activity) and a 5-item physical-impairment domain (MPFID-PI; scores range from 5 to 25, with higher scores indicating greater physical impairment due to migraine), as well as a global question to assess the overall effect of migraines. For the analysis, these scores were averaged over a period of 1 month and then linearly transformed to a 100-point scale. Safety was monitored throughout the trial through reporting of adverse events and serious adverse events with the use of definitions from the *Medical Dictionary for Regulatory Activities*, version 19.0. The safety assessment included evaluation of laboratory values, vital signs, electrocardiograms, and anti-erenumab antibodies (additional information about the safety assessments is provided in the Supplementary Appendix).

#### END POINTS

The primary objective of the trial was to compare erenumab with placebo with regard to the primary end point of the change in mean number of migraine days per month from baseline to the final 3 months (months 4 through 6) of the double-blind treatment phase. A migraine day was defined as any calendar day on which the patient had onset, continuation, or recurrence of a qualified migraine as recorded in the electronic diary. A qualified migraine was defined as a migraine (with or without aura) lasting at least 30 minutes and manifesting with at least two pain features, at least one associated nonpain feature, or both (information on migraine features is provided in the Supplementary Appendix). Any calendar day on which acute migraine-specific medication was used was counted as a migraine day. The first-tier secondary end points were at least a 50% reduction from baseline in the mean number of migraine days per month and the change from baseline in the mean number of days of use of acute migraine-specific medication (including triptans or ergotamine derivatives) per month, and the second-tier secondary end points were the change

**Table 1. Baseline Demographic and Clinical Characteristics of the Patients.\***

Characteristic	Placebo (N=319)	Erenumab, 70 mg (N=317)	Erenumab, 140 mg (N=319)
Age (range) — yr	41.3±11.2 (18–65)	41.1±11.3 (18–63)	40.4±11.1 (19–65)
Female sex — no. (%)	274 (85.9)	268 (84.5)	272 (85.3)
Geographic region — no. (%)			
North America	158 (49.5)	159 (50.2)	160 (50.2)
Other†	161 (50.5)	158 (49.8)	159 (49.8)
Age at migraine onset — yr	21.2±10.2	21.4±11.0	20.7±9.9
Acute headache medication use — no. (%)			
Migraine-specific‡	191 (59.9)	179 (56.5)	192 (60.2)
Non-migraine-specific	244 (76.5)	243 (76.7)	256 (80.3)
Migraine-preventive medication use — no. (%)§			
No current or previous use	178 (55.8)	175 (55.2)	187 (58.6)
Previous use only	131 (41.1)	133 (42.0)	124 (38.9)
Current use¶	10 (3.1)	9 (2.8)	8 (2.5)
History of preventive treatment failure — no. (%)	127 (39.8)	127 (40.1)	116 (36.4)
Lack of efficacy	90 (28.2)	89 (28.1)	83 (26.0)
Unacceptable side effects	78 (24.5)	65 (20.5)	62 (19.4)
Assessment of migraine during baseline phase			
Migraine days per month	8.2±2.5	8.3±2.5	8.3±2.5
Headache days per month	9.3±2.6	9.1±2.6	9.3±2.5
Migraine attacks per month	5.1±1.5	5.2±1.5	5.2±1.4
Days of use of acute migraine-specific medication per month‡	3.4±3.4	3.2±3.4	3.4±3.5
Monthly MPFID everyday-activities score**	13.7±9.1	14.0±8.9	13.1±8.3
Monthly MPFID physical-impairment score**	12.2±9.4	12.6±9.6	12.0±9.0

\* Plus-minus values are means ±SD. Data in the table are for the full analysis set (all patients who underwent randomization). There were no significant between-group differences in baseline characteristics. Percentages may not total 100 because of rounding.

† Other includes Austria, Belgium, the Czech Republic, Finland, Germany, the Netherlands, Poland, Slovakia, Sweden, Turkey, and the United Kingdom.

‡ During the baseline phase, 557 patients (58.5%) used triptan-based medications and 4 patients (0.4%) used ergotamine-based medications (safety analysis set).

§ The summary of treatment with migraine-preventive medications is based on actual data collected rather than on randomization stratification.

¶ The use of one stable migraine-preventive medication was allowed, in accordance with a late protocol amendment. Three patients (0.3%) used topiramate; 7 (0.7%) used beta blockers; 7 (0.7%) used tricyclic antidepressants; 4 (0.4%) used serotonin-norepinephrine reuptake inhibitors; 1 (0.1%) used flunarizine, verapamil, or lomerizine; 2 (0.2%) used lisinopril or candesartan; and 3 (0.3%) used other medications.

|| Treatment-failure categories were not mutually exclusive; a patient could be included in both categories.

\*\* The Migraine Physical Function Impact Diary (MPFID) contains a 7-item everyday-activities domain and a 5-item physical-impairment domain, as well as a global question to assess the overall effect of migraines. The scores were averaged over a period of 1 month and then linearly transformed to a 100-point scale, with higher scores representing greater migraine burden on functioning.

from baseline in both the MPFID-PI score and MPFID-EA score. Secondary end points were assessed and averaged over the final 3 months of the double-blind treatment phase.

#### STATISTICAL ANALYSIS

The primary end point and continuous secondary end points were analyzed with the use of a linear mixed-effects model without any imputation of

**Table 2. Clinical Responses and Patient-Reported Outcomes over the Final 3 Months of the Double-Blind Treatment Phase (Months 4, 5, and 6).\***

Outcome	Placebo (N=316)	Erenumab, 70 mg (N=312) <sup>†</sup>	Erenumab, 140 mg (N=318) <sup>†</sup>
Migraine days per month			
Change from baseline	-1.8±0.2	-3.2±0.2	-3.7±0.2
Difference vs. placebo (95% CI)	—	-1.4 (-1.9 to -0.9)	-1.9 (-2.3 to -1.4)
≥50% Reduction from baseline in migraine days per month			
No. of patients (%)	84 (26.6)	135 (43.3)	159 (50.0)
Odds ratio (95% CI)	—	2.13 (1.52 to 2.98)	2.81 (2.01 to 3.94)
Days of use of acute migraine-specific medication per month			
Change from baseline	-0.2±0.1	-1.1±0.1	-1.6±0.1
Difference vs. placebo (95% CI)	—	-0.9 (-1.2 to -0.6)	-1.4 (-1.7 to -1.1)
Monthly MPFID everyday-activities score			
Change from baseline	-3.3±0.4	-5.5±0.4	-5.9±0.4
Difference vs. placebo (95% CI)	—	-2.2 (-3.3 to -1.2)	-2.6 (-3.6 to -1.5)
Monthly MPFID physical-impairment score			
Change from baseline	-2.4±0.4	-4.2±0.4	-4.8±0.4
Difference vs. placebo (95% CI)	—	-1.9 (-3.0 to -0.8)	-2.4 (-3.5 to -1.4)

\* Plus-minus values are least-squares means ±SE. The analysis included patients who underwent randomization, received at least one dose of the randomly assigned trial regimen, and had at least one postbaseline measurement for migraine days per month during the double-blind treatment phase (efficacy analysis set).

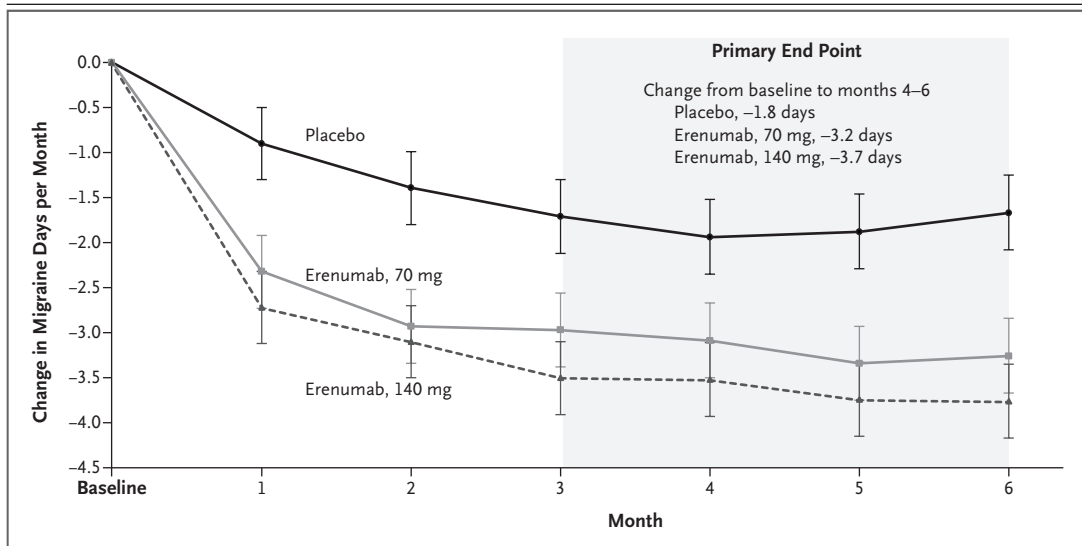
<sup>†</sup> P<0.001 for all pairwise comparisons between erenumab and placebo. P values were unadjusted, and significance was determined for all primary and secondary end points after adjustment for multiplicity.

missing data. Sensitivity analyses were conducted with multiple imputation under missing-at-random and missing-not-at-random assumptions. For the secondary end point of a 50% or greater reduction in mean migraine days per month, a stratified Cochran-Mantel-Haenszel test was used after imputation of missing data as nonresponse. Sensitivity analyses for this end point included a generalized linear mixed-effects model without any imputation of missing data. Further information on the sensitivity analyses is provided in the Supplementary Appendix. The significance of the between-group differences with regard to the primary and secondary end points was determined after multiplicity adjustment with a prespecified hierarchical gatekeeping procedure and Hochberg-based testing procedures to maintain the two-sided, study-wise, type I error rate at an alpha level of 0.05. The primary end point was tested separately for each erenumab dose at an alpha level of 0.04 for 70 mg and of 0.01 for 140 mg.

First-tier and second-tier secondary end points were then tested sequentially with the use of the procedure detailed in the Supplementary Appendix.

The full analysis set in the final protocol included all the patients who underwent randomization. The efficacy end points are reported with the use of the following efficacy analysis set: patients who received at least one dose of erenumab or placebo and had at least one postbaseline measurement for migraine days per month during the double-blind treatment phase, analyzed according to randomly assigned trial regimen. The efficacy analysis set meets the criteria for a full analysis set.<sup>25</sup> The safety analysis set included all the patients who underwent randomization and received at least one dose of erenumab or placebo, analyzed according to randomly assigned trial regimen unless the dose received throughout the double-blind treatment phase differed from the one that had been randomly assigned.





**Figure 1. Primary End Point.**

Least-squares mean changes from baseline in migraine days per month during the double-blind treatment phase are shown. The I bars represent 95% confidence intervals. Changes from baseline in mean migraine days over the final 3 months (months 4, 5, and 6) in both erenumab dose groups differed significantly from those in the placebo group ( $P < 0.001$  for each comparison). Data were analyzed with the use of a repeated-measures, linear mixed-effects model including trial group, baseline value, stratification factors, scheduled visit, and the interaction of trial group with scheduled visit, and the analysis was based on the data as observed with no imputation of missing values. Patients were given erenumab or placebo at day 1 (baseline) and at months 1, 2, 3, 4, and 5. The figure is based on the efficacy analysis set (patients who received at least one dose of erenumab or placebo and had at least one post-baseline measurement for migraine days per month during the double-blind treatment phase).

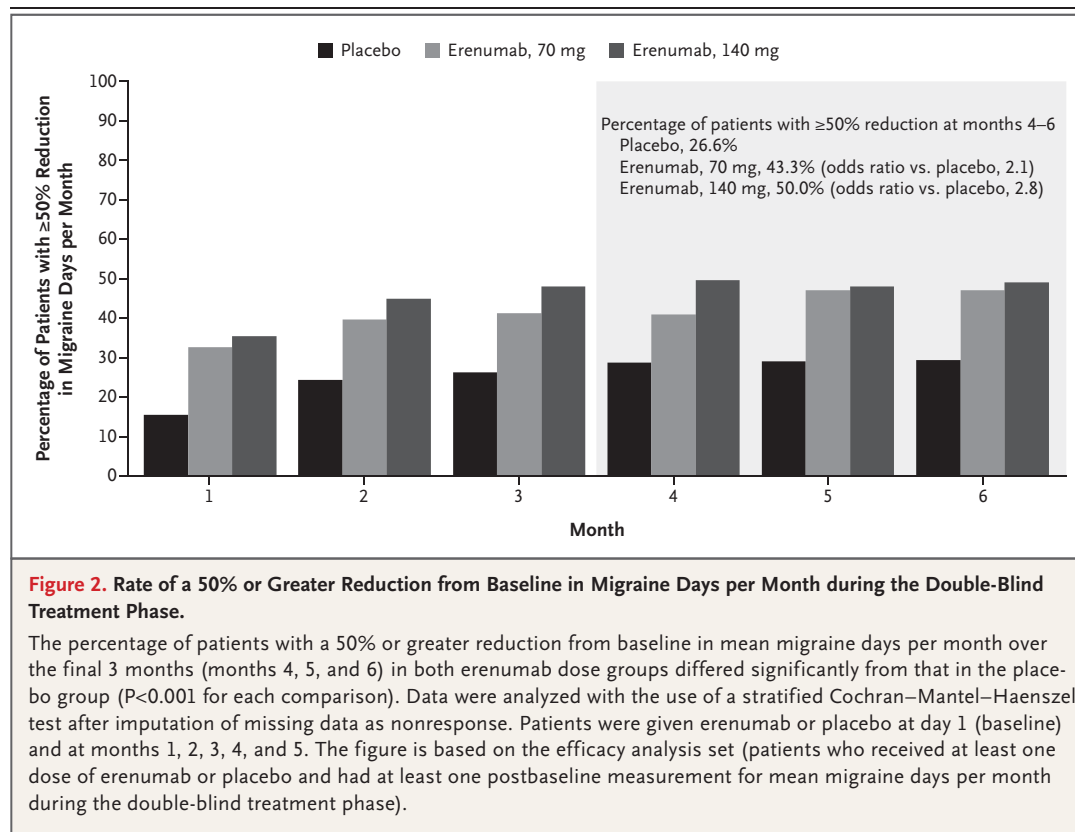
## RESULTS

### PATIENTS

A total of 955 patients underwent randomization (317 to the 70-mg erenumab group, 319 to the 140-mg erenumab group, and 319 to the placebo group), and 858 patients (89.8%) completed the 6-month double-blind treatment phase (Fig. S1 in the Supplementary Appendix). The groups were balanced with respect to demographic and clinical characteristics (Table 1, and Table S1 in the Supplementary Appendix). The mean age of the patients was 40.9 years, 405 (42.4%) were currently using or had previously used migraine-preventive medication, and 370 (38.7%) had discontinued their use of a previous preventive medication because of insufficient efficacy or unacceptable side effects, as documented in patient records or reported by the patient. During the baseline phase, all three trial groups had a mean of 8.3 migraine days per month, 562 patients (58.8%) used acute migraine-specific medications, and 27 patients (2.8%) used one migraine-preventive medication.

### END POINTS

From baseline to the final 3 months of the double-blind treatment phase, the reduction in mean migraine days per month was 3.2 days in the 70-mg erenumab group and 3.7 days in the 140-mg erenumab group, as compared with 1.8 days in the placebo group ( $P < 0.001$  for each dose vs. placebo) (Table 2 and Fig. 1). Erenumab at either dose was superior to placebo with regard to all secondary end points over the final 3 months of the double-blind treatment phase. At least a 50% reduction in mean migraine days per month from baseline to months 4 through 6 was achieved for 43.3% of patients in the 70-mg erenumab group and 50.0% of patients in the 140-mg erenumab group, as compared with 26.6% in the placebo group ( $P < 0.001$  for each dose vs. placebo). The odds of having at least a 50% reduction in mean migraine days at months 4 through 6 were 2.1 and 2.8 times greater for the 70-mg and 140-mg groups, respectively, than for the placebo group ( $P < 0.001$  for both comparisons) (Table 2 and Fig. 2). From baseline to the final 3 months of the



double-blind treatment phase, the mean number of days of use of acute migraine-specific medication per month was reduced by 1.1 days in the 70-mg erenumab group and by 1.6 days in the 140-mg erenumab group, as compared with 0.2 days for the placebo group ( $P < 0.001$  for each dose vs. placebo) (Table 2, and Fig. S2 in the Supplementary Appendix).

The effect of migraine on patient-reported physical functioning was determined with the use of the MPFID. Transformed MPFID-EA scores (on a scale of 0 to 100, with higher values representing greater interference of migraine with everyday activity) were reduced from baseline by 5.5 in the 70-mg erenumab group and by 5.9 in the 140-mg erenumab group, as compared with 3.3 in the placebo group ( $P < 0.001$  for each dose vs. placebo) (Table 2, and Fig. S3 in the Supplementary Appendix). Transformed MPFID-PI scores (on a scale of 0 to 100, with higher values representing greater physical impairment due to migraine) were reduced by 4.2 in the 70-mg erenumab group and by 4.8 in the 140-mg erenumab group, as compared with 2.4 in the placebo group

( $P < 0.001$  for each dose vs. placebo) (Table 2, and Fig. S4 in the Supplementary Appendix).

#### SAFETY

A total of 572 (90.4%) of the 633 patients who received at least one dose of erenumab and 278 (87.1%) of the 319 patients who received at least one dose of placebo received all six planned doses. The frequency and severity of adverse events, serious adverse events, and adverse events leading to discontinuation of the trial regimen were similar between the erenumab groups and the placebo group (Table 3, and Table S3 in the Supplementary Appendix). Numerically more instances of injection-site pain occurred in the 70-mg erenumab group than in the placebo group. A total of 35 of the 628 patients (5.6%) for whom postbaseline antibody data were available tested positive for anti-erenumab binding antibodies (8.0% of patients in the 70-mg group and 3.2% of patients in the 140-mg group), one of whom, in the 70-mg erenumab group, tested positive for neutralizing antibodies (0.2%). No clinically meaningful differences between the erenumab groups

**Table 3. Adverse Events Reported during the Double-Blind Treatment Phase.\***

Event	Placebo (N = 319)	Erenumab, 70 mg (N = 314)	Erenumab, 140 mg (N = 319)
Adverse event	201 (63.0)	180 (57.3)	177 (55.5)
Adverse events reported by $\geq 2\%$ of patients in any trial group			
Nasopharyngitis	32 (10.0)	31 (9.9)	35 (11.0)
Upper respiratory tract infection	18 (5.6)	21 (6.7)	15 (4.7)
Sinusitis	7 (2.2)	7 (2.2)	11 (3.4)
Constipation	4 (1.3)	5 (1.6)	11 (3.4)
Arthralgia	6 (1.9)	7 (2.2)	7 (2.2)
Fatigue	8 (2.5)	6 (1.9)	7 (2.2)
Nausea	6 (1.9)	7 (2.2)	6 (1.9)
Influenza	6 (1.9)	4 (1.3)	8 (2.5)
Urinary tract infection	7 (2.2)	5 (1.6)	7 (2.2)
Back pain	7 (2.2)	6 (1.9)	6 (1.9)
Injection-site pain	1 (0.3)	10 (3.2)	1 (0.3)
Migraine	10 (3.1)	4 (1.3)	3 (0.9)
Hypertension	8 (2.5)	5 (1.6)	0
Adverse event leading to discontinuation of trial regimen	8 (2.5)	7 (2.2)	7 (2.2)
Serious adverse event†	7 (2.2)	8 (2.5)	6 (1.9)

\* Data are for the safety analysis set (all patients who underwent randomization and received at least one dose of erenumab or placebo, analyzed according to randomly assigned trial regimen unless the dose received throughout the double-blind treatment phase differed from the one that had been randomly assigned). More than one adverse event could be reported by a patient.

† Serious adverse events are listed in Table S3 in the Supplementary Appendix.

and the placebo group were observed with regard to the results of hepatic-function testing, creatinine levels, total neutrophil counts, vital signs, or electrocardiographic findings. The results of hepatic-function tests are provided in Table S4 in the Supplementary Appendix. No deaths occurred during the double-blind treatment phase of the trial.

## DISCUSSION

Migraine-preventive treatment with subcutaneous erenumab, a monoclonal antibody to the canonical CGRP receptor, at a monthly dose of 70 mg or 140 mg resulted in a mean reduction in the frequency of migraine days that was significantly greater (by almost 2 days) than that associated with placebo. As compared with placebo, erenumab treatment also resulted in greater reductions

from baseline in the use of acute migraine-specific medications and in the effect of migraine on functioning in adults with episodic migraine.

Typically, a clinical response to migraine therapy has been defined as at least a 50% reduction in mean migraine days per month.<sup>26</sup> The rate of a 50% or greater reduction in mean migraine days in the 140-mg erenumab group was 50.0%, as compared with 26.6% in the placebo group. The clinical benefit of erenumab was corroborated by significantly greater reductions in the number of days per month that acute migraine-specific medications were used in each of the erenumab dose groups, as compared with the placebo group. This trial also assessed the effect of migraine on patients' lives after treatment with erenumab. The observed reductions in physical-impairment and daily-activity scores associated with each dose of erenumab versus placebo sug-



gest that the reduction in migraine frequency translated into a reduction in the effect of migraine on patients. The treatment response achieved with erenumab was apparent from the first efficacy time point at month 1, which suggests that patients had an early benefit (Table S2 in the Supplementary Appendix).

During the 6-month double-blind treatment phase of this trial, no cardiovascular safety signal was observed, and the overall safety profile of erenumab was similar to that of placebo. A total of 90.4% of the patients who received erenumab and 87.1% of the patients who received placebo received all planned doses. Fewer than 3% of patients withdrew from the trial because of adverse events, a rate numerically lower than the rates reported for oral migraine-preventive treatments in studies of similar duration, although a direct comparison with these agents was not made in this trial.<sup>27</sup>

A limitation of this trial was the exclusion of patients who had had no therapeutic response to more than two classes of migraine-preventive drugs (see the Supplementary Appendix for definitions). However, patients could be included in the trial if they had discontinued previous migraine-preventive treatment because of insufficient

efficacy, a lack of sustained response, or unacceptable side effects, and erenumab was found to have efficacy, despite the fact that 38.7% of the patients had previously not had a beneficial effect from migraine-preventive drugs. Efficacy was similarly demonstrated in a phase 2 trial of erenumab involving patients with chronic migraine, in which 68% of patients had previously discontinued migraine-preventive medication because of a lack of efficacy or unacceptable side effects.<sup>24</sup>

The double-blind treatment phase of this trial, conducted over a period of 6 months in patients with episodic migraine, together with other phase 2 and 3 trials of erenumab for the treatment of episodic and chronic migraine,<sup>22,24,28</sup> suggest that erenumab may be useful for the prevention of episodic migraine. Further trials are needed to determine the long-term safety of erenumab and the durability of its effects.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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