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RESEARCH SUBMISSION

Long-term efficacy and safety during open-label erenumab treatment in Japanese patients with episodic migraine

Fumihiko Sakai MD, PhD[1] | Takao Takeshima MD, PhD[2] | Yoshihisa Tatsuoka MD, PhD[3] | Koichi Hirata MD, PhD[4] | Sunfa Cheng MD[5] | Yotaro Numachi MD, PhD[6] | Cheng Peng PhD[7] | Fei Xue MD[8] | Daniel D. Mikol MD, PhD[5]

[1]Neurology, Saitama International Headache Center, Saitama, Japan

[2]Headache Center, Department of Neurology, Tominaga Hospital, Osaka, Japan

[3]Department of Neurology, Tatsuoka Neurology Clinic, Kyoto, Japan

[4]Department of Neurology, Dokkyo Medical University, Tochigi, Japan

[5]Global Development, Amgen Inc., Thousand Oaks, CA, USA

[6]Research & Development, Amgen K.K., Tokyo, Japan

[7]Global Biostatistical Science, Amgen Inc., Thousand Oaks, CA, USA

[8]Global Safety, Amgen Inc., Thousand Oaks, CA, USA

Correspondence
Fumihiko Sakai, Neurology, Saitama International Headache Center, Saitama, Japan.
Email: fsakai@mist.dti.ne.jp

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Abstract

Objective: To assess long-term (up to 2 years) efficacy, tolerability, and safety of erenumab for the prevention of episodic migraine (EM) in Japanese patients.

Background: Previously published results from the double-blind treatment phase (DBTP) of a phase 2 clinical study have demonstrated the efficacy and safety of erenumab in Japanese patients with EM.

Methods: Patients completing the 24-week placebo-controlled DBTP could continue into the 76-week open-label treatment phase (OLTP), receiving erenumab 70 mg or 140 mg subcutaneously once monthly. The initial dose in the OLTP was erenumab 70 mg monthly, which was later changed to 140 mg. After study completion, the following were assessed: change from baseline in monthly migraine days (MMD), change from baseline in monthly acute migraine-specific medication days (MSMD), percentage of patients achieving ≥50% and ≥75% reduction in MMD, change from baseline in the 6-item Headache Impact Test (HIT-6™) score, and safety (exposure-adjusted patient-incidence of adverse events [AEs], calculated as number of patients per 100 patient-years).

Results: Of 475 patients enrolled in the DBTP, 459 (96.6%) continued in the OLTP. The mean (SD) MMD was 7.9 (2.3) at baseline with the overall change from baseline at week 100 of −2.9 (4.1) days. The monthly acute MSMD was 5.7 (2.8) at baseline with change from baseline at week 100 of −1.7 (3.7) days. The proportion of patients who achieved ≥50% and ≥75% reduction in MMD from baseline at week 100 was 177/398 (44.5%) and 94/398 (23.6%), respectively. The HIT-6™ score was 58.4 (5.4) at baseline with a change of −6.4 (8.2) at week 100. The exposure-adjusted patient-incidence of AEs during the OLTP was 207.1/100 patient-years for the combined erenumab group, similar to that observed for either erenumab (271.0/100 patient-years) or placebo (257.3/100 patient-years) during the DBTP, and no new safety signals were detected during the OLTP.

Abbreviations: AEs, adverse events; DBTP, double-blind treatment phase; EM, episodic migraine; HIT-6™, 6-item Headache Impact Test; MMD, monthly migraine days; MSMD, migraine-specific medication days; OLTP, open-label treatment phase; SAE, serious adverse event; SC, subcutaneously; SD, standard deviation.

Conclusion: Long-term erenumab treatment in Japanese patients with EM demonstrated sustained efficacy for up to 2 years, with a safety profile similar to previous studies, supporting erenumab as a potential new therapy for EM prevention in Japan.

KEYWORDS
efficacy, episodic migraine, erenumab, Japanese, long-term, safety

INTRODUCTION

In Japan, migraine affects approximately 8% of the population.[1] Even though a substantial proportion of patients with migraine are candidates for preventive therapy, a retrospective analysis indicated that only 15% of Japanese migraine patients were using preventive treatment at index and the discontinuation rates ranged from 67% to 83%.[2] The reason for the low use of preventive therapy and high discontinuation rates is often attributed to insufficient efficacy and side effects of available treatments, underscoring a major unmet need for new preventive therapies.[3] Studies to assess the long-term efficacy, tolerability, and safety of preventive treatments are needed, especially considering that patients might receive preventive therapy for many years.

Erenumab, a fully human monoclonal antibody that selectively targets and blocks the calcitonin gene-related peptide receptor complex, has been approved in the United States and European Union for migraine prevention. Multiple global clinical studies have demonstrated the efficacy and safety of erenumab in the prevention of episodic migraine (EM) and chronic migraine (CM), including patients whose previous preventive treatments were deemed unsuccessful.[4–7] Results from a 4.5-year+ open-label treatment phase (OLTP)[4] support the sustained efficacy and favorable safety profile of erenumab.[8,9] Erenumab has also exhibited sustained efficacy and safety for the prevention of CM.[10] The 24-week placebo-controlled double-blind treatment phase (DBTP) of this phase 2 study in Japanese patients with EM demonstrated efficacy and safety of monthly subcutaneous injections of erenumab.[11] In this descriptive study, we report the long-term efficacy, safety, and tolerability of erenumab during the 1.5-year OLTP.

METHODS

Study design

This was a multicenter, 76-week, OLTP following a 24-week double-blind, randomized phase 2 clinical trial (NCT02630459), conducted at 43 centers with headache specialists in Japan.[11] The OLTP started on June 22, 2016 (first patient entered OLTP) to June 5, 2019 (last patient completed the 12-week safety follow-up phase). Patients with EM received placebo or erenumab 28, 70, or 140 mg administered subcutaneously (SC) once monthly (every 4 weeks) during the DBTP. Patients who entered the OLTP initially received erenumab 70 mg SC monthly. A protocol amendment increased the dose to 140 mg monthly to evaluate the long-term safety of the higher dose. Patients who had started the OLTP and had completed their pre-scheduled week 48 visit at the time of the amendment continued to receive erenumab 70 mg monthly throughout the OLTP; patients who had started the OLTP but had not yet completed the week 48 visit increased dose from 70 to 140 mg monthly at the next visit, and continued on 140 mg monthly until week 100; patients who were still in the DBTP and had not yet entered the OLTP at the time of protocol amendment approval received erenumab 140 mg monthly throughout the OLTP (Figure 1).

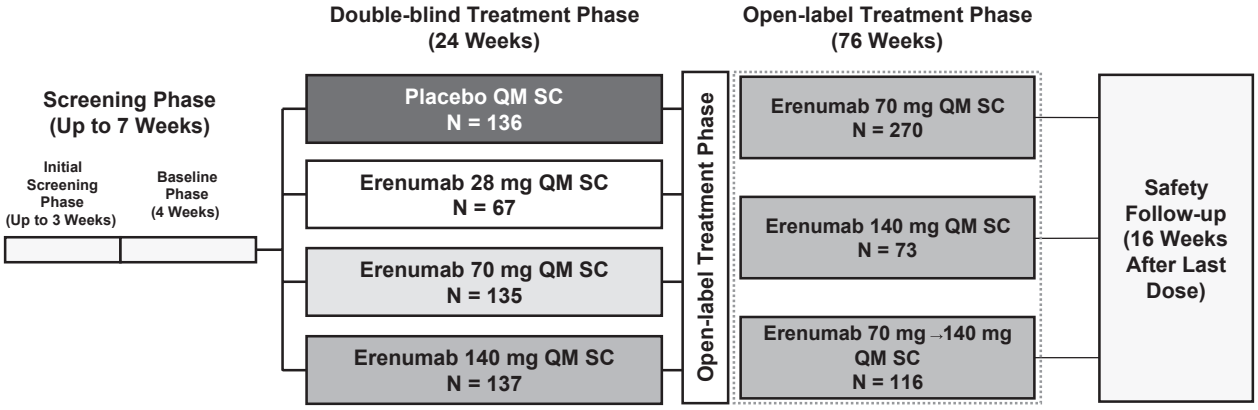

FIGURE 1 Study design. Durations and number of patients are shown for the double-blind and open-label treatment phases. In the OLTP, patients remained on erenumab 70 mg monthly if they had started the OLTP and had completed their pre-scheduled week 48 visit; the dose was increased from 70 to 140 mg monthly at the next visit for patients who started the OLTP but had not yet completed the week 48 visit; and erenumab 140 mg monthly was reserved for patients who were still in the DBTP and had not yet entered the OLTP at the time of protocol amendment approval. DBTP, double-blind treatment phase; OLTP, open-label treatment phase; QM, once monthly; SC, subcutaneous

The protocol was reviewed and approved by an independent ethics committee or institutional review board at each clinical site. Written informed consent was signed by each patient before the start of any procedures. The study was conducted in accordance with the International Council for Harmonization Good Clinical Practice Guideline and conforms to the provisions of the Declaration of Helsinki. All authors had access to the data.

Patients

Eligibility criteria for enrollment in the parent study have been reported previously.[11] Key inclusion criteria included age ≥20 and ≤65 years with a history of migraine (with or without aura) for ≥12 months based on the International Headache Society Classification ICHD-3 beta[12] based on medical records and/or patient self-report, and ≥4 and <15 migraine days per month on average across the 3 months prior to screening. Patients were excluded if they had no therapeutic response to >2 migraine-preventive treatment categories, 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 were taking >1 migraine-preventive medication. To be eligible to continue in the OLTP, patients had to complete the DBTP without discontinuation of the investigational treatment, continue to provide informed consent, and be considered appropriate for continued treatment by the investigator.

Study outcomes

Efficacy endpoints for the analysis of the OLTP were assessed across all eligible patients receiving erenumab 70 mg or 140 mg (dose groups combined) and included change from baseline in monthly migraine days (MMD), change from baseline in monthly acute migraine-specific medication days (MSMD), and achievement of ≥50% or ≥75% reduction in MMD. A qualified migraine headache was defined as migraine with or without aura lasting at least 30 min with at least two pain features or at least one associated non-pain symptom. Any calendar day on which patients had onset, continuation, or recurrence of a qualified migraine headache was considered a migraine day. Any calendar day on which patients used an acute migraine-specific medication was also counted as a migraine day. Efficacy data were collected with an electronic diary daily during pre-specified time intervals: over weeks 24–52, weeks 72–76, and weeks 96–100. The adverse impact of headache on quality-of-life was measured using the 6-item self-reported Headache Impact Test (HIT-6™),[13,14] with higher scores indicating a more severe headache impact. Patients completed the HIT-6™ while in the clinic, using the same electronic diary.

Safety endpoints included all adverse events (AEs), clinical laboratory values, vital signs, electrocardiograms, and anti-erenumab antibodies. At each clinic visit, sites asked patients about the occurrence of AEs. AEs were coded according to the Medical Dictionary for Regulatory Activities version 22.0 and severity was graded using the Common Terminology Criteria for Adverse Events version 4.03. Tolerability was monitored by collecting safety data throughout the OLTP and during a 16-week safety follow-up phase.

Analysis method

The power calculation for determining the sample size for the DBTP has been reported previously.[11] The sample size for the OLTP was determined by the number of patients who completed the DBTP and continued in the OLTP. The analysis included all patients who received at least one dose of erenumab in the OLTP. The study was descriptive in nature, therefore no formal statistical testing or comparisons were prespecified. For efficacy analyses, descriptive summaries were reported. Reported estimates include the mean (SD) MMD, monthly MSMD change from baseline, percentage of patients achieving ≥50% and ≥75% reduction in MMD, and mean (SD) HIT-6™ score. For safety analyses, AEs were summarized as exposure-adjusted patient incidence rates by the dose level at which the AE occurred. The exposure-adjusted patient incidence rate for a given event in a given period was defined as the number of patients with at least 1 reported incidence of the event in a given time, divided by total exposure time (patient-years) for all exposed patients at risk for reporting the treatment-emergent AE. For patients with events, only the time until the first event contributed to the total at risk time. For patients with no events, the exposure time is calculated as the time from the first dose to the last follow-up assessment. Results are presented per 100 patient-years. In the absence of a comparator during the OLTP, assessment of exposure-adjusted patient incidence rates allows appropriate contextualization of AE rates occurring during the longer OLTP versus the shorter DBTP. The longer follow-up time of the OLTP is accounted for by adjusting for exposure time, which yields results for the DBTP and OLTP normalized to equal exposure periods (i.e., events per 100 patient-years). Data were reported as observed, without imputation for missing data. For monthly intervals with ≥14 days of eDiary days, monthly frequency measurements (e.g., migraine days) were prorated to 28-day equivalents. For monthly intervals <14 days of eDiary use, all monthly measurements were set as missing. In determining percentages of patients with a ≥50% or ≥75% reduction from baseline in MMD, missing data were imputed as non-response. Cumulative average monthly measurements of migraine and non-migraine headaches were calculated as if there was no headache or medication use to report on days with missing data. For HIT-6™ and safety data, missing data were not imputed. All descriptive analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patients

A total of 475 patients enrolled in the parent study and 459 (96.6%) patients entered the OLTP. The baseline characteristics of the OLTP population are presented in Table 1. The mean

TABLE 1 Baseline characteristics

Characteristic	Total study population in OLTP (*N* = 459)
Age, mean (SD), years	43.9 (8.5)
Sex, female, *n* (%)	385 (83.8)
Body mass index, mean (SD), kg/m^2	22.0 (3.4)
Migraine-preventive medication use, *n* (%)	
Naïve	155 (33.8)
Previous use only	260 (56.6)
Concomitant use	44 (9.6)
HIT-6™ total score, mean (SD)	58.4 (5.4)
Disease characteristics	
MMDs, mean (SD)	7.9 (2.3)
Monthly headache days, mean (SD)	9.2 (2.5)
Acute migraine-specific medication use, *n* (%)	424 (92.4)
Monthly acute MSMD[a], mean (SD)	5.7 (2.8)

Abbreviations: HIT-6™, 6-item Headache Impact Test; MMDs, monthly migraine days; MSMD, migraine-specific medication days; OLTP, open-label treatment phase; SD, standard deviation.
[a]Migraine-specific medication: triptans and ergot derivatives.

(standard deviation [SD]) age of patients was 43.9 (8.5) years and the majority (83.8%) were female. Two hundred and sixty patients (56.6%) had previously used migraine preventive medications. Concomitant migraine preventive medication was used by 44 patients (9.6%). During the OLTP, 270, 73, and 116 patients received erenumab 70 mg alone, 140 mg alone, and increased from 70 to 140 mg, respectively. Of the 459 patients, 428 (93.2%) completed the OLTP (Figure 2). Thirty-one patients (6.8%) discontinued erenumab during the OLTP, with 22 of those patients (4.8%) discontinuing because of patient request, 6 patients (1.3%) because of AEs, and 3 (0.7%) for other reasons.

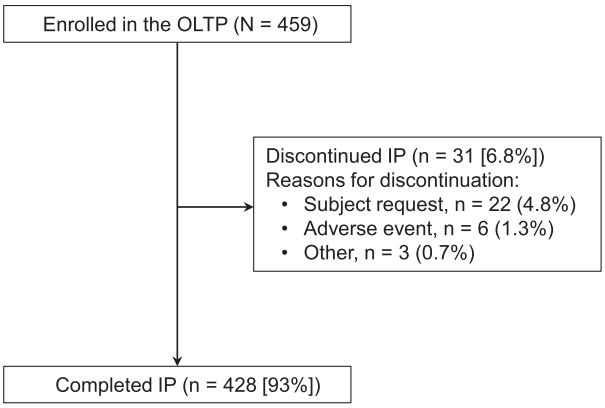

FIGURE 2 Patient disposition. IP, investigational product; OLTP, open-label treatment phase

Efficacy

The mean (SD) baseline MMD of the OLTP population (prior to the DBTP) was 7.9 (2.3) days. At week 24 of the DBTP, the mean (SD) MMD was decreased by 1.3 (3.7), 2.3 (3.7), and 2.2 (4.3) days in patients receiving erenumab 28, 70, and 140 mg, respectively, compared with an increase of 0.1 (3.8) days in the placebo group (Figure 3). During the OLTP, overall the mean (SD) MMD change from baseline at week 100 was −2.9 (4.1) days.

At week 24 of the DBTP, 25.8%, 29.6%, and 36.0% of patients receiving erenumab 28, 70, and 140 mg, respectively, achieved ≥50% MMD reduction compared with 11.8% in the placebo group (Figure 4), and 7.7%, 14.6%, and 13.4% of patients receiving erenumab 28, 70, and 140 mg achieved ≥75% MMD reduction compared with 5.2% in the placebo group (Figure 5). The proportion of patients achieving ≥50% and ≥75% reduction from baseline in MMD at week 100 was 44.5% (Figure 4) and 23.6% (Figure 5), respectively.

The mean (SD) monthly acute MSMD at baseline was 5.7 (2.8) days. At week 24 of the DBTP, the mean monthly acute MSMD was decreased from baseline by 0.4 (3.7), 1.1 (3.1), and 1.5 (3.3) days in patients receiving erenumab 28, 70, and 140 mg, respectively, compared with an increase of 1.0 (3.3) days in the placebo group (Figure 6). During the OLTP, the mean (SD) MSMD change from baseline at week 100 was −1.7 (3.7) days. Among the subset of patients who used acute migraine-specific medication at baseline, the mean (SD) monthly acute MSMD at baseline was 6.1 (2.3) with change from baseline at week 100 of −2.0 (3.7) days.

Patient-reported outcomes

At week 24 of the DBTP, the HIT-6™ score was decreased by 1.8, 4.5, and 4.6 points in the erenumab 28, 70, and 140 mg groups, respectively, compared with a decrease of 2.5 points in the placebo group (Figure 7). The difference from placebo for the erenumab

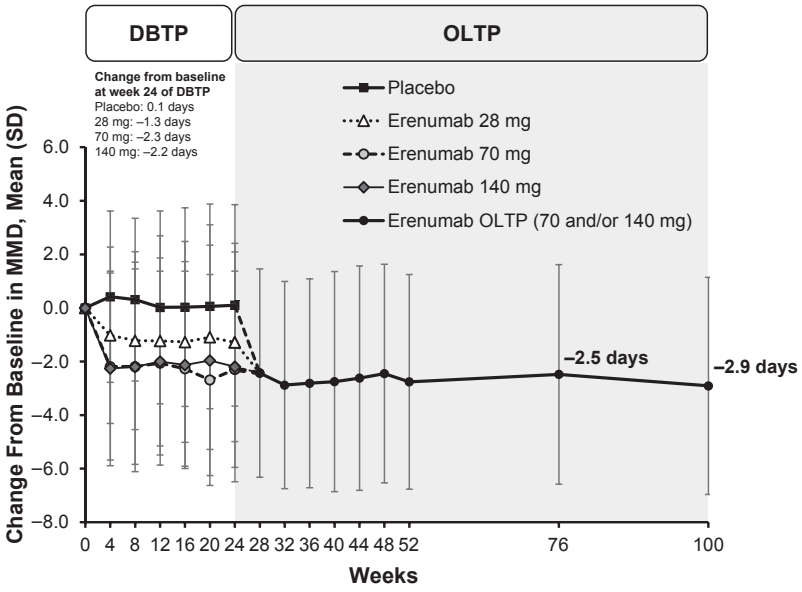

FIGURE 3 Change (mean [SD]) from baseline in MMD. Efficacy in the DBTP is shown by the randomized dose groups. Efficacy in the OLTP is shown for the total population. DBTP, double-blind treatment phase; MMD, monthly migraine days; OLTP, open-label treatment phase; SD, standard deviation

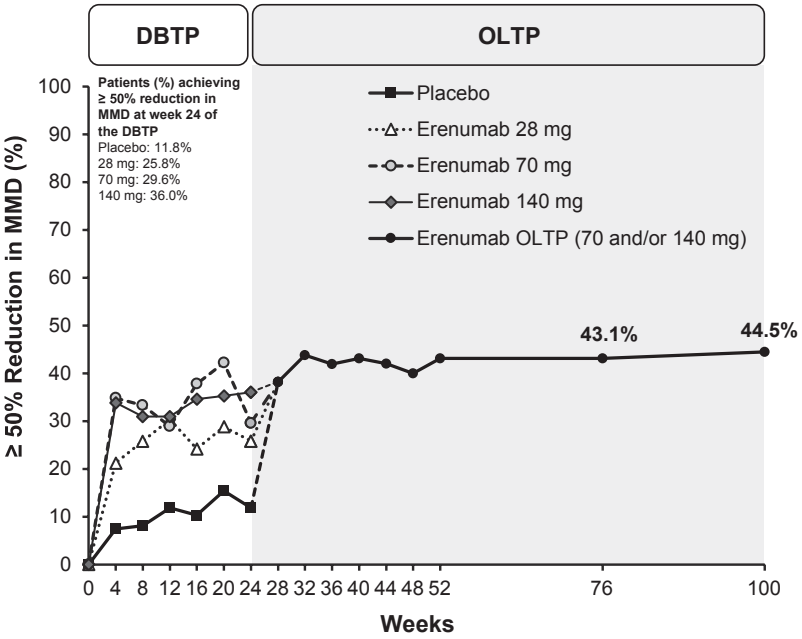

FIGURE 4 Patients achieving ≥50% reduction from baseline in MMD. Efficacy in the DBTP is shown by the randomized dose groups. Efficacy in the OLTP is shown for the total population. DBTP, double-blind treatment phase; MMD, monthly migraine days; OLTP, open-label treatment phase

dose groups exceeded the between-group minimally important difference of −1.5.[15] The mean (SD) HIT-6™ change from baseline was sustained up to week 100 (−6.4 [8.2] points).

Safety

Mean (SD) durations of exposure to erenumab during the OLTP were 13.7 (7.3) and 16.4 (3.1) months for the 70 mg (*n* = 386) and 140 mg (*n* = 189) dose, respectively. Mean exposure to the 70 and/or 140 mg doses combined was 18.3 (3.0) months.

Overall, 91.9% (422/459) of patients had treatment-emergent AEs during the OLTP (Table 2), with overall exposure-adjusted patient incidence rates of 207.1/100 patient-years and 211.7 and 213.8/100 patient-years for erenumab 70 and 140 mg, respectively. The overall exposure-adjusted incidence rate was lower in the OLTP than the placebo (257.3/100 patient-years) and total erenumab (271.0/100 patient-years) rates observed during the DBTP. Most AEs were classified as CTCAE grade 1–2, indicating mild to moderate severity. The overall exposure-adjusted serious adverse event (SAE) patient incidence rate was 3.7/100 patient-years in the OLTP, which was intermediate between the placebo (6.5/100 patient-years) and erenumab (1.9/100 patient-years) rates observed in the DBTP; rates for the DBTP were based on a small number of overall SAEs (3 combined erenumab groups, 4 placebo). Six patients discontinued treatment due to AEs (0.8/100 patient-years) in the OLTP, less than the placebo (1.6/100 patient-years), and erenumab (1.3/100 patient-years) rates in the DBTP. There were no fatal AEs.

The most frequent AEs, defined as ≥3.0/100 patient-years in the total erenumab group during the OLTP, included nasopharyngitis,

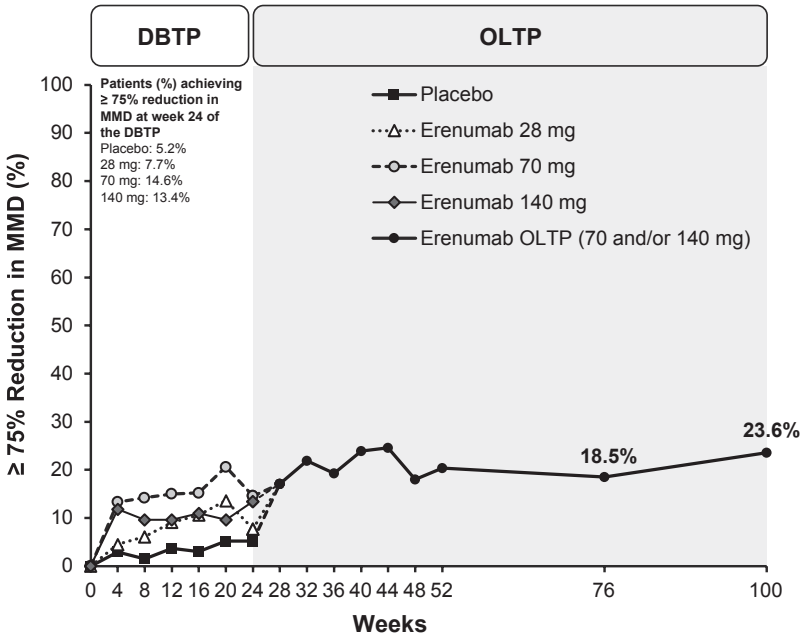

FIGURE 5 Patients achieving ≥75% reduction from baseline in MMD. Efficacy in the DBTP is shown by the randomized dose groups. Efficacy in the OLTP is shown for the total population. DBTP, double-blind treatment phase; MMD, monthly migraine days; OLTP, open-label treatment phase

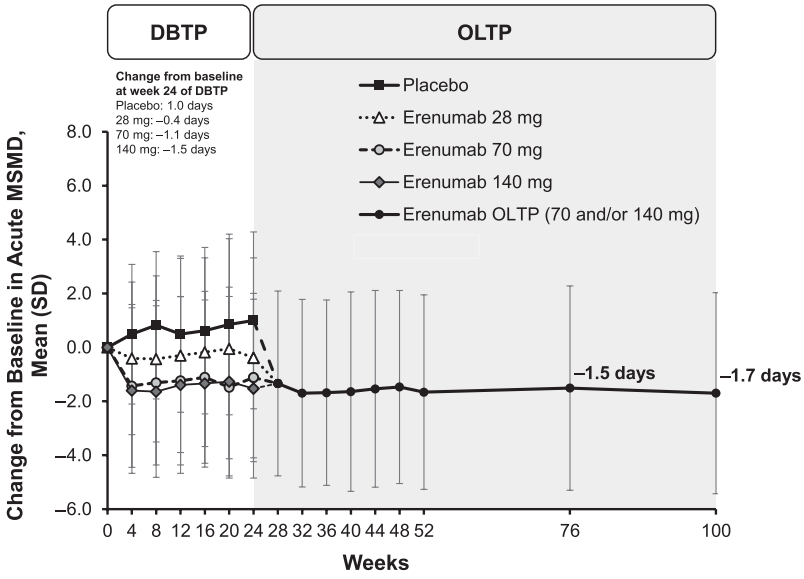

FIGURE 6 Change (mean [SD]) from baseline in monthly acute MSMD. Efficacy in the DBTP is shown by the randomized dose groups. Efficacy in the OLTP is shown for the total population. DBTP, double-blind treatment phase; MSMD, migraine-specific medication days; OLTP, open-label treatment phase; SD, standard deviation

influenza, gastroenteritis, back pain, pharyngitis, abdominal pain upper, dental caries, cystitis, and bronchitis (Table 2). Constipation occurred at an overall exposure-adjusted patient incidence rate of 2.6/100 patient-years during the OLTP, compared with the placebo and overall erenumab rates of 3.2/100 patient-years and 9.9/100 patient-years, respectively, during the DBTP. During the DBTP, 60.0% (9/15) of patients who developed constipation did so within 1 month of receiving the first dose of erenumab. The median duration of constipation was 71 days. About 36.8% (7/19) of patients who experienced constipation in the OLTP reported onset within 1 month after the first dose of erenumab in the OLTP and 42.1% (8/19) of patients reported constipation at month 4 or later after the first dose. No patients discontinued erenumab due to constipation AEs during the OLTP. The median duration of constipation during the OLTP was 167 days. No clear pattern of time to onset from the initial treatment was observed for any of the constipation events. There was one case of serious constipation during the OLTP due to postoperative ileus, which was not related to erenumab. The majority of constipation events were transient and did not recur with continued treatment. There were no clinically meaningful changes in vital signs, electrocardiograms, or laboratory results, in particular no relevant changes in hepatic alanine aminotransferase or aspartate aminotransferase.

During the DBTP, 8 (2.1%) of 388 patients developed anti-erenumab binding antibodies. During the OLTP, 7 (1.5%) of 459 patients newly developed anti-erenumab binding antibodies: of these, four patients initiated erenumab dosing during the OLTP and three patients received erenumab during the DBTP. Of the 15 patients who developed binding antibodies during the DBTP or OLTP of the study, 11 were transient, with a negative result upon last assessment. No patients developed neutralizing antibodies. No differences in safety were noted among the patients who developed antibodies compared with the antibody-negative population.

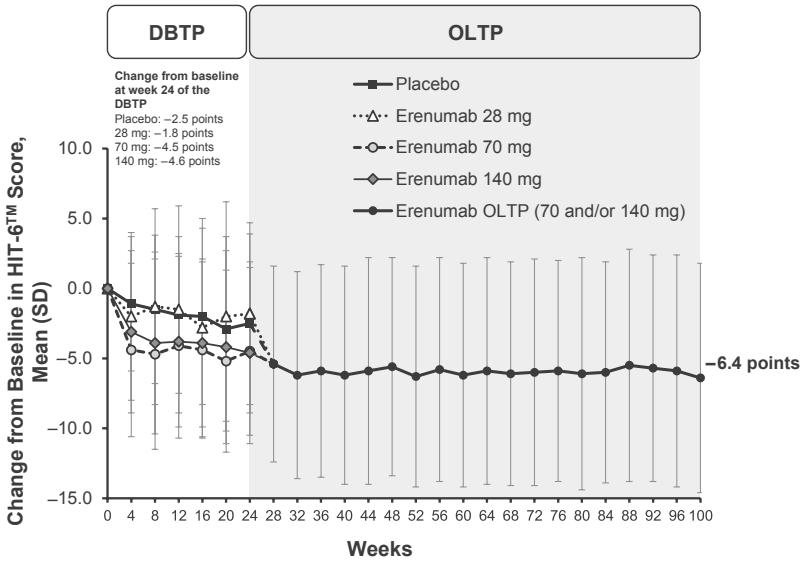

FIGURE 7 Change (mean [SD]) from baseline in HIT-6™ score. DBTP, double-blind treatment phase; HIT-6™, 6-item Headache Impact Test; OLTP, open-label treatment phase; SD, standard deviation

TABLE 2 Exposure-adjusted patient incidence rates of adverse events

	Double-blind treatment phase		
	Placebo (*N* = 136)	Total erenumab (*N* = 338)	Open-label treatment phase (*N* = 459)
	n (*r*)	*n* (*r*)	*n* (*r*)
All adverse events	93 (257.3)	233 (271.0)	422 (207.1)
Grade ≥ 3	4 (6.5)	4 (2.6)	28 (3.9)
Serious	4 (6.5)	3 (1.9)	27 (3.7)
Leading to discontinuation of investigational product	1 (1.6)	2 (1.3)	6 (0.8)
Most frequent AEs[a]			
Nasopharyngitis	41 (79.5)	106 (81.5)	274 (60.1)
Influenza	4 (6.5)	5 (3.2)	75 (10.9)
Gastroenteritis	4 (6.4)	9 (5.8)	41 (5.8)
Back pain	2 (3.2)	11 (7.2)	34 (4.7)
Pharyngitis	3 (4.8)	11 (7.2)	28 (3.9)
Abdominal pain upper	1 (1.6)	8 (5.2)	26 (3.6)
Dental caries	3 (4.8)	11 (7.1)	26 (3.6)
Cystitis	3 (4.8)	4 (2.6)	26 (3.6)
Bronchitis	1 (1.6)	3 (1.9)	22 (3.0)

Abbreviations: AE, adverse event; OLTP, open-label treatment phase; *r*, exposure-adjusted patient incidence rate.

[a]Frequent AEs ≥3.0/100 patient-years in the total erenumab group during OLTP. AEs were coded according to the Medical Dictionary for Regulatory Activities version 22.0 and severity was graded using the Common Terminology Criteria for Adverse Events version 4.03.

DISCUSSION

The data from the OLTP of this study demonstrated the long-term safety and efficacy of erenumab for up to 2 years in Japanese patients with EM. Preventive treatment with erenumab resulted in durable, stable reduction in MMD and improvement in quality of life. Each of the efficacy endpoints, change from baseline in MMD and MSMD as well as achievement of ≥50% and ≥75% response, showed sustained improvement during the OLTP. For example, the percentage of patients achieving ≥50% (44.5%) and ≥75% response (23.6%) at week 100 in the combined 70 + 140 mg erenumab groups was considerably higher than at week 24 of the DBTP (26%–36% and 8%–15% for ≥50% and ≥75%, respectively). The safety profile of erenumab remained consistent with that observed during the DBTP with no increase in events, no new safety signals, and no dose dependency of events over the OLTP. The long-term safety of

erenumab in the Japanese population was consistent with that seen in global studies of migraine.[8,9]

There was prompt reduction in MMD and MSMD in the first 4 weeks of the OLTP for patients who received erenumab 28 mg and placebo during the DBTP and sustained reduction in the erenumab 70 and 140 mg groups. The mean reductions from baseline in MMD and monthly acute MSMD at week 100 (−2.9 and −1.7 days, respectively) were greater than those observed during the DBTP. The treatment effect on monthly acute MSMD is slightly underestimated since 8% of patients did not use migraine-specific medication at baseline, thus MSMD could only remain the same (no use) or increase for these patients. While the efficacy in the OLTP could be affected by the open-label nature of erenumab administration and drop-out of patients over time, albeit low in the OLTP, these results suggest at least sustained efficacy with the long-term erenumab treatment. In addition to clinical outcomes, during the OLTP erenumab also achieved a sustained reduction in HIT-6™ score from baseline (reduction of 6.4).

Safety and tolerability profiles of erenumab during the OLTP were similar to those observed for erenumab and placebo in the DBTP and there were no new safety concerns. The majority of the exposure-adjusted patient incidence rates for the frequent AEs were similar or lower than the incidence rates observed in the DBTP. Most AEs were grade 1 or grade 2 in severity with no grade 4 severity AEs or fatal AEs. Of 459 patients who continued into the OLTP, only 31 (7%) discontinued treatment and very few (1.3%) discontinuations were due to AEs, in which each AE occurred in only 1 patient. This contrasts with current migraine preventive therapies in Japan that are associated with high discontinuation rates.[3,16] The high patient retention rates in this 2-year clinical trial highlight the favorable long-term tolerability profile of erenumab and patient satisfaction with the therapy, which is of particular importance in chronic conditions. No new safety concerns were identified during the OLTP. During the DBTP, the immunogenicity of erenumab in Japanese patients was lower in comparison with what had been observed in global studies.[17] The incidence of anti-erenumab antibodies remained low throughout the OLTP, with most transient in nature and none were neutralizing. No notable safety findings were identified in patients with anti-erenumab binding antibodies.

The limitations of the OLTP results are the lack of a comparator for efficacy and safety and the lack of blinding during the OLTP. Nonetheless, this 1.5-year, long-term study demonstrated erenumab to be safe and well-tolerated in Japanese patients with EM. The favorable safety profile, sustained efficacy, and low discontinuation rates support the prolonged use of erenumab for migraine prevention in Japanese patients.

CONCLUSION

Long-term treatment with erenumab for up to 2 years demonstrated sustained efficacy, safety, and tolerability of erenumab in Japanese patients with EM. The spectrum of AEs was similar to those observed during the placebo-controlled period, and there were no new safety concerns.

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INSTITUTIONAL REVIEW BOARD APPROVAL

The protocol was reviewed and approved by an independent ethics committee or institutional review board at each of 43 clinical sites.

CONFLICT OF INTEREST

Fumihiko Sakai has received consulting fees from Amgen Inc. 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. Sunfa Cheng, Yotaro Numachi, Cheng Peng, Fei Xue, and Daniel D. Mikol are employees and stockholders of Amgen Inc.

AUTHOR CONTRIBUTIONS

Conception and design: Sunfa Cheng, Daniel D. Mikol. *Acquisition of data*: Fumihiko Sakai, Takao Takeshima, Yoshihisa Tatsuoka, Koichi Hirata, Sunfa Cheng, Cheng Peng, Daniel D. Mikol. *Analysis and interpretation of data*: Fumihiko Sakai, Takao Takeshima, Yoshihisa Tatsuoka, Koichi Hirata, Sunfa Cheng, Yotaro Numachi, Cheng Peng, Fei Xue, Daniel D. Mikol. *Drafting the manuscript*: Sunfa Cheng, Cheng Peng, Fei Xue, Daniel D. Mikol. *Revising it for intellectual content*: Fumihiko Sakai, Takao Takeshima, Yoshihisa Tatsuoka, Koichi Hirata, Sunfa Cheng, Yotaro Numachi, Cheng Peng, Fei Xue, Daniel D. Mikol. *Final approval of the completed manuscript*: Fumihiko Sakai, Takao Takeshima, Yoshihisa Tatsuoka, Koichi Hirata, Sunfa Cheng, Yotaro Numachi, Cheng Peng, Fei Xue, Daniel D. Mikol.

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DATA AVAILABLITY STATEMENT

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

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