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Research Submission

A Randomized Phase 2 Study of Erenumab for the Prevention of Episodic Migraine in Japanese Adults

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Objective.—A phase 2, double-blind, placebo-controlled study to evaluate the efficacy and safety of erenumab for the prevention of episodic migraine in Japanese patients was conducted.

Background.—Previous global clinical studies have demonstrated the efficacy of erenumab in the prevention of migraine.

Methods.—Patients were randomized to placebo or erenumab 28, 70, or 140 mg administered subcutaneously once per month for 6 months. The primary endpoint was change from baseline in mean monthly migraine days over months 4-6 of the double-blind treatment phase. Secondary endpoints included the proportion of patients achieving ≥50% reduction from baseline in mean monthly migraine days (≥50% response) and change from baseline in mean monthly acute migraine-specific medication treatment days (MSMD) and mean Headache Impact Test (HIT-6™) scores. Efficacy outcomes were also determined at months 1, 2, and 3.

Results.—Four hundred and seventy five patients were randomized 2:1:2:2 to placebo and erenumab 28, 70, and 140 mg, respectively. Greater reductions in monthly migraine days were observed for erenumab vs placebo with differences of –1.25 (95% CI: –2.10 to –0.41; *P* = .004), –2.31 (95% CI: –3.00 to –1.62; *P* < .001), and –1.89 (95% CI: –2.58 to –1.20; *P* < .001) days for erenumab 28, 70, and 140 mg. The odds of having a ≥50% response were 3.2, 5.6, and 4.7 times greater for erenumab 28 mg (95% CI: 1.30-7.88; *P* = .009), 70 mg (95% CI: 2.60-12.06; *P* < .001), and 140 mg (95% CI: 2.24-9.99; *P* < .001) than for placebo. Greater reductions from baseline in mean acute monthly MSMD were observed for erenumab vs placebo with differences of –1.07 (95% CI: –1.80 to –0.35; *P* = .004), –2.07 (95% CI: –2.66 to –1.49; *P* < .001), and –2.04 (95% CI: –2.63 to –1.45; *P* < .001) days for erenumab 28, 70, and 140 mg. Erenumab 70 and 140 mg also resulted in greater improvements in HIT-6™ scores. The safety profile was similar across treatment groups. The most common adverse event was nasopharyngitis, which occurred in 29.4% of patients in the placebo group and 28.9%-33.3% of patients in the erenumab groups.

Conclusion.—Monthly subcutaneous injections of erenumab 70 mg demonstrated statistically significant and numerically maximal efficacy with a favorable safety profile, suggesting that erenumab is a potential new therapy for migraine prevention in Japan.

Key words: erenumab, phase 2 trial, headache, episodic migraine, migraine prevention

Abbreviations: CI confidence interval, DBTP double-blind treatment phase, HIT-6 headache impact test, IP investigational product, LSM least squares mean, MMD monthly migraine days, MPFID Migraine Physical Function Impact Diary, MSMD migraine-specific medication treatment days, OR odds ratio, SLE systemic lupus erythematosus

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INTRODUCTION

Migraine occurs in approximately 8% of the Japanese population above the age of 15 years.[1] Pharmacologic interventions for migraine include acute and preventive medications. Although acute migraine-specific medications are used to stop migraines, the goal of preventive treatment is to reduce the frequency and severity of migraine.[2] A number of medications, including lomerizine, valproate, propranolol, amitriptyline, and verapamil, are used in Japan for migraine prophylaxis;[3] however, these agents were not originally developed for migraine prevention and often have limited efficacy and poor tolerability.[4,5]

Placebo-controlled studies of migraine-preventive medications in a Japanese patient population are sparse. In a placebo-controlled, double-blind study of lomerizine, improvement in migraine was statistically significantly greater in the 2 lomerizine dose groups vs placebo.[6] In contrast, a placebo-controlled study of topiramate demonstrated no statistically significant improvement in outcome measures in either of the 2 topiramate dose groups compared with placebo (NCT01081795, unpublished data). There is, therefore, a need for novel therapies to prevent migraine in Japanese patients.

Erenumab (erenumab-aooe in the United States) is a fully human, anti-calcitonin gene-related peptide receptor antibody that is approved in several countries for migraine prevention. To date, 3 global, randomized, double-blind, placebo-controlled, clinical studies have demonstrated the efficacy of erenumab in the prevention of episodic migraine, including patients who had failed previous preventive migraine treatments. In each study, erenumab 140 and/or 70 mg statistically significantly reduced migraine frequency and acute migraine-specific medication use, increased the odds of achieving a ≥50% reduction from baseline in monthly migraine days (MMD), and improved measures of health-related quality of life.[7-10] Erenumab has also demonstrated efficacy in the prevention of chronic migraine,[11] including patients who had failed previous preventive migraine treatments.[12]

The previous global studies did not include Japanese patients. Consequently, as part of the development of erenumab in Japan, we conducted a double-blind, randomized, placebo-controlled, phase 2 study to evaluate the efficacy and safety of erenumab for the prevention of episodic migraine specifically in Japanese patients.

PATIENTS AND METHODS

Study Design.—This phase 2, randomized, double-blind, placebo-controlled study was conducted in Japan at 43 centers with on-site headache specialists and enrolled adult Japanese patients with a history of episodic migraine. The study investigators were responsible for evaluating patient eligibility and enrolling patients into the study. The study comprised a ≤3-week screening phase, 4-week baseline phase, 24-week double-blind treatment phase (DBTP), 76-week open-label treatment phase (increased from 52 weeks after a protocol amendment), and 12-week safety follow-up phase (16 weeks after the last dose of investigational product) (Supporting Fig. 1). Results from the DBTP of the study are reported.

Three dose levels of erenumab (28, 70, and 140 mg) were evaluated. In previous global studies in episodic migraine,[7,9,10] erenumab 70 mg led to statistically significant improvements in multiple outcome measures, whereas improvements with 21 and 7 mg monthly doses were not statistically significant.[7] Exposure-response modeling suggested that reduction in MMD were dose dependent; therefore, a higher 140-mg dose and a lower 28-mg dose were included in the present study to investigate dose-response; the 28-mg dose was expected to result in numerical improvements in MMD, but not to show consistent improvements in most or all efficacy endpoints.

Patients were randomized 2:1:2:2 to placebo or erenumab 28, 70, or 140 mg. Randomization was based on a schedule generated by the study sponsor

Conflict of Interest: Fumihiko Sakai has received consulting fees from Amgen. Takao Takeshima and Yoshihisa Tatsuoka have nothing to disclose. Koichi Hirata has received royalties from Amgen, Astellas, Daiichi Sankyo, Eisai, Merck Sharp & Dohme, and Pfizer. Robert Lenz, Yi Wang, Sunfa Cheng, and Daniel D. Mikol are employees and stockholders of Amgen Inc. Toshiyasu Hirama is an employee of Amgen Astellas BioPharma K.K. and a stockholder of Amgen Inc.
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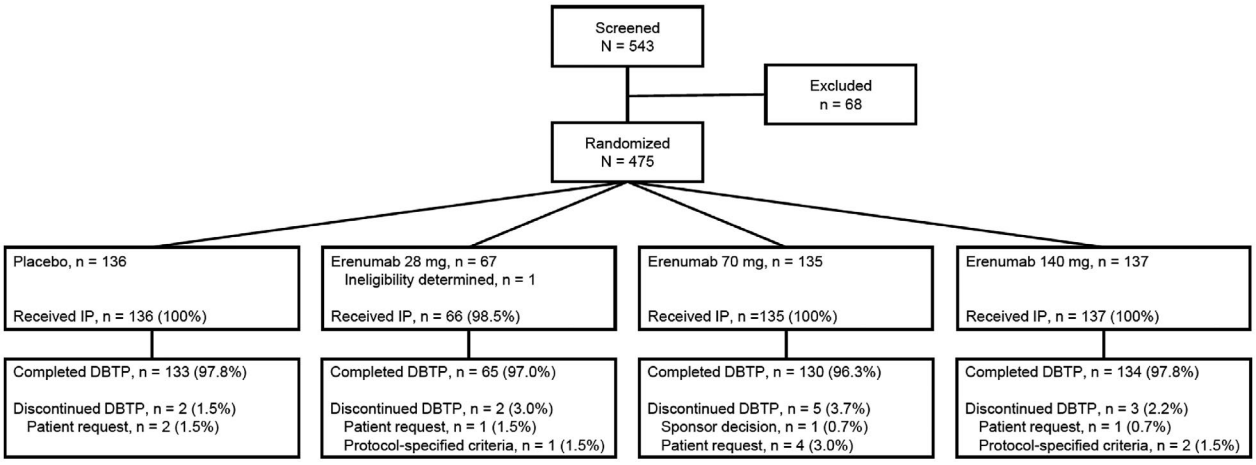

Fig. 1.—Flow of patients through the DBTP of the study. Patients were enrolled between January 6, 2016 and April 10, 2017, and the last patient completed the DBTP on October 2, 2017. Double-blind treatment phase (DBTP); investigational product (IP).

and was centrally executed using an interactive voice response system (Fig. 1). Randomization was stratified by migraine preventive treatment status: current use, previous use only, and no current or previous use. All patients and study personnel were blinded to the investigational products and doses. Patients received investigational product subcutaneously once per month throughout the study.

The protocol was approved by the ethics committee or institutional review board at each clinical site, and all patients provided a signed informed consent before the start of any study-related 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. All authors were given access to the study data.

Participants.—Eligible patients were ≥20-≤65 years old with a history of migraine (with or without aura) for ≥12 months (according to the International Headache Society Classification ICHD-3 beta[13]) based on medical records and/or patient self-report, and migraine frequency of ≥4 and <15 migraine days per month on average across the 3 months prior to screening. During the baseline phase, patients must have demonstrated ≥80% compliance with their handheld electronic diary (eDiary), and migraine frequency was confirmed based on eDiary calculations.

Patients were excluded if they were >50 years old at migraine onset, had a history of cluster headache or hemiplegic migraine, had no therapeutic response to >2 migraine-preventive treatment categories (see Supplementary Material), had received botulinum toxin within 4 months before or during the baseline phase, had used devices or procedures for migraine prevention within 2 months before the baseline phase, or was 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. The complete list of inclusion and exclusion criteria are provided in the Supplementary Material.

Study Procedures.—Patients used an eDiary every day throughout the baseline phase and DBTP to report information about their migraine headaches, non-migraine headaches, and acute headache medication use. Clinical outcome assessments included dates and times of the start and end of migraine headache or non-migraine headache, worst headache pain severity and features, headache symptoms, and use of acute headache medications with date of dosing and number of doses per date.

Patients also used their eDiary to complete a number of patient-reported outcomes questionnaires, including headache impact scores, as measured by the validated Headache Impact Test (HIT-6™);[14-16] migraine pain interference with daily activities, as measured by the Migraine Symptoms Interference Scale; and overall impact on everyday activities, as measured by the validated Migraine Physical Function Impact Diary (MPFID)[17] global question.

Patients could receive any concomitant medications or treatments for adequate supportive care, except for the excluded medications listed in the Supplementary Materials. Concomitant medications were recorded on each patient's case report form or eDiary.

Patients had monthly clinic visits for laboratory tests and collection of vital signs. Safety was monitored throughout the study via reporting of adverse events and serious adverse events (defined according to the Medical Dictionary for Regulatory Activities version 20.1 and graded using the Common Terminology Criteria for Adverse Events version 4.03), laboratory values, vital signs, electrocardiograms, and anti-erenumab antibodies.

Endpoints.—The primary endpoint was the change from baseline in mean MMD over months 4-6 of the DBTP. A migraine day was defined as any calendar day on which the patient had onset, continuation, or recurrence of a qualified migraine headache (migraine with or without aura lasting at least 30 minutes with either ≥2 pain features or ≥1 associated nonpain symptom). Use of an acute migraine-specific medication on a calendar day was considered a migraine day.

Secondary efficacy endpoints were the proportion of patients achieving at least a 50% reduction from baseline in mean MMD over months 4-6 (≥50% response) and change from baseline in mean monthly acute migraine-specific medication treatment days (MSMD) over months 4-6.

Health-related quality of life endpoints were the change from baseline in mean score over months 4-6 in HIT-6™, Migraine Symptoms Interference Scale, and the MPFID global question. The between-group minimally important difference for HIT-6™ is defined as a 1.5-point decrease (–1.5).[18]

All efficacy outcomes were also determined at months 1, 2, and 3.

Statistical Analyses.—Assuming a change from baseline in mean MMD over months 4-6 of –1.12 days and –1.30 days for the 70- and 140-mg dose groups, respectively, vs placebo and a common standard deviation of 2.8 days (based on a clinical study of topiramate in Japanese patients with migraine, NCT01081795), the planned sample size was 131 patients for the placebo, and erenumab 70- and 140-mg dose groups, providing 90% and 96% power, respectively, for a 2-sided test with significance level of .05 to demonstrate the superiority of erenumab.

Statistical analyses were done using SAS version 9.4. Change from baseline in mean MMD (primary endpoint) and change from baseline in mean MSMD (monthly and over months 4-6) were analyzed using a repeated measures linear mixed-effects model that included treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit, without imputation of missing data. Change from baseline in mean MMD was tested for each erenumab treatment group compared with placebo sequentially at a 2-sided significance level of .05 in the order of erenumab 140 mg vs placebo, 70 mg vs placebo, and 28 mg vs placebo. The lower erenumab dose group was tested only when the higher dose group was considered statistically significant. This sequential testing procedure was only performed for the primary endpoint. Data from months 1 to 6 were included in the linear mixed-effects model, and the test of treatment difference between erenumab and placebo over months 4-6 was done using a contrast based on the average of the least squares mean (LSM) difference over months 4-6.

Analysis of ≥50% reduction from baseline in mean MMD was done at each month and over months 4-6. Month 4-6 data were pooled to calculate mean MMD, and ≥50% reduction from baseline in mean MMD was analyzed using a stratified Cochran-Mantel-Haenszel test with missing data imputed as nonresponse. The odds ratio for each erenumab group vs placebo group and associated 95% confidence intervals (CI) are provided.

Normality of the continuous primary and secondary endpoints was verified from histograms, boxplots, and normal probability plots. For all efficacy endpoints, nominal *P* values are provided for the comparison between each erenumab group vs placebo group without multiplicity adjustment.

The efficacy analysis set included all randomized patients who received ≥1 dose of placebo or erenumab and had ≥1 measurement of change from baseline in MMD during the entire DBTP, analyzed according to randomized treatment.

Patient incidence of adverse events was summarized by preferred term. The safety analysis set included

all randomized patients who received ≥1 dose of placebo or erenumab, analyzed according to randomized treatment unless the incorrect dose was received during the DBTP.

RESULTS

Patient Disposition and Baseline Characteristics.—A total of 475 patients were randomized – 136 to placebo, 67 to erenumab 28 mg, 135 to erenumab 70 mg, and 137 to erenumab 140 mg (Fig. 1). Overall, 99.8% (474/475) of patients received ≥1 dose of erenumab or placebo in the DBTP, and 97.3% (462/475) of patients completed the DBTP; 1.5% (2/133) of patients in the placebo group and 3.0% (2/65), 3.7% (5/130), and 2.2% (3/134) of patients in the erenumab 28-, 70-, and 140-mg groups, respectively, discontinued the DBTP. Reasons for discontinuing the DBTP were patient request (1.5% [2/133] placebo, 1.5% [1/65] erenumab 28 mg, 3.0% [4/130] erenumab 70 mg, and 0.7% [1/134] erenumab 140 mg), protocol-specified criteria (1.5% [1/65] erenumab 28 mg and 1.5% [2/134] erenumab 140 mg), and sponsor decision (0.7% [1/130] erenumab 70 mg).

Baseline characteristics were generally well balanced across treatment groups (Table 1). Most patients (81.8%-86.8%) were female; the median age was between 43 and 45 years; and almost all patients (90.4%-95.6%) were taking acute migraine-specific medications. Baseline number of migraine days per month was between 7.7 and 8.1, and days of acute migraine-specific medication use per month was between 5.4 and 5.9. There was an imbalance in the percentage of patients who failed treatment with previous migraine-preventive medications – 65.1% (54/137) in the erenumab 140-mg group compared with 53.0% (44/136), 48.8% (20/67), and 48.9% (43/135) in the placebo, erenumab 28-mg, and erenumab 70-mg groups, respectively.

Baseline HIT-6™ scores were similar across treatment groups, with scores between 57 and 59 representing substantial impact to patients due to headache.[14,16] Baseline Monthly Average Migraine Symptoms Interference scores and total MPFID scores were also similar across treatment groups (Table 1).

Efficacy.—*MMD*.—In the DBTP, all doses of erenumab resulted in a statistically significantly greater reduction in mean MMD compared with placebo at all time points ($P < .05$ for erenumab 28 mg; $P < .001$ for erenumab 70 and 140 mg; Fig. 2). Over months 4-6 of the DBTP, the mean MMD was reduced by 1.19 (95% CI: –1.91 to –0.47), 2.25 (95% CI: –2.78 to –1.73), and 1.83 (95% CI: –2.35 to –1.31) days in the erenumab 28-, 70-, and 140-mg groups, respectively, compared with an increase of 0.06 (95% CI: –0.46 to 0.58) days in the placebo group (Table 2). Differences from placebo were –1.25 (95% CI: –2.10 to –0.41), –2.31 (95% CI: –3.00 to –1.62), and –1.89 (95% CI: –2.58 to –1.20) days for the erenumab 28-, 70-, and 140-mg groups, respectively ($P = .004$ for the 28-mg group; $P < .001$ for the 70- and 140-mg groups).

At Least 50% Response.—In the DBTP, all doses of erenumab resulted in a statistically significantly higher percentage of patients having a ≥50% response compared with placebo at all timepoints ($P < .05$ for erenumab 28 mg; $P < .001$ for erenumab 70 and 140 mg; Fig. 3). A ≥50% response over months 4-6 was achieved by 19.7% (13/66), 28.9% (39/135), and 27.2% (37/136) of patients who received erenumab 28, 70, and 140 mg, respectively, compared with 7.4% of those receiving placebo. The odds of having a ≥50% response over months 4-6 were 3.21 (95% CI: 1.30-7.88), 5.60 (95% CI: 2.60-12.06), and 4.73 (95% CI: 2.24-9.99) times greater for the 28-, 70-, and 140-mg groups, respectively, than for the placebo group ($P = .009$ for the 28-mg group; $P < .001$ for the 70- and 140-mg groups; Table 2).

Monthly Acute MSMD.—In the DBTP, the 70- and 140-mg doses of erenumab resulted in a statistically significantly greater reduction in mean monthly acute MSMD compared with placebo at all time points ($P < .001$; Fig. 4). Over months 4-6 of the DBTP, the mean monthly acute MSMD was reduced by 0.19 (95% CI: –0.80 to 0.43), 1.19 (95% CI: –1.64 to –0.74), and 1.16 (95% CI: –1.60 to –0.71) days in the erenumab 28-, 70-, and 140-mg groups, respectively, compared with an increase of 0.88 days in the placebo group. Differences from placebo were –1.07 (95% CI: –1.80 to –0.35), –2.07 (95% CI: –2.66 to –1.49), and –2.04 (95% CI: –2.63 to –1.45) days for the 28-, 70-, and 140-mg groups, respectively ($P = .004$ for the 28-mg group; $P < .001$ for the 70- and 140-mg groups; Table 2).

Patient-Reported Outcomes.—*HIT-6™*.—The 70- and 140-mg doses of erenumab resulted in greater reductions (improvements) in HIT-6™ scores over

Table 1.—Baseline Demographics and Clinical Characteristics

	Placebo (N = 136)	Erenumab 28 mg (N = 67)	Erenumab 70 mg (N = 135)	Erenumab 140 mg (N = 137)
Sex, female, n (%)	118 (86.8)	55 (82.1)	115 (85.2)	112 (81.8)
Age, years, median (range)	45 (21-61)	43 (22-57)	44 (20-64)	45 (23-64)
Body mass index, kg/m^2, mean (SD)	22.1 (3.5)	22.1 (3.5)	21.6 (3.5)	22.0 (3.5)
Migraine with aura,† n (%)	33 (24.3)	15 (22.4)	39 (28.9)	37 (27.0)
Migraine without aura,† n (%)	127 (93.4)	64 (95.5)	121 (89.6)	130 (94.9)
Migraine-preventive medication use, n (%)				
No current or previous use	47 (34.6)	23 (34.3)	45 (33.3)	45 (32.8)
Previous use only	76 (55.9)	38 (56.7)	80 (59.3)	77 (56.2)
Current use	13 (9.6)	6 (9.0)	10 (7.4)	15 (10.9)
Acute headache medication use, n (%)				
Migraine-specific	130 (95.6)	61 (91.0)	122 (90.4)	126 (92.0)
Nonmigraine-specific	75 (55.1)	44 (65.7)	86 (63.7)	81 (59.1)
Failed previous migraine-preventive medications, n (%)	44 (53.0)	20 (48.8)	43 (48.9)	54 (65.1)
Assessment of migraine at baseline, mean (SD)				
Migraine days per month	7.7 (2.3)	7.7 (2.1)	7.8 (2.3)	8.1 (2.4)
Headache days per month	9.1 (2.6)	8.9 (2.2)	9.0 (2.4)	9.6 (2.6)
Days of acute migraine-specific medication use per month	5.6 (2.5)	5.5 (2.8)	5.4 (2.9)	5.9 (2.9)
HIT-6™ total score,‡ mean (SD)	58.7 (5.1)	57.4 (6.6)	58.9 (5.3)	58.2 (4.9)
Monthly Average Migraine Symptoms Interference,‡ mean (SD)	1.1 (0.5)	1.2 (0.7)	1.2 (0.7)	1.2 (0.6)
Overall impact of migraine on everyday activities,‡, § mean (SD)	9.6 (4.8)	10.2 (6.0)	10.5 (6.1)	10.5 (5.5)

N = number of randomized patients.
†Patients may have reported migraine with aura and/or migraine without aura.
‡Baseline scores are reported for patients who received ≥1 dose of investigational product and had ≥1 change from baseline measurement in monthly migraine days (placebo, N = 136; erenumab 28 mg, N = 66; 70 mg, N = 135; 140 mg, N = 136).
§As measured using the Migraine Physical Function Impact Diary.
HIT-6™ = Headache Impact Test; SD = standard deviation.

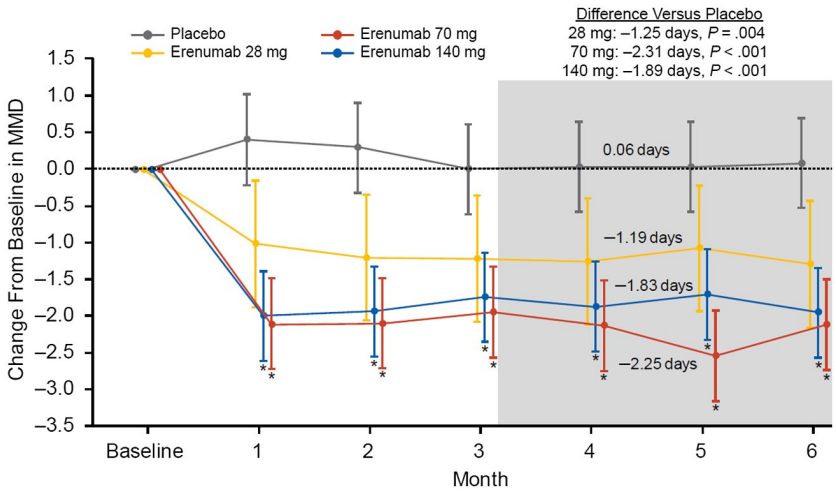

Fig. 2.—Change from baseline in MMD. Data are shown as LSM with 95% CIs. The gray-shaded area represents months 4-6. Confidence interval (CI); least squares mean (LSM); monthly migraine days (MMD). *Denotes statistical significance.

months 4-6 compared with placebo; the between-group differences for the 70- and 140-mg groups vs placebo were statistically significant ($P < .001$ and $P = .001$, respectively) and exceeded the between-group minimally important difference for HIT-6™ (–1.5; Table 2). The odds of achieving a clinically meaningful ≥5-point reduction (improvement) from baseline in HIT-6™ scores over months 4-6 were 1.54 (95% CI: 0.93-2.54) and 1.76 (95% CI: 1.07-2.89) times greater for the 70- and 140-mg groups, respectively, than for the placebo group ($P = .092$ and $P = .024$, respectively; Table 2).

Monthly Average Migraine Symptoms Interference.—Treatment with erenumab 70 and 140 mg resulted in greater reductions (improvements) in Monthly Average Migraine Symptoms Interference scores over months 4-6 compared with placebo. The between-group differences for the 70- and 140-mg groups vs placebo were statistically significant ($P < .001$; Table 2).

MPFID.—Treatment with erenumab 70 and 140 mg resulted in greater reductions (improvements) in the overall impact of migraine on everyday activities score over months 4-6 compared with placebo. The between-group differences for the 70- and 140-mg groups vs placebo were statistically significant ($P < .001$; Table 2).

Safety.—Most patients (98.5% [134/136], 98.5% [65/66], 94.1% [127/135], and 97.1% [133/137] in the placebo, and erenumab 28-, 70-, and 140-mg groups, respectively) received all 6 planned doses of investigational product in the DBTP.

The incidence of adverse events, grade ≥3 adverse events, serious adverse events, and adverse events leading to the discontinuation of investigational product were similar across treatment groups (Table 3). There was no dose relationship among groups for the incidence of the most frequently reported adverse events (in ≥2% of patients in any group), which were nasopharyngitis, constipation, pharyngitis, back pain, dental caries, gastroenteritis, and upper abdominal pain (Table 3). There was a higher incidence of injection site adverse events in the erenumab groups compared with the placebo group, all occurring in 3% or less of patients; among all injection site reactions, the highest incidence was injection site pain (2 patients [3%] in the 28-mg group). The incidence of constipation was 1.5% (2/136), 4.4% (6/135), and 5.1% (7/137) in the placebo, and erenumab 70- and 140-mg groups, respectively.

Seven patients had serious adverse events, 3 in the erenumab groups and 4 in the placebo group. Serious adverse events in the erenumab group (1 patient each) were grade 4 systemic lupus erythematosus (SLE) leading to withdrawal of erenumab (considered related to treatment), grade 3 hand fracture, and grade 2 gastroenteritis and intestinal tuberculosis. The patient reporting the adverse event of SLE was a 49-year-old female who had rheumatoid arthritis for approximately 12 years (currently treated with methotrexate and prednisolone) and a history of easy bruising in her mid-teens (no workup). She had received 6 doses of erenumab when she presented with pancytopenia (manifested by decreased platelet and white blood cell counts), and she was eventually diagnosed with SLE by Systemic Lupus International Collaborating Clinics Classification criteria. The patient was treated with steroids, and 8 months after the last dose of erenumab, her disease was reported as stable. Serious adverse events in the placebo group (1 patient each) were grade 3 hemorrhoids, grade 3 migraine, grade 2 prinzmetal angina, and grade 3 renal cell carcinoma.

Three patients had adverse events leading to the withdrawal of investigational product – 1 in the placebo group due to migraine, 1 in the 70-mg group due to SLE (described above), and 1 in the 70-mg group due to pruritic rash. No deaths occurred during the DBTP.

During the DBTP, 8/338 patients (2.4%) developed anti-erenumab binding antibodies after administration of erenumab – 4 in the 28-mg group, 4 in the 70-mg group, and none in the 140-mg group. None of these patients developed neutralizing antibodies against erenumab.

DISCUSSION

In this population of Japanese patients with episodic migraine, preventive treatment with erenumab 70 and 140 mg led to statistically significant improvements in each of the efficacy endpoints – change from baseline in MMD and MSMD as well as achievement of ≥50% response. Consistent with findings from previous global studies of episodic and chronic migraine,[19] responses to erenumab in the Japan study were

Table 2.—*Clinical Responses and Patient-Reported Outcomes over Months 4-6 of the Double-Blind Treatment Phase*

	Placebo (N = 136)	Erenumab 28 mg (N = 66)	Erenumab 70 mg (N = 135)	Erenumab 140 mg (N = 136)
Migraine days per month				
Change from baseline, LSM (95% CI)	0.06 (–0.46 to 0.58)	–1.19 (–1.91 to –0.47)	–2.25 (–2.78 to –1.73)	–1.83 (–2.35 to –1.31)
Difference from placebo, LSM (95% CI)		–1.25 (–2.10 to –0.41)	–2.31 (–3.00 to –1.62)	–1.89 (–2.58 to –1.20)
		P = .004	*P* < .001	*P* < .001
Patients with ≥50% reduction from baseline in migraine days per month (≥50% response)				
n (%)	10 (7.4)	13 (19.7)	39 (28.9)	37 (27.2)
OR† (95% CI)		3.21 (1.30 to 7.88)	5.60 (2.60 to 12.06)	4.73 (2.24 to 9.99)
		P = .009	*P* < .001	*P* < .001
Days of use of acute migraine-specific medication per month				
Change from baseline, LSM (95% CI)	0.88 (0.44 to 1.33)	–0.19 (–0.80 to 0.43)	–1.19 (–1.64 to –0.74)	–1.16 (–1.60 to –0.71)
Difference from placebo, LSM (95% CI)		–1.07 (–1.80 to –0.35)	–2.07 (–2.66 to –1.49)	–2.04 (–2.63 to –1.45)
		P = .004	*P* < .001	*P* < .001
HIT-6™				
Change from baseline, LSM (95% CI)	–2.2 (–3.1 to –1.3)	–2.5 (–3.7 to –1.2)	–4.3 (–5.2 to –3.4)	–4.2 (–5.1 to –3.3)
Difference from placebo, LSM (95% CI)		–0.3 (–1.7 to 1.2)	–2.1 (–3.3 to –0.9)	–2.0 (–3.2 to –0.8)
		P = .73	*P* < .001	*P* = .001
Achievement of ≥5-point reduction from baseline in HIT-6™				
n (%)	43 (31.6)	17 (25.8)	56 (41.5)	61 (44.9)
Difference from placebo, %, OR (95% CI)		–5.9, 0.75 (0.38 to 1.47)	9.9, 1.54 (0.93 to 2.54)	13.2, 1.76 (1.07 to 2.89)
		P = .40	*P* = .092	*P* = .024
Monthly Average Migraine Symptoms Interference				
Change from baseline, LSM (95% CI)	–0.04 (–0.14 to 0.06)	–0.19 (–0.33 to –0.05)	–0.36 (–0.46 to –0.26)	–0.34 (–0.44 to –0.24)
Difference from placebo, LSM (95% CI)		–0.15 (–0.31 to 0.01)	–0.32 (–0.45 to –0.19)	–0.30 (–0.43 to –0.17)
		P = .069	*P* < .001	*P* < .001
Overall impact of migraine on everyday activities‡				
Change from baseline, LSM (95% CI)	0.20 (–0.70 to 1.10)	–1.23 (–2.47 to 0.02)	–2.32 (–3.23 to –1.41)	–2.13 (–3.02 to –1.23)
Difference from placebo, LSM (95% CI)		–1.43 (–2.90 to 0.04)	–2.52 (–3.72 to –1.33)	–2.33 (–3.52 to –1.14)
		P = .056	*P* < .001	*P* < .001

The analysis included randomized patients who received ≥1 dose of investigational product and had ≥1 postbaseline measurement during the double-blind treatment phase. The adjusted analysis utilized a generalized linear mixed model, which included treatment, visit, treatment by visit interaction, stratification factor (previous/current treatment with migraine-preventive medication), and baseline value as covariates and assumed a first-order autoregressive covariance structure. *P* values for pairwise comparisons were nominal *P* values without multiplicity adjustment.

†The common ORs and *P* values were obtained from a Cochran-Mantel-Haenszel test, stratified by prior/current treatment with migraine prophylactic medication.

‡As measured using the Migraine Physical Function Impact Diary.

CI = confidence interval; HIT-6™ = Headache Impact Test; LSM = least squares means; OR = odds ratio.

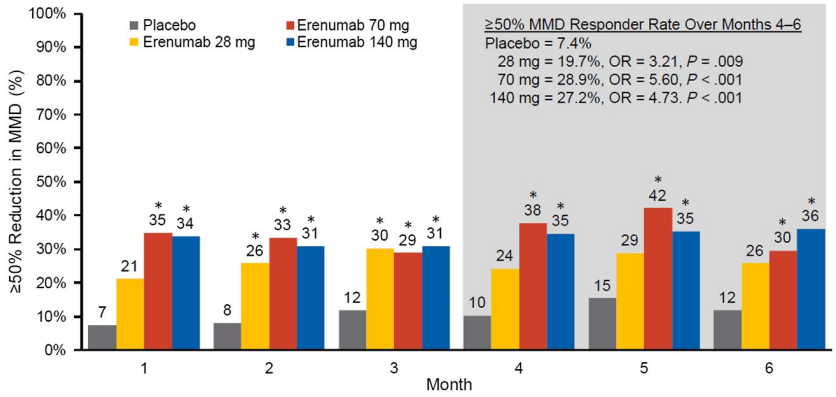

Fig. 3.—Patients achieving ≥50% reduction from baseline in MMD. Data are shown as percentages. The gray-shaded area represents months 4-6. Monthly migraine days (MMD); odds ratio (OR). *Denotes statistical significance.

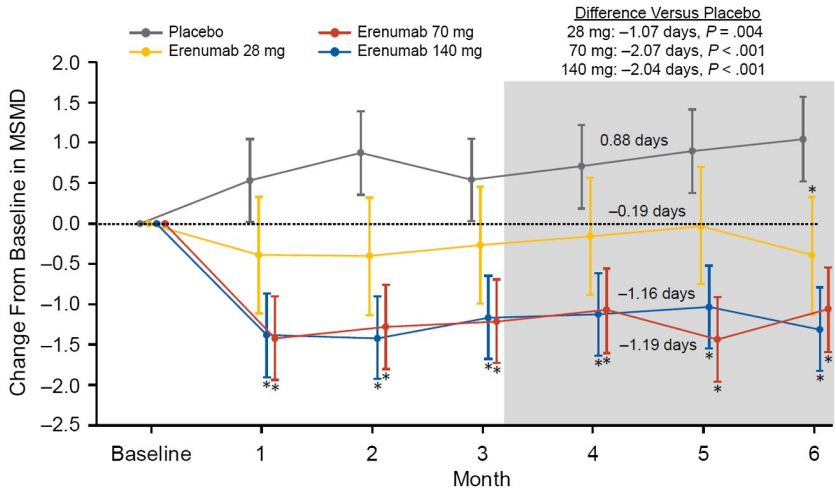

Fig. 4.—Change from baseline in MSMD. Data are shown as LSM with 95% CIs. The gray-shaded area represents months 4-6. Confidence interval (CI); least squares mean (LSM); migraine-specific medication treatment days (MSMD). *Denotes statistical significance.

observed at the earliest measured time point (month 1) and were maintained over the 6 months of the DBTP. Improvements in outcome measures were similar in the erenumab 70- and 140-mg groups, except for the slightly greater numeric effect of erenumab 70 mg on change from baseline in MMD; partial efficacy was observed for the 28-mg group.

In this Japanese patient population, the erenumab 70-mg dose appeared to be as effective as the 140-mg dose in improving patient outcomes. In the global STRIVE study, however, maximal efficacy was observed with the 140-mg dose.[9] Because the Japanese population had a lower body mass index than the global study population (22.0 vs 27.2 kg/m^2), this finding is likely attributable to differences in erenumab exposure between the 2 populations.

The placebo-corrected treatment differences for the primary and secondary endpoints of this study are similar to those observed in global studies, demonstrating consistency of a clinically meaningful treatment effect of erenumab across global and Japanese migraine populations. A very low placebo response was observed in the current study: the placebo group demonstrated no reductions in MMD or MSMD at any time point. Factors that may contribute to a lower placebo response in our study are that most of the

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

n (%)	Placebo (N = 136)	Erenumab 28 mg (N = 66)	Erenumab 70 mg (N = 135)	Erenumab 140 mg (N = 137)
Adverse events	92 (67.6)	40 (60.6)	95 (70.4)	95 (69.3)
Adverse events in ≥2% of patients in any group				
Nasopharyngitis	40 (29.4)	22 (33.3)	39 (28.9)	45 (32.8)
Constipation	2 (1.5)	0 (0.0)	6 (4.4)	7 (5.1)
Pharyngitis	3 (2.2)	3 (4.5)	5 (3.7)	3 (2.2)
Back pain	2 (1.5)	3 (4.5)	7 (5.2)	1 (0.7)
Dental caries	3 (2.2)	2 (3.0)	6 (4.4)	2 (1.5)
Gastroenteritis	4 (2.9)	2 (3.0)	2 (1.5)	5 (3.6)
Upper abdominal pain	1 (0.7)	1 (1.5)	5 (3.7)	2 (1.5)
Grade ≥3 adverse events	4 (2.9)	1 (1.5)	3 (2.2)	0 (0.0)
Serious adverse events	4 (2.9)	1 (1.5)	1 (0.7)	1 (0.7)
Adverse events leading to discontinuation of investigational product	1 (0.7)	0 (0.0)	2 (1.5)	0 (0.0)

Adverse events were graded using Common Terminology Criteria for Adverse Events version 4.03 and coded using Medical Dictionary for Regulatory Activities version 20.1. Analysis of safety included all patients who received ≥1 dose of investigational product, analyzed according to randomized treatment unless the incorrect dose was received during the double-blind treatment phase.

participating clinical sites were headache specialty centers, and a high proportion of enrolled patients were current/previous users of migraine-preventive treatments and used acute migraine-specific medications during the baseline phase. Compared with a global study similar in design,[9] a much higher proportion of patients in the current study used acute migraine-specific medications at baseline (92.4% of the Japanese study population and 58.8% of the global study population). Previous/current use of acute/preventive migraine medications may have lowered the patients' expectation for improvement in migraine while participating in the study – lower patient expectation is associated with a lower placebo response.[20] In a recent study of erenumab comprised entirely of treatment-experienced patients with episodic migraine who had failed at least 2 previous preventive treatments, the placebo response was close to 0.[8] In our study, the mean MMD was increased by 0.06 days in the placebo group, and only 7.4% of patients in the placebo group achieved a ≥50% response. Given the variable placebo response rates in different studies, which may be attributable to study population characteristics, intervention type, and variations in study design, the most appropriate way to contextualize response in a specific study is relative to the placebo response, in the form of an odds ratio. This conveys the odds of achieving a threshold of response relative to the odds for the placebo group. In the current study, the odds of achieving a ≥50% MMD response over months 4-6 were approximately 5 times greater for patients on erenumab than the odds for patients in the placebo group.

In addition to improving clinical outcomes, erenumab 70 and 140 mg improved all measures of patient-reported outcomes compared with placebo. The MPFID score is a reliable and validated psychometric measure,[17] and the overall impact of migraine on the everyday activities component of MPFID statistically significantly improved with erenumab 70- and 140-mg groups compared with placebo. The odds of achieving a clinically meaningful ≥5-point reduction in HIT-6™ scores was statistically significant in the erenumab 140-mg group, but not in the 70-mg group. In addition, the between-group differences in HIT-6™ scores at 70 and 140 mg vs placebo over months 4-6 exceeded the between-group minimally important difference for HIT-6™ (–1.5) and were comparable to the global study.[21] These data demonstrate clinically meaningful improvements in quality of life among Japanese patients receiving erenumab.

The overall incidence of adverse events was consistent with the global studies, and there were no notable differences among the treatment groups. Nasopharyngitis and constipation were the only events

that occurred at an incidence of ≥2% in the erenumab group in both the Japan and the global study. Based on global studies, constipation has been identified as an adverse drug reaction with erenumab, and in the current Japan study, there was a higher and dose-dependent incidence of constipation in the erenumab groups. The incidence of serious adverse events and adverse events leading to treatment discontinuation was low in both studies and comparable across the erenumab and placebo groups. The immunogenicity of erenumab in Japanese patients was lower than what has been observed globally; however, immunogenicity in this patient population will continue to be assessed in the ongoing open-label extension study. Overall, our data indicate that erenumab has a similar safety profile among Japanese and (predominantly) Caucasian patients.

A limitation of the current analysis is that it focuses on the 6-month DBTP of the study and does not inform on the long-term safety or sustained efficacy of erenumab in this patient population; however, long-term data will be available when the 76-week open-label part of the study is completed. Long-term (up to 64 weeks) efficacy and safety of erenumab in patients with episodic migraine has been demonstrated in a global open-label extension study.[22]

CONCLUSION

In this placebo-controlled study of erenumab for the prevention of episodic migraine in Japanese patients, monthly subcutaneous injections of erenumab 70 mg demonstrated numerically maximal efficacy with a favorable safety profile. The results of our study suggest that erenumab is a potential new therapy for migraine prevention in Japan. A phase 3 study in Japanese patients is planned.

DATA SHARING STATEMENT

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

PREVIOUS PRESENTATION

These data were presented in part at the 46th Congress of the Japanese Headache Society; Kobe, Japan; November 16-17, 2018.

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