

RESEARCH SUBMISSIONS

Erenumab treatment for migraine prevention in Japanese patients: Efficacy and safety results from a Phase 3, randomized, double-blind, placebo-controlled study

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Abstract

Objectives: Erenumab is a human anti-calcitonin gene-related peptide receptor monoclonal antibody approved for migraine prevention. Global studies have demonstrated its efficacy in chronic and episodic migraine (EM). Here we report the outcomes from a Phase 3 study of erenumab in Japanese patients with chronic migraine (CM) or EM.

Methods: Japanese patients with EM (<15 headache days/month, including ≥ 4 migraine days/month) or CM (≥ 15 headache days/month, including ≥ 8 migraine days/month) were randomized 1:1 to placebo or erenumab 70 mg once monthly for a 24-week double-blind treatment phase (DBTP). The primary endpoint of change from baseline in mean monthly migraine days (MMD) over months 4, 5, and 6 of the DBTP was compared between erenumab and placebo groups. Secondary efficacy and safety endpoints were also assessed.

Results: A total of 261 patients were randomized to placebo ($n = 131$) or erenumab 70 mg ($n = 130$); all patients were included in the efficacy and safety analyses. The mean (standard deviation) MMD at baseline was 11.84 (5.70) for the placebo group and 12.40 (5.99) for erenumab 70 mg. The mean (standard error) change in MMD was -1.98 (0.38) for the placebo group ($n = 131$) and -3.60 (0.38) for erenumab 70 mg ($n = 130$). The difference in MMD reduction between groups was -1.67 (95% CI: $-2.56, -0.78, p < 0.001$) for EM and -1.57 (95% CI: $-3.39, 0.24, p = 0.089$) for CM. Adverse events (AEs) were consistent with earlier studies. The most frequent AEs (placebo, erenumab) were nasopharyngitis (28.2% and 26.9%, respectively), back pain (4.6% and 5.4%), and constipation (0.8% and 4.6%).

Conclusion: Treatment with erenumab 70 mg once monthly demonstrated favorable efficacy and safety findings in Japanese patients with EM or CM.

KEYWORDS

chronic migraine, episodic migraine, erenumab, Japan

Abbreviations: AEs, adverse events; CGRP, calcitonin gene-related peptide; CI, confidence interval; CM, chronic migraine; CTCAEs, Common Terminology Criteria for Adverse Events; DBTP, double-blind treatment phase; EM, episodic migraine; MMD, monthly migraine days; OLTP, open-label treatment period; OR, odds ratio; SD, standard deviation; SE, standard error; TEAEs, treatment-emergent AEs.

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INTRODUCTION

Migraine is a disabling disease with high prevalence worldwide. Although acute medications are commonly used for alleviating migraine symptoms, there is an unmet medical need for migraine prevention. In a US survey, one third of patients with migraine met criteria for preventive therapy, but only 13% of migraine patients were actually receiving preventive therapy at the time of the survey.¹ Discontinuation of migraine preventive therapies such as beta-blockers, anti-epileptics, and antidepressants has been attributed to side effects and limited efficacy.² This highlights the importance of novel migraine preventive treatments.

The prevalence of migraine in Japan is approximately 8%.³ Despite this relatively high prevalence, there are limited options approved for migraine prevention available to physicians in Japan compared with other countries.⁴ In Japanese patients with migraine, use of preventive therapy is low with a high rate of discontinuation after a brief period of treatment, and a low rate of reinitiation.⁵ Furthermore, the majority of patients treated with preventive medications are older and with more comorbidities than those treated with acute medications.⁵ Thus, patients and physicians in Japan have a particular need for additional preventive treatment options.

Erenumab (erenumab-aooe in the United States⁶) is a human immunoglobulin G2 that inhibits the action of calcitonin gene-related peptide (CGRP) by binding to the CGRP receptor and fully antagonizing its function.⁷ To date, erenumab 70 and 140 mg administered subcutaneously once monthly has been approved as a migraine preventive medication in more than 60 countries, including the United States and countries in Europe.^{6,8} Erenumab has been proven efficacious and safe in a number of global studies in patients with chronic migraine (CM) or episodic migraine (EM).⁹⁻¹² In Japanese patients with EM, erenumab 70 mg once monthly showed significant efficacy and a favorable safety profile in a Phase 2 trial, with comparable efficacy of the 70 and 140 mg doses; however, erenumab is not yet approved in Japan.¹³

In this study, we report on the primary efficacy and safety outcomes from a Phase 3 study of monthly erenumab treatment in Japanese patients with CM or EM. Based on the efficacy results from a Phase 2 study in Japanese patients,¹³ a dose of 70 mg erenumab was selected and compared with placebo. We hypothesized that patients with migraine would achieve greater reduction from baseline in mean monthly migraine days (MMD) with erenumab treatment compared with placebo.

MATERIALS AND METHODS

Study design

This is a Phase 3, randomized, double-blind, placebo-controlled study in Japanese patients with EM or CM (clinicaltrials.gov identifier NCT03812224) conducted at 41 centers across Japan. The study consisted of a 3-week initial screening period, a 4-week baseline period, a 24-week double-blind treatment phase (DBTP), a 28-week open-label

treatment period (OLTP), and an 8-week safety follow-up period, beginning 12 weeks after the last dose of investigational product. This is a report of results from the DBTP of the study. The protocol was reviewed and approved by an independent ethics committee or institutional review board at each clinical site. All patients provided written informed consent before the start of any procedures. The study was conducted in accordance with the International Council for Harmonisation Good Clinical Practice Guideline and conforms to the provisions of the Declaration of Helsinki. Early stopping guidelines were not applicable for this analysis, and there was no data safety monitoring board.

Site personnel evaluated eligibility, obtained informed consent, and enrolled patients. Enrollment ended when the predetermined sample size was obtained. The first patient was enrolled on April 12, 2019, and the last patient ended the DBTP on February 18, 2020. Patients were randomized in a ratio of 1:1 to placebo or erenumab 70 mg (Figure 1) and stratified by migraine type (EM or CM) and migraine preventive treatment status (ever used [i.e., any current or prior use] or never used). Randomization was prepared by the sponsor and assigned by the interactive response technology system. After randomization, patients received the investigational product once a month subcutaneously. Treatment assignment and future assignments were blinded to all patients, site personnel, and sponsor staff throughout the DBTP through use of an interactive response technology system.

Participants

Japanese patients ≥ 20 to ≤ 65 years of age were eligible for participation if they had provided informed consent prior to study initiation; had a history of migraine (with or without aura) for ≥ 12 months before screening, according to the *International Classification of Headache Disorders*, 3rd edition,¹⁴ based on medical records and/or patient self-report, and had CM or EM over the 3 months before screening. CM was defined as ≥ 15 headache days per month, of which ≥ 8 met criteria as migraine days. EM was defined as 4 to < 15 headache days per month, of which ≥ 4 met criteria as migraine days. During the 4-week baseline phase, patients had to have the same migraine type as assessed by their handheld electronic diary (eDiary) during screening and had to have demonstrated $\geq 80\%$ compliance with their eDiary. At the day 1 study visit, investigators confirmed that patients met inclusion criteria based on data recorded in the eDiary during the baseline period.

Patients were not eligible if they were > 50 years of age at migraine onset; had a history of cluster headache or hemiplegic migraine; were unable to differentiate migraine from other headaches; had migraine with continuous pain, in which the patient does not experience any pain-free periods (of any duration); had no therapeutic response to > 3 migraine preventive treatment categories; received botulinum toxin within 4 months; use of an opioid- or butalbital-containing analgesic on ≥ 4 days per month within 2 months; had current or any prior use of a CGRP monoclonal antibody; used devices or procedures for migraine prevention within 2 months, or

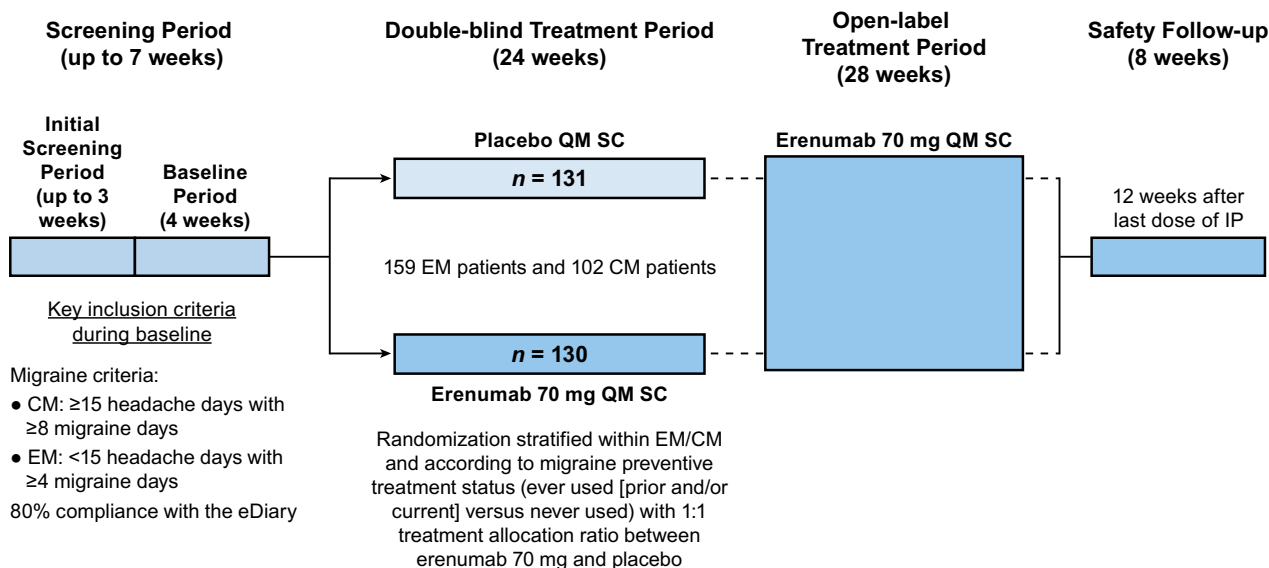


FIGURE 1 Study schema. CM, chronic migraine; eDiary, electronic diary; EM, episodic migraine; IP, investigational product; QM, once monthly; SC, subcutaneously [Color figure can be viewed at wileyonlinelibrary.com]

were taking >1 migraine preventive medication. One migraine preventive medication was allowed with no changes to the dose within 2 months before the start of the baseline phase and throughout the study. Patients using triptans and ergot derivatives were excluded only if they used these medications daily for migraine prevention. Efforts were made throughout the study to avoid introducing new acute migraine-specific medication. Patients were also excluded if they had myocardial infarction, stroke, transient ischemic attack, unstable angina, coronary artery bypass surgery, or other revascularization procedure within 12 months, or if they had a history or evidence of any other clinically significant disorder that would pose a risk to patient safety or interfere with the study evaluation.

Clinical outcome assessments

Patients used an eDiary to report clinical outcome assessments daily during the DBTP. Clinical outcome assessments included the date and time of headache start and end; the worst pain severity of the headache; pain features (e.g., one-sided, throbbing, worsens with exercise/physical activity); associated symptoms (e.g., aura, nausea, vomiting, photophobia, phonophobia), and use of acute headache medications.

Endpoints

The primary endpoint was the change from baseline in mean MMD over months 4, 5, and 6 of the DBTP. A migraine day was defined as any calendar day in which the patient experienced a qualified migraine headache, defined as a headache with or without aura, lasting for ≥ 4 h and having either ≥ 2 pain features or ≥ 1 associated symptom; or a day during which an acute migraine-specific medication was administered regardless of the headache duration, pain features, and associated symptoms. Secondary efficacy endpoints included the achievement

of a $\geq 50\%$ reduction from baseline in mean MMD, and the change from baseline in mean monthly acute migraine-specific medication treatment days over months 4, 5, and 6 of the DBTP.

Safety endpoints were also assessed during the DBTP. The incidence and grade of adverse events (AEs) was measured, using the grading scale from the Common Terminology Criteria for Adverse Events (CTCAEs), version 4.0.¹⁵ Furthermore, patients' clinical laboratory values and vital signs, such as their systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature, were assessed. Patients were also assessed for the presence of anti-erenumab antibodies in blood serum samples taken during the DBTP.

Statistical analyses

The planned sample size was 115 patients per treatment group (approximately 70 subjects with EM and 45 subjects with CM, not including 10% dropout), to provide a $\geq 90\%$ power to detect a treatment difference of -2.11 MMD in the change from baseline between the erenumab 70 mg group and the placebo group, with a standard deviation (SD) of 4.71, based on a two-sided *t* test with a significance level of 0.05. The estimated effect size of the treatment was a weighted average from the results of the Japanese EM study¹³ and global CM study,¹² based on the EM/CM ratio in the number of subjects. The global CM study was used for comparison because no study has previously been conducted in Japanese patients with CM. The assumed treatment variability was also estimated from the aforementioned erenumab studies. Although the study was not powered to achieve statistical significance for the primary efficacy endpoint within each EM or CM cohort, the probability of achieving a point estimate of a clinically meaningful treatment difference of at least -1.0 MMD¹⁶ between the erenumab 70 mg group and the placebo group was 93% in the EM cohort and 88% in the CM cohort.

Baseline characteristics were summarized using the mean and SD, or the number (*n*) and percentage (%) of patients in each group. All endpoints were analyzed based on the entire (EM + CM) population. Preplanned subgroup analyses (e.g., EM, CM) were conducted to assess directional treatment effect but were not powered to demonstrate statistical significance.

The continuous primary and secondary endpoints were analyzed using linear mixed-effects models based on observed monthly data from the 24-week DBTP, which included treatment, visit, treatment-by-visit interaction, stratification factors, and baseline values as covariates. Model assumptions included random intercept, visit, and first-order autoregressive covariance structure, which was reasonable because repeated-measures endpoints had evenly spaced time intervals. Stratification factors were migraine type (EM or CM) and migraine preventive treatment status (ever used or never used). Adjusted analysis results for mean over months 4, 5, and 6 were obtained from the same model using contrasts. Statistical significance was defined as $p < 0.05$ (two-sided). Nominal *p*-values were not adjusted for multiplicity. Missing data were not imputed, and a missing-at-random assumption was used for the linear mixed-effects model. Sensitivity analyses were performed for the primary endpoint and included the last observation carried forward to handle missing data with an analysis of covariance model, and multiple imputation with assumptions of missing-at-random and missing-not-at-random to handle missing data. The dichotomous secondary endpoint was analyzed using a Cochran-Mantel-Haenszel test, stratified by stratification factors, with missing data imputed as nonresponse. Sensitivity analyses for the secondary endpoint included a generalized linear mixed-effects model without imputation of missing data beyond the missing-at-random assumption, and a logistic regression model for each visit after missing data were imputed as nonresponders. When performing analysis for the binary secondary endpoint, nonresponder imputation was conducted for four patients. The common odds ratio (OR) of erenumab 70 mg to placebo over months 4, 5, and 6 of the DBTP with a 95% confidence interval (95% CI) and the nominal *p*-value were provided. Statistical analyses were performed using SAS software, version 9.4 (Cary, NC, USA).

The efficacy analysis set comprised all randomized patients who received at least one dose of the investigational product and had at least one change from baseline measurement in MMD during the DBTP. The safety analysis set comprised all randomized patients who received at least one dose of the investigational product. All AEs were tabulated by treatment group, by system organ class, and by preferred term.

RESULTS

Patient population

A total of 261 patients were randomized to monthly erenumab 70 mg (*n* = 130) or placebo (*n* = 131). Among all randomized patients, 159 patients had EM and 102 patients had CM (Figure 1). All randomized patients met criteria for and were included in the efficacy

and safety analysis sets. Patient demographics and baseline characteristics were generally comparable between groups (Table 1).

All patients received at least one dose of the investigational product. A total of 254 (97.3%) patients completed the DBTP of the study (placebo, *n* = 127/131 [96.9%]; erenumab 70 mg, *n* = 127/130 [97.7%]) (Figure 2). Seven patients did not complete the DBTP for the following reasons: patient request (placebo, *n* = 4; erenumab 70 mg, *n* = 2) and noncompliance (erenumab 70 mg, *n* = 1).

Efficacy

Treatment with erenumab 70 mg was associated with a significant reduction of MMD from baseline, compared with placebo (Figure 3). Over months 4, 5, and 6 of the DBTP, the least squares mean (standard error [SE]) change in MMD from baseline was -1.98 (0.38) for the placebo group and -3.60 (0.38) for the erenumab 70 mg group. The overall difference in MMD reduction between groups was -1.62 (95% CI: -2.52 , -0.73 , $p < 0.001$). Looking at the migraine type subgroups, the difference in MMD reduction between erenumab and placebo was -1.67 (95% CI: -2.56 , -0.78 , $p < 0.001$) for patients with EM and -1.57 (95% CI: -3.39 , 0.24 , $p = 0.089$) for patients with CM. In addition to reducing mean MMDs from baseline, erenumab reduced monthly headache days (migraine and nonmigraine) compared with placebo. Over months 4, 5, and 6 of the DBTP, the least squares mean (SE) change in monthly headache days from baseline was -2.57 (0.41) for the placebo group and -3.85 (0.41) for the erenumab 70 mg group. The overall difference in reduction of monthly headache days from baseline between groups was -1.28 (95% CI: -2.22 , -0.33 , $p = 0.008$).

Erenumab treatment also led to a larger number of patients achieving a $\geq 50\%$ reduction of MMD. The odds of achieving a $\geq 50\%$ reduction from baseline in mean MMD over months 4, 5, and 6 of the DBTP was significantly greater for erenumab 70 mg compared with placebo; 16.8% (22/131) of patients achieved $\geq 50\%$ reduction from baseline in mean MMD with placebo versus 31.5% (41/130) of patients with erenumab 70 mg (Figure 4). The OR was 2.33 for erenumab 70 mg to placebo (95% CI: 1.29, 4.23, $p = 0.005$).

The erenumab 70 mg group showed a significantly larger reduction in mean monthly acute migraine-specific medication treatment days from baseline, compared with placebo (Figure 5). Over months 4, 5, and 6 of the DBTP, the least squares mean (SE) change from baseline was -1.10 (0.32) for the placebo group and -2.57 (0.32) for the erenumab 70 mg group. The overall difference between groups was -1.47 (95% CI: -2.24 , -0.71 , $p < 0.001$).

Safety

Safety results were tabulated from the entire 24-week DBTP (Table 2). Overall, there were similar incidences of treatment-emergent AEs (TEAEs) among erenumab and placebo recipients. The most

TABLE 1 Patient demographics and baseline characteristics

Characteristic	Placebo (N = 131)	Erenumab 70 mg QM (N = 130)	Total (N = 261)
Age in years—mean (SD)	44.6 (9.3)	44.2 (8.5)	44.4 (8.9)
Female, n (%)	116 (88.5)	111 (85.4)	227 (87.0)
Asian, n (%)	131 (100.0)	130 (100.0)	261 (100.0)
BMI in kg/m ² —mean (SD)	21.61 (3.32)	22.15 (3.43)	21.88 (3.38)
Migraine type ^a , n (%)			
Episodic migraine	80 (61.1)	79 (60.8)	159 (60.9)
Chronic migraine	51 (38.9)	51 (39.2)	102 (39.1)
Prior migraine preventive treatment status, n (%)			
Ever used	102 (77.9)	100 (76.9)	202 (77.4)
Prior use only	50 (38.2)	60 (46.2)	110 (42.1)
Prior and current use	41 (31.3)	31 (23.8)	72 (27.6)
Current use only	11 (8.4)	9 (6.9)	20 (7.7)
Never used	29 (22.1)	30 (23.1)	59 (22.6)
Prior migraine preventive treatment failure, n (%)			
Failed ≥1 prior preventive medication class	58 (44.3)	59 (45.4)	117 (44.8)
Failed ≥2 prior preventive medication classes	33 (25.2)	30 (23.1)	63 (24.1)
Acute headache medication use, n (%)	130 (99.2)	129 (99.2)	259 (99.2)
Acute migraine-specific medication use, n (%)	124 (94.7)	125 (96.2)	249 (95.4)

Abbreviations: N, total number of patients; n, subset of patients in group; QM, once monthly; SD, standard deviation.

^aBased on actual data collected instead of randomization stratification.

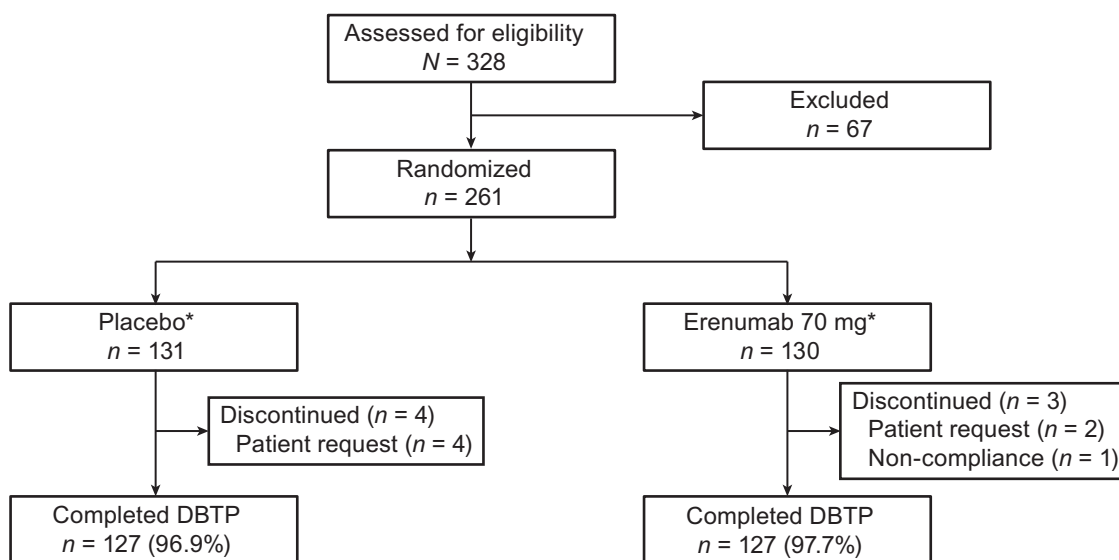


FIGURE 2 Flow of patients through the DBTP of the study. *All randomized patients received ≥1 dose of the investigational product and had ≥1 monthly migraine day measurement and were included in the efficacy and safety analysis sets. DBTP, double-blind treatment phase; N, total number of patients; n, subset of patients

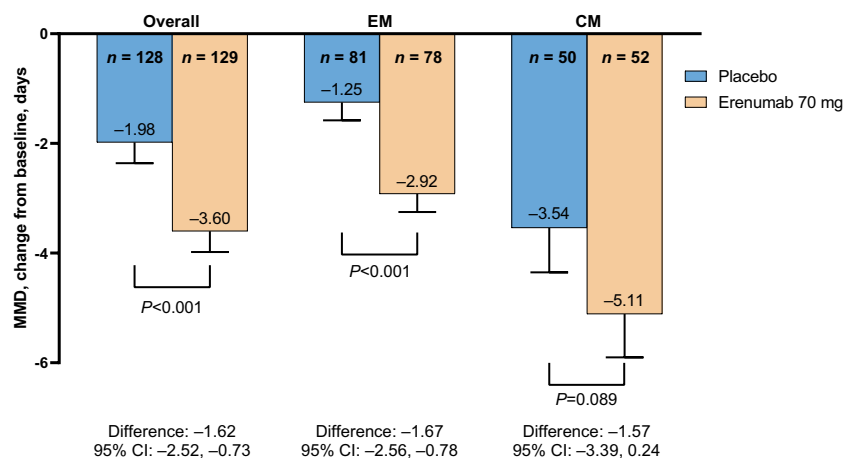


FIGURE 3 Change in MMD over months 4, 5, and 6. Mean change is shown inside each bar. Error bars indicate SE. Mean difference between groups along with a 95% CI and *p*-value is reported on the right. CM, chronic migraine; EM, episodic migraine; MMD, monthly migraine days [Color figure can be viewed at wileyonlinelibrary.com]

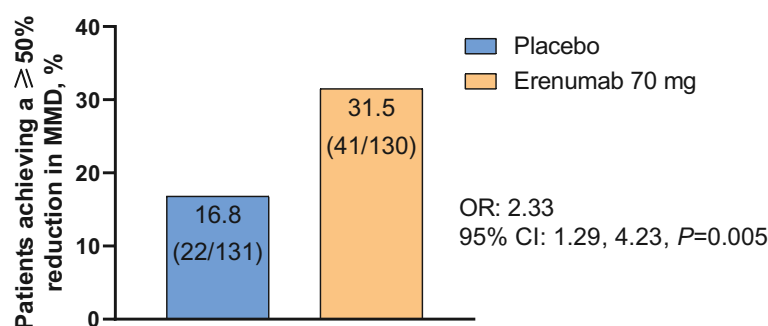


FIGURE 4 Percentage of patients achieving a $\geq 50\%$ reduction in MMD over months 4, 5, and 6. Percentage is calculated as $n/N \times 100\%$, where *n* = subset of patients achieving $\geq 50\%$ reduction in MMD; *N* = total number of patients. Percentage and *n/N* are shown inside each bar. MMD, monthly migraine days; OR, odds ratio [Color figure can be viewed at wileyonlinelibrary.com]

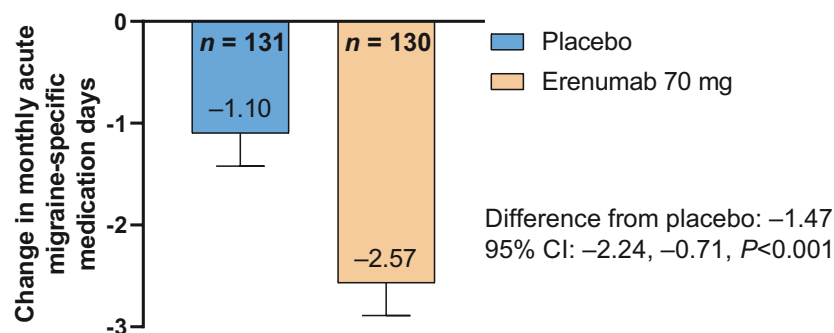


FIGURE 5 Change in monthly acute migraine-specific medication days over months 4, 5, and 6. Mean change is shown inside each bar. Error bars indicate SE. Mean difference between groups along with a 95% CI and *p*-value is reported on the right [Color figure can be viewed at wileyonlinelibrary.com]

frequent ($\geq 4\%$) TEAEs during the DBTP were nasopharyngitis (placebo, $n = 37/131$ [28.2%]; erenumab 70 mg, $n = 35/130$ [26.9%]), back pain (placebo, $n = 6/131$ [4.6%]; erenumab 70 mg, $7/130$ [5.4%]) and constipation (placebo, $n = 1/131$ [0.8%]; erenumab 70 mg, $6/130$ [4.6%]). One patient reported a TEAE of hypertension (placebo, $1/131$ [0.8%], grade 2). Four patients reported serious AEs during the DBTP ($n = 2$ in each group). None of the serious AEs were found to be treatment related.

A total of 5.4% ($n = 7/129$) of patients developed anti-erenumab-binding antibodies during the DBTP (Table 2). Of those patients, two developed transient antibodies, and five had persistent antibodies at the last time point in the DBTP. None of the antibodies were found to be neutralizing based on a validated in vitro neutralizing assay.

DISCUSSION

The data from the DBTP of this Phase 3 study demonstrated the efficacy and safety of erenumab 70 mg in Japanese patients with CM or EM. Compared with placebo, treatment with erenumab 70 mg once monthly was associated with a greater reduction in mean MMD and a greater percentage of patients achieving a $\geq 50\%$ reduction in MMD. In addition, there was a significant decrease in the use of acute migraine-specific medications among erenumab 70 mg recipients compared with placebo. Lastly, generally TEAEs occurred at similar rates between groups. Constipation was more frequent in patients treated with erenumab 70 mg than in placebo recipients. Constipation was also more frequent in erenumab recipients in the DBTP of the Phase 2 study in Japanese patients with EM¹³; however, the rate of

TABLE 2 Summary of safety results during the double-blind treatment phase (DBTP)

	Placebo (N = 131) n (%)	Erenumab 70 mg QM (N = 130) n (%)
Treatment-emergent adverse events (TEAEs) ^a	77 (58.8)	85 (65.4)
CTCAEs grade ≥2	66 (50.4)	72 (55.4)
CTCAEs grade ≥3	2 (1.5)	4 (3.1)
CTCAEs grade ≥4	1 (0.8)	0 (0.0)
TEAEs leading to IP discontinuation	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)
Most frequent TEAEs (≥3% in either treatment group)		
Nasopharyngitis	37 (28.2)	35 (26.9)
Back pain	6 (4.6)	7 (5.4)
Constipation	1 (0.8)	6 (4.6)
Pharyngitis	4 (3.1)	5 (3.8)
Stomatitis	2 (1.5)	5 (3.8)
Diarrhea	1 (0.8)	5 (3.8)
Musculoskeletal stiffness	1 (0.8)	5 (3.8)
Gastroenteritis	4 (3.1)	4 (3.1)
Dental caries	2 (1.5)	4 (3.1)
Serious adverse events	2 (1.5)	2 (1.5)
Intervertebral disc protrusion	0 (0.0)	1 (0.8)
Appendicitis	1 (0.8)	0 (0.0)
Ovarian adenoma	1 (0.8)	0 (0.0)
Brain contusion ^b	0 (0.0)	1 (0.8)
Clavicle fracture ^b	0 (0.0)	1 (0.8)
Skull fracture ^b	0 (0.0)	1 (0.8)
Subarachnoid hemorrhage ^b	0 (0.0)	1 (0.8)
Wound ^b	0 (0.0)	1 (0.8)
Postbaseline anti-erenumab antibody formation during DBTP	NA	129
Developed binding anti-erenumab antibodies	NA	7 (5.4)
Transient ^c	NA	2 (28.6)
Developed neutralizing anti-erenumab antibodies	NA	0 (0.0)

Note: % = $n/N \times 100\%$.

Abbreviations: N, number of patients in the safety analysis set; n, number of patients reporting at least one occurrence; NA, not applicable; QM, once monthly.

^aCoded using MedDRA version 22.1. CTCAEs version 4.03.

^bFrom Patient 60934023019 who reported five serious TEAEs due to a bike accident, which was not treatment related.

^cNegative result at the patient's last time point tested within the DBTP. The percentages for the transient rows are derived from the number of patients who developed antibody-positive binding/neutralizing antibodies during DBTP.

constipation did not increase during the 76-week OLTP.¹⁷ Results from the 28-week OLTP of this Phase 3 study are forthcoming.

For both EM and CM subgroups, the treatment difference for change from baseline in MMD was greater than a 1-day reduction, a threshold considered clinically meaningful.¹⁶ Results were statistically significant for the larger EM subgroup but not for the smaller

CM subgroup. However, it should be noted that the subgroups were not powered to show statistically significant differences.

The baseline characteristics of both the EM and CM subgroups in this study were fairly similar to EM and CM study populations outside of Japan (e.g., baseline MMD for the EM and CM subgroups were 8.3 and 18.6 days, respectively, compared with 8.3 and 17.9 days

reported in global studies^{10,12}). An important difference is the considerably more prominent use of acute migraine-specific medications in this study (95.4% of patients used acute migraine-specific medications, compared with 56.5% and 75% of patients in global EM and CM studies^{10,12}). This difference may exist because concurrent preventive medications were allowed in this study but have largely been excluded from global studies and because all sites in this study were headache centers or centers with care provided by headache specialists.

The efficacy and safety results from this study are in agreement with previous studies evaluating erenumab 70 mg in CM or EM globally.⁹⁻¹² In Japanese patients, the efficacy of erenumab was demonstrated in a Phase 2 study in EM.¹³ There was a notable difference in the placebo response between the two studies on Japanese patients. More specifically, in the Phase 2 study there was almost no placebo response, whereas in the current study the placebo response was more consistent with that observed in global studies. The reasons underlying the different placebo responses in these two studies are unclear. Aside from inclusion of CM patients in the current study, baseline characteristics were otherwise similar. However, the Phase 3 study was conducted after results of the Phase 2 study were available and several CGRP pathway monoclonal antibodies (erenumab, galcanezumab, fremanezumab)^{8,18,19} had been approved outside of Japan, such that the expectation of efficacy was likely greater. The results presented here are relatively short term, up to 6 months of treatment. However, a global Phase 2 study showed sustained efficacy of erenumab 70 mg for 5 years in patients with EM,²⁰ whereas long-term efficacy in CM has also been shown in a 1-year study outside of Japan²¹ and a 2-year open-label extension study in Japanese patients. The low rates of discontinuation in this study and in the OLTP of the Phase 2 study in Japanese patients¹⁷ are consistent with the observed efficacy and safety findings in this study. The demonstrated tolerability of erenumab in this population contrasts with current use of preventive therapy in Japan.

This study has a number of limitations. As mentioned earlier, the placebo response in this study differs from that reported in Japanese patients, although there are some possible explanations that may have led to higher efficacy expectations, such as the approval of other CGRP pathway monoclonal antibodies for migraine prevention, and the availability of results on the efficacy of erenumab after the Phase 2 study. Furthermore, in the present study, the point estimate for change in MMD was similar in the EM and CM subgroups as in the overall study population. Demonstrated efficacy in EM and CM is required for a migraine prevention indication, and inclusion of patients with both migraine types in the same study is efficient and allows for determination of point estimates of efficacy for both subgroups. However, demonstration of statistically significant efficacy should not be expected for individual subgroups. Because the study was not powered to demonstrate statistical significance in the subgroups and the CM subgroup had a low number of patients, no conclusions can be drawn about efficacy in EM versus CM. Additionally, given the small size of these subgroups, the CIs for efficacy are relatively wide. Nonetheless, results from the CM subgroup are consistent with efficacy findings that have been demonstrated in a global CM study.¹²

CONCLUSIONS

Treatment with erenumab 70 mg once monthly demonstrated favorable efficacy and safety findings in Japanese patients with EM or CM. The AEs reported with erenumab treatment were largely similar to those observed in the placebo group, and their incidence was consistent with earlier studies. No new safety concerns were reported.

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CONFLICT OF INTEREST

Takao Takeshima: Nothing to disclose. Fumihiko Sakai: Consulting fees from Amgen. Koichi Hirata: Royalties from Amgen, Astellas, Daiichi Sankyo, Eisai, Merck Sharp & Dohme, and Pfizer. Noboru Imai: Nothing to disclose. Yasuhiko Matsumori: Nothing to disclose. Ryuji Yoshida: Employee of Amgen. Cheng Peng: Employee and stockholder of Amgen. Sunfa Cheng: Employee and stockholder of Amgen. Daniel D. Mikol: Employee and stockholder of Amgen Inc.

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Study concept and design: Sunfa Cheng, Daniel D. Mikol. *Acquisition of data:* Cheng Peng. *Analysis and interpretation of data:* Takao Takeshima, Fumihiko Sakai, Koichi Hirata, Noboru Imai, Yasuhiko Matsumori, Ryuji Yoshida, Cheng Peng, Sunfa Cheng, Daniel D. Mikol. *Drafting of the manuscript:* Cheng Peng, Sunfa Cheng, Daniel D. Mikol. *Revising it for intellectual content:* Takao Takeshima, Fumihiko Sakai, Koichi Hirata, Noboru Imai, Yasuhiko Matsumori, Ryuji Yoshida, Cheng Peng, Sunfa Cheng, Daniel D. Mikol. *Final approval of the completed manuscript:* Takao Takeshima, Fumihiko Sakai, Koichi Hirata, Noboru Imai, Yasuhiko Matsumori, Ryuji Yoshida, Cheng Peng, Sunfa Cheng, Daniel D. Mikol.

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DATA AVAILABILITY STATEMENT

Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: <http://www.amgen.com/datasharing>.

INSTITUTIONAL REVIEW BOARD APPROVAL

Study approval was granted by the IRB at each participating center.

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