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Long-term efficacy and safety of erenumab in Japanese patients with episodic and chronic migraine: Results from a 28-week open-label treatment period of a randomized trial

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ABSTRACT

Objectives: To evaluate the 1-year efficacy and safety of once-monthly erenumab 70 mg following a 24-week double-blind treatment period (DBTP) of a phase 3 randomized study of Japanese patients with episodic migraine (EM) or chronic migraine (CM).

Design: Multicenter open-label study.

Setting: A total of 41 centers in Japan.

Participants: Patients completing the DBTP continued into the 28-week open-label treatment period (OLTP). 254 of 261 (97.3%) randomized patients continued into the OLTP; 244 (93.5%) completed treatment.

Interventions: Once monthly subcutaneous erenumab 70 mg.

Main Outcome measures: Changes from baseline in monthly migraine days (MMD), monthly acute migraine-specific medication treatment days (MSMD), proportion of ≥50% and ≥75% responders in MMD reduction from baseline, and the incidence and exposure-adjusted incidence of treatment-emergent adverse events (TEAEs).

Results: At week 24 of the DBTP, the mean (SE) change from baseline in MMD for the erenumab group was –3.8 (0.4) days (EM, –3.0 [0.4]; CM, –5.2 [0.8]); in MSMD, –2.6 (0.4) days (EM, –2.1 [0.4]; CM, –3.4 [0.7]). At the end of the OLTP (52 weeks postbaseline), the mean (SE) change from baseline in MMD was –4.7 (0.3) days (EM, –3.4 [0.3]; CM, –6.9 [0.6]); in MSMD, –3.3 (0.3) days (EM, –2.4 [0.3]; CM, –4.6 [0.5]). The proportion of ≥50% responders for MMD reduction in the erenumab group was 34.1% at week 24; 44.4% at week 52. The exposure-adjusted incidence of TEAEs was 219.7 per 100 patient-years during the OLTP (DBTP, 251.0 for the erenumab group). The most common TEAEs during the OLTP were nasopharyngitis, constipation, and influenza. No new safety concerns were identified.

Conclusions: Erenumab demonstrated a persistent efficacy in Japanese patients with EM or CM for up to 1 year. Overall safety results from the OLTP were consistent with those from the DBTP.

Clinical Trials Registration Number: NCT03812224

Funding: This study was funded by Amgen.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study represents the longest follow-up experience with erenumab in Japanese patients with CM
- The duration of the 28-week OLTP was short
- This study lacked a comparator arm

INTRODUCTION

Migraine is a common neurological disease worldwide and a leading cause of disability associated with significant personal and societal effects.[1-3] In Japan, 6% to 8% of the population is affected by migraine, which places a substantial burden on patients and society related to quality of life, work productivity, and costs.[4-7] Because of concerns related to inadequate efficacy and poor tolerability, the use of standard of care oral preventive medications is low and is associated with high rates of discontinuation.[6,8-11] Therefore, there is an unmet need for new migraine preventive medications.

Erenumab (erenumab-aooe in the United States), a fully human monoclonal antibody against the calcitonin gene-related peptide (CGRP) receptor, has been approved for the preventive treatment of adult migraine in over 70 countries worldwide, including the United States (2018), Europe (2018), and Japan (2021).[12,13] The sustained efficacy and safety of erenumab in the preventive treatment of episodic migraine (EM) and chronic migraine (CM) have been demonstrated in several global clinical studies.[14-18] In Japan, approval was based on two clinical studies in adult patients with EM or CM, which demonstrated erenumab to be safe and efficacious.[19,20] Sustained efficacy and safety of erenumab for up to 2 years in Japanese patients with EM have also been demonstrated.[21]

Here, we report on the long-term (up to 1 year) efficacy, safety, and tolerability of once-monthly erenumab 70 mg during a 28-week open-label treatment period (OLTP) after a 24-week double-blind treatment period (DBTP) of a phase 3 study, which demonstrated favorable efficacy and safety results for erenumab 70 mg in EM and CM.[20]

METHODS

Study design

This multicenter (41 centers across Japan), 28-week OLTP followed a 24-week, randomized, double-blind, placebo-controlled, phase 3 study of once-monthly erenumab 70 mg in patients with EM or CM in Japan (ClinicalTrials.gov identifier NCT03812224) (Figure S1). The first patient entered the OLTP on October 2, 2019, and the last patient ended the OLTP on November 20, 2020. Randomization was stratified by migraine status (EM or CM) and migraine preventive treatment status (ever used or never used) and was assigned by the sponsor using an interactive response technology system. During the DBTP, patients received once-monthly erenumab 70 mg or placebo in a 1:1 ratio; in the OLTP, all patients received once-monthly erenumab 70 mg. Independent ethics committee or institutional review boards at each site (Table S1) reviewed and approved the protocol and signed the informed patient consent forms before study initiation. The study conforms to the guidelines set by the International Council for Harmonisation for Good Clinical Practice and by the Pharmaceuticals and Medical Devices Agency (PMDA). The study was designed according to the European Medicines Agency (EMA) guideline on Clinical Investigation of Medicinal Products for the Treatment of Migraine, the International Headache Society (IHS) Guidelines for Controlled Trials of Drugs in Migraine, and advice given by the PMDA.[22,23].

Patient and Public Involvement Statement

No patients or public representatives were involved in the design, conduct, reporting, or dissemination efforts of the study results.

Patients

Patients who completed the DBTP (parent study) in each treatment group were eligible to participate in the OLTP and receive once-monthly erenumab 70 mg. Key eligibility criteria in the

parent study included Japanese patients aged 20 through 65 years with a history of migraine with or without aura (based on medical records or patient self-report) for at least 12 months before screening, as defined in the third edition of the *International Classification of Headache Disorders* (ICHD-3) of the IHS, and a diagnosis of EM (<15 headache days/month, ≥4 monthly migraine days [MMD]) or CM (≥15 headache days/month, ≥8 MMD) over the 3 months before screening. A detailed description of the eligibility criteria in the parent study has been described previously.[20]

Endpoints and assessments

Efficacy outcomes during the OLTP included changes from baseline in MMD and monthly acute migraine-specific medication treatment days (MSMD), and the proportion of patients who achieved at least a 50% or 75% reduction in MMD from baseline.

A migraine day was defined as a migraine (with or without aura) that lasted for at least 4 hours and had at least two of the following pain features: unilateral, throbbing, moderate to severe, or exacerbated with exercise or physical activity; or was associated with nausea, vomiting, or photophobia and phonophobia. A migraine day also included a day in which a patient took a migraine-specific medication during aura or to treat a headache regardless of the duration and associated symptoms. A qualified headache day was a day characterized by onset, continuation, or recurrence of a headache and met one of the following criteria: a migraine headache treated with acute migraine-specific medication, a non-migraine headache that lasted for at least 4 hours, or a headache for which acute headache treatment was used. An acute migraine-specific medication treatment day was defined as any day during which migraine-specific medication was used.

Safety endpoints included the incidence and exposure-adjusted incidence of treatment-emergent adverse events (TEAEs), clinical laboratory values and vital signs, and the incidence of anti-erenumab antibodies. Exposure-adjusted rates (per 100 patient-years) were calculated

by dividing the number of patients with at least one reported occurrence of the TEAE of interest by the total time at risk for reporting the TEAE (patient-year) multiplied by 100. The time at risk was defined as the time from the first dose of erenumab to the onset of the TEAE or the end of study date. Reporting exposure-adjusted rates normalizes the rates of adverse events occurring during the DBTP and OLTP to equal exposure periods (ie, events per 100 patient-years), and thus allows for a proper comparison between the DBTP and OLTP.

Statistical analysis

Analysis was performed after all patients had completed safety follow-up at the end of the study and included patients who received at least one dose of erenumab 70 mg in the OLTP. Efficacy and safety data were tabulated by the double-blind treatment group. Efficacy endpoints were analyzed by using descriptive statistics based on observed data without imputation and were tabulated by visit. No formal testing was conducted. Patient incidence and exposure-adjusted incidence of TEAEs were tabulated by treatment group and by system organ class and preferred term. All analyses were performed using SAS System 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patients

Of the 261 patients enrolled and randomized in the parent study (erenumab 70 mg, n = 130; placebo, n = 131), 254 (97.3%) entered the OLTP and received at least one dose of the investigational product (IP) and 244 (93.5%) completed the IP. Ten patients (3.8%) discontinued the IP for the following reasons: patient request (n = 4; 1.5%), COVID-19 control measures (n = 4; 1.5%), adverse event (n = 1; 0.4%), and pregnancy (n = 1; 0.4%) (Figure S2). Overall, the mean age of patients was 44.4 years, 87% were female, and the majority (76.6%) had used or were using migraine preventive treatment at baseline (Table 1).

Table 1. Baseline demographics and characteristics

	Total (N = 261)
Age, mean (SD), years	44.4 (8.9)
Sex, female, n (%)	227 (87.0)
Migraine type*, n (%)	
EM	159 (60.9)
CM	102 (39.1)
Migraine preventive treatment use, n (%)	
Ever used (including prior and/or current users)	200 (76.6)
Never used	61 (23.4)
Baseline clinical characteristics of the OLTP population (N = 254)	
MMD, mean (SE)	12.2 (0.4)
MSMD, mean (SE)	9.4 (0.4)
MHD, mean (SE)	13.8 (0.4)

*Based on actual data collected instead of randomization stratification. N = number of patients in the analysis set. n = number of patients with observed data. CM, chronic migraine; EM, episodic migraine; MHD, monthly headache days; MMD, monthly migraine days; MSMD, monthly acute migraine-specific medication treatment days; OLTP, open-label treatment period; SD, standard deviation; SE, standard error of the mean.

Efficacy

In the OLTP population (N = 254; EM, n = 155; CM, n = 99), the mean (standard error of the mean [SE]) MMD at baseline was 12.2 (0.4) days (EM, 8.3 [0.2] days; CM, 18.2 [0.4] days) and the mean (SE) MSMD was 9.4 (0.4) days (EM, 6.8 [0.3] days; CM, 13.6 [0.6] days) (Table 1). At the end of the DBTP at week 24, the mean (SE) change from baseline in MMD for the erenumab 70 mg group was –3.8 (0.4) days (EM, –3.0 [0.4] days; CM, –5.2 [0.8] days]) and –1.7 (0.5) days for the placebo group; at the end of the OLTP at week 52, the mean (SE) change was –4.7 (0.3) days (EM, –3.4 [0.3]; CM, –6.9 [0.6]) (Figure 1, Table 2).

At the end of the DBTP at week 24, the mean (SE) change from baseline in MSMD for the erenumab 70 mg group was –2.6 (0.4) days (EM, –2.1 [0.4]; CM, –3.4 [0.7]) and –0.7 (0.4) days for the placebo group; at the end of the OLTP at week 52, the mean (SE) change was –3.3 (0.3) days (EM, –2.4 [0.3] days; CM, –4.6 [0.5] days) (Figure 1, Table 2). Throughout the 28-week OLTP, erenumab 70 mg demonstrated persistent efficacy in MMD and MSMD reduction in patients with EM or CM.

At week 24 of the DBTP, the proportion of patients who achieved at least a 50% reduction in MMD from baseline was 34.1% with erenumab 70 mg (EM, 39.7%; CM, 25.5%) and 19.1% with placebo (Figure 2, Table 2). The response was maintained and numerically higher throughout the OLTP than it was during the DBTP. At week 36 of the OLTP, 52.8% of the patients achieved the 50% threshold for MMD reduction (EM, 58.8%; CM, 43.0%); at week 52, it was 44.4% (EM, 46.3%; CM, 41.7%). The results were similar for patients responding at the 75% threshold for MMD reduction (Figure 2).

Table 2. Efficacy results during the OLTP

	EM (N = 155)	**CM (N = 99)**	**Total (N = 254)**
Change from baseline in MMD, mean (SE)			
	n = 78	n = 51	n = 129
Week 24*	–3.0 (0.4)	–5.2 (0.8)	–3.8 (0.4)
	n = 153	n = 93	n = 246
Week 36	–3.7 (0.3)	–8.0 (0.6)	–5.3 (0.3)
	n = 147	n = 96	n = 243
Week 52	–3.4 (0.3)	–6.9 (0.6)	–4.7 (0.3)
Change from baseline in MSMD, mean (SE)			
	n = 78	n = 51	n = 129
Week 24*	–2.1 (0.4)	–3.4 (0.7)	–2.6 (0.4)
	n = 153	n = 93	n = 246
Week 36	–2.8 (0.3)	–5.2 (0.5)	–3.7 (0.3)
	n = 147	n = 96	n = 243
Week 52	–2.4 (0.3)	–4.6 (0.5)	–3.3 (0.3)

Achievement of ≥50% MMD response, n (%)			
Week 24*	n = 78 31 (39.7)	n = 51 13 (25.5)	n = 129 44 (34.1)
Week 36	n = 153 90 (58.8)	n = 93 40 (43.0)	n = 246 130 (52.8)
Week 52	n = 147 68 (46.3)	n = 96 40 (41.7)	n = 243 108 (44.4)

Efficacy by EM and CM subgroups at week 24 of the DBTP and during the OLTP. *Data are shown for patients in the erenumab 70 mg group at week 24 of the DBTP in the efficacy analysis set. N = number of patients in the open-label analysis set; n = number of patients with observed data. CM, chronic migraine; DBTP, double-blind treatment period; EM, episodic migraine; MMD, monthly migraine days; MSMD, monthly acute migraine-specific medication treatment days; OLTP, open-label treatment period; SE, standard error of the mean.

Safety

The mean (standard deviation) exposure to erenumab 70 mg during the OLTP was 192.6 (20.0) days (total exposure to open-label treatment, 133.9 patient-years). The majority of patients (92.1%) received all seven doses of erenumab 70 mg during the OLTP.

During the OLTP, the incidence of TEAEs was 71.3% (181/254) (Table 3). The exposure-adjusted incidence of TEAEs during the OLTP was 219.7 per 100 patient-years, which is similar to that in the erenumab group (251.0 per 100 patient-years) and in the placebo group (197.7 per 100 patient-years) during the DBTP. The majority of patients (62.2% [158/254]) experienced TEAEs of grade 2 or less. The most common (≥5 per 100 patient-years) TEAEs reported with erenumab (OLTP vs DBTP) were nasopharyngitis (32.8 vs 67.2 per 100 patient-years), constipation (7.8 vs 10.3 per 100 patient-years), influenza (6.6 vs 1.7 per 100 patient-years), gastroenteritis (6.5 vs 6.8 per 100 patient-years), and urticaria (5.9 vs 1.7 per 100 patient-years). Seven patients (2.8%) reported serious adverse events with erenumab during the OLTP,

corresponding to an exposure-adjusted rate of 4.1 per 100 patient-years, which is similar to the rate reported during the DBTP in each treatment group (3.4 per 100 patient-years). During the OLTP, one patient with a serious adverse event discontinued treatment because of a grade 3 serious adverse event of drug eruption, which was considered by the investigator to be unrelated to erenumab treatment. No deaths were reported during the study. No clinically significant changes in laboratory values or vital signs were observed throughout the OLTP.

Of the 254 patients in the OLTP, nine (3.5%) developed anti-erenumab binding antibodies for the first time (negative or no result before the first OLTP dose), which is consistent with that observed during the DBTP (5.4%) (Table 3). Of the nine patients who were positive for binding antibodies during the OLTP, six received placebo during the DBTP and three received erenumab during the DBTP and the OLTP. During the entire study, 16 patients (6.3%) developed anti-erenumab binding antibodies after erenumab treatment, of which 6 (37.5%) had transient antibodies (negative result at the last assessment). No patients developed anti-erenumab neutralizing antibodies.

Table 3. Safety results during the DBTP and OLTP

	DBTP		OLTP
	Placebo (N = 131)	**Erenumab 70 mg (N = 130)**	**Total (N = 254)**
All TEAEs, n (%) [r]	78 (59.5) [197.7]	86 (66.2) [251.0]	181 (71.3) [219.7]
Grade ≥2	67 (51.1) [159.2]	72 (55.4) [180.6]	158 (62.2) [159.9]
Grade ≥3	2 (1.5) [3.4]	4 (3.1) [6.8]	12 (4.7) [7.1]
Serious AEs	2 (1.5) [3.4]	2 (1.5) [3.4]	7 (2.8) [4.1]
Leading to IP discontinuation	0 (0.0) [0.0]	0 (0.0) [0.0]	1 (0.4) [0.6]
Fatal AEs	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]
Most common TEAEs, n (%) [r]*			
Nasopharyngitis	37 (28.2) [74.4]	35 (26.9) [67.2]	49 (19.3) [32.8]
Constipation	1 (0.8) [1.7]	6 (4.6) [10.3]	13 (5.1) [7.8]

Influenza	2 (1.5) [3.4]	1 (0.8) [1.7]	11 (4.3) [6.6]
Gastroenteritis	4 (3.1) [6.7]	4 (3.1) [6.8]	11 (4.3) [6.5]
Urticaria	0 (0.0) [0.0]	1 (0.8) [1.7]	10 (3.9) [5.9]
Developed anti-erenumab antibodies, n (%)			
Developed binding anti-erenumab antibodies	NA	n' = 129 7 (5.4)	n' = 254 9 (3.5)
Transient†	NA	2 (28.6)	4 (44.4)
Developed neutralizing anti-erenumab antibodies	NA	NA	NA

*Exposure-adjusted rates of TEAEs of at least 5 per 100 patient-years during the OLTP. †A negative result was reported at the patient's last time point within the study period. N = number of patients in the analysis set; n = number of patients with at least one occurrence of a TEAE or number of patients who developed anti-erenumab antibodies; n' = patients with a postbaseline result during the DBTP or OLTP; r = exposure-adjusted patient incidence rate per 100 patient-years. AE, adverse event; DBTP, double-blind treatment period; IP, investigational product; NA, not applicable; OLTP, open-label treatment period; TEAE, treatment-emergent adverse event.

DISCUSSION

The results of this 28-week OLTP study of erenumab 70 mg in Japanese patients with EM or CM demonstrated a persistence of efficacy for up to 1 year and a safety profile similar to that reported during the DBTP. From week 24 of the DBTP to the end of the OLTP at week 52, the reduction from baseline in MMD and MSMD, and the proportion of ≥50% and ≥75% responders in MMD reduction were maintained.

The incidence and exposure-adjusted incidence of TEAEs during the OLTP were consistent with those from the DBTP and previous studies,[18,20,21] except for influenza and urticaria, which were numerically higher during the OLTP than they were during the DBTP. Furthermore, although the exposure-adjusted rates of constipation during the OLTP (7.8 per 100 patient-years) were consistent with those during the DBTP (10.0 per 100 patient-years), they were

higher than those reported during the OLTP of the phase 2 study in Japanese patients with EM (2.6 per 100 patient-years).[21] In addition, no new safety concerns regarding clinically relevant changes in laboratory assessments and vital signs were identified throughout the OLTP. The high proportion of patients completing erenumab treatment reflects the excellent tolerability and sustained efficacy. The high retention rate prevents the bias that may be seen in open-label extension studies where patients may drop out for diminished efficacy, thus skewing the efficacy results over time.

This study represents the longest follow-up experience with erenumab in Japanese patients with CM and shows long-term efficacy and safety that are comparable to that seen in a global long-term study of erenumab in patients with CM.[24] In the global study, the reduction in MMD and MSMD after 52 weeks for the erenumab 70 mg group was –7.8 days and –5.8 days, respectively; 47.4% of the patients achieved at least a 50% reduction from baseline in MMD. Nonetheless, these data support long-term treatment with erenumab in Japanese patients with EM and CM.

CONCLUSION

Erenumab demonstrated a persistence of efficacy for up to 1 year in Japanese patients with EM or CM and had a safety profile similar to that observed in the DBTP. No new safety signals were identified during the OLTP.

Ethics Approval

This study involved human patients and was approved by ethics committees and institutional review boards listed in the supplementary appendix (Table S1).

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Author contributions

SC and GPL contributed to the conception and design of the study and acquired the data. All authors analyzed and interpreted the data. All authors drafted the manuscript and critically reviewed and revised the manuscript for intellectual content. All authors provided final approval of the version to be published.

Conflict of Interest Statement

KH reports royalties from Amgen, Astellas, Daiichi Sankyo, Eisai, Merck Sharp & Dohme, and Pfizer. TT has nothing to disclose. FS reports consulting fees from Amgen. RY, RK, MH, DY, GPL, and SC are employees of and own stock in Amgen. YN owns stock in Amgen.

Institutional review board approval

The Institutional review boards at each study center (Table S1) approved the study protocol, informed consent forms, and any materials provided to the patients.

Data availability statement

Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request.

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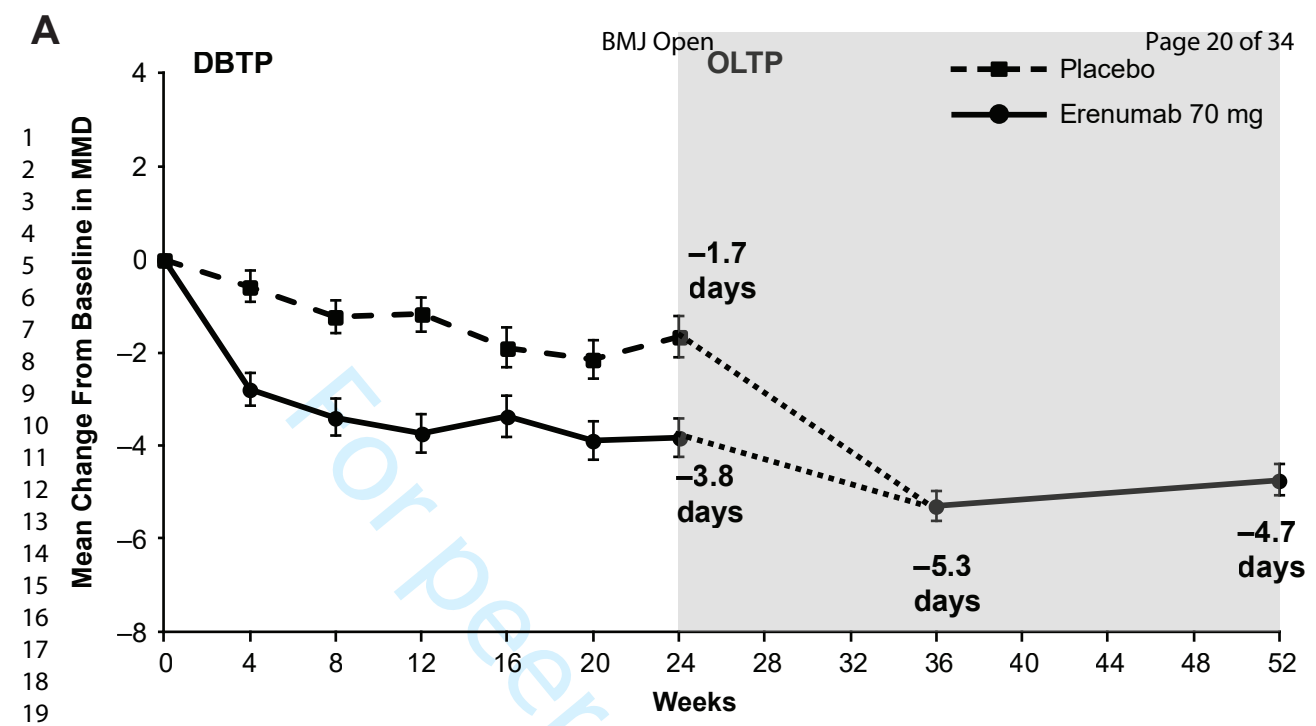
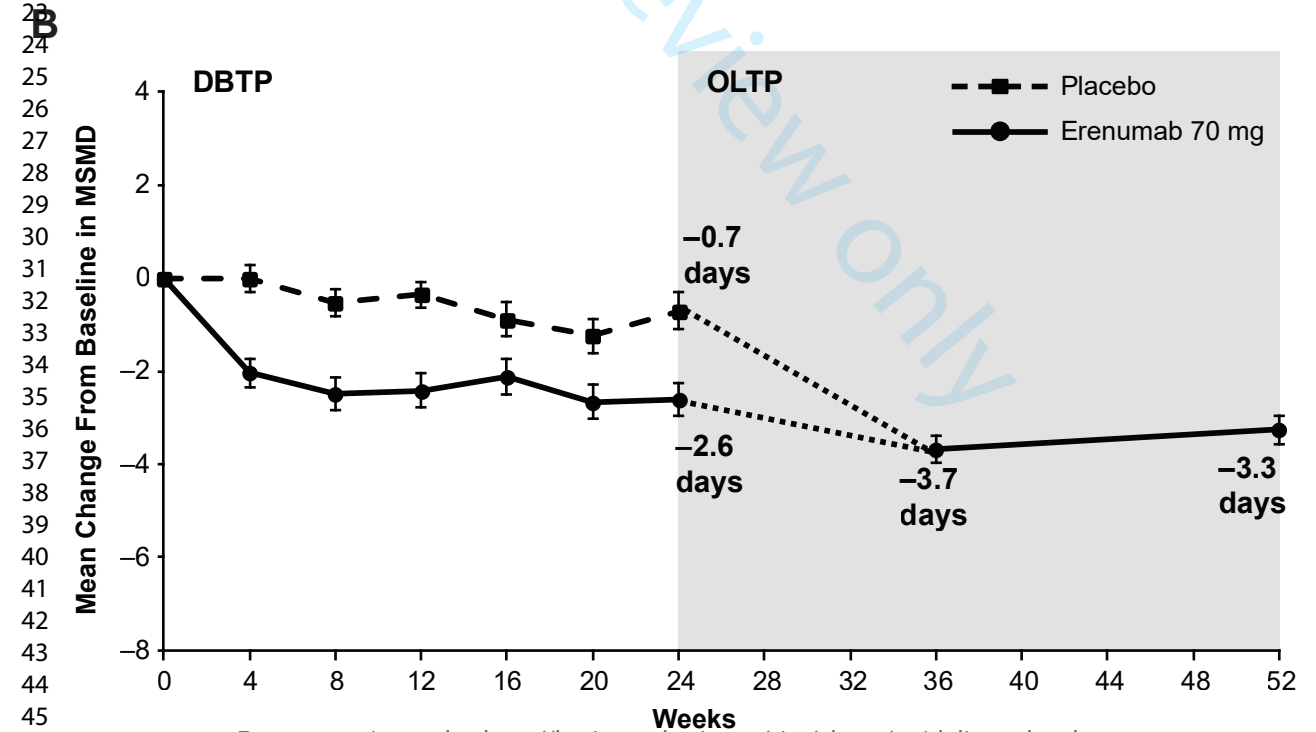
24. Tepper SJ, Ashina M, Reuter U, et al. Long-term safety and efficacy of erenumab in patients with chronic migraine: Results from a 52-week, open-label extension study. *Cephalalgia* 2020;40(6):543-53.

Figure 1. Change in (A) MMD and (B) MSMD from baseline. The mean (SE) change from baseline in MMD and MSMD during the DBTP and OLTP is shown for the treatment groups. For the OLTP, data are shown for the total population. The dotted line indicates that patients in the placebo group during the DBTP received erenumab 70 mg during the OLTP starting at week 24. *The number of patients in the efficacy analysis set during the DBTP. Error bars represent SE. n = number of patients with observed data. DBTP, double-blind treatment period; MMD, monthly migraine days; MSMD, monthly acute migraine-specific medication treatment days; OLTP, open-label treatment period; SE, standard error of the mean.

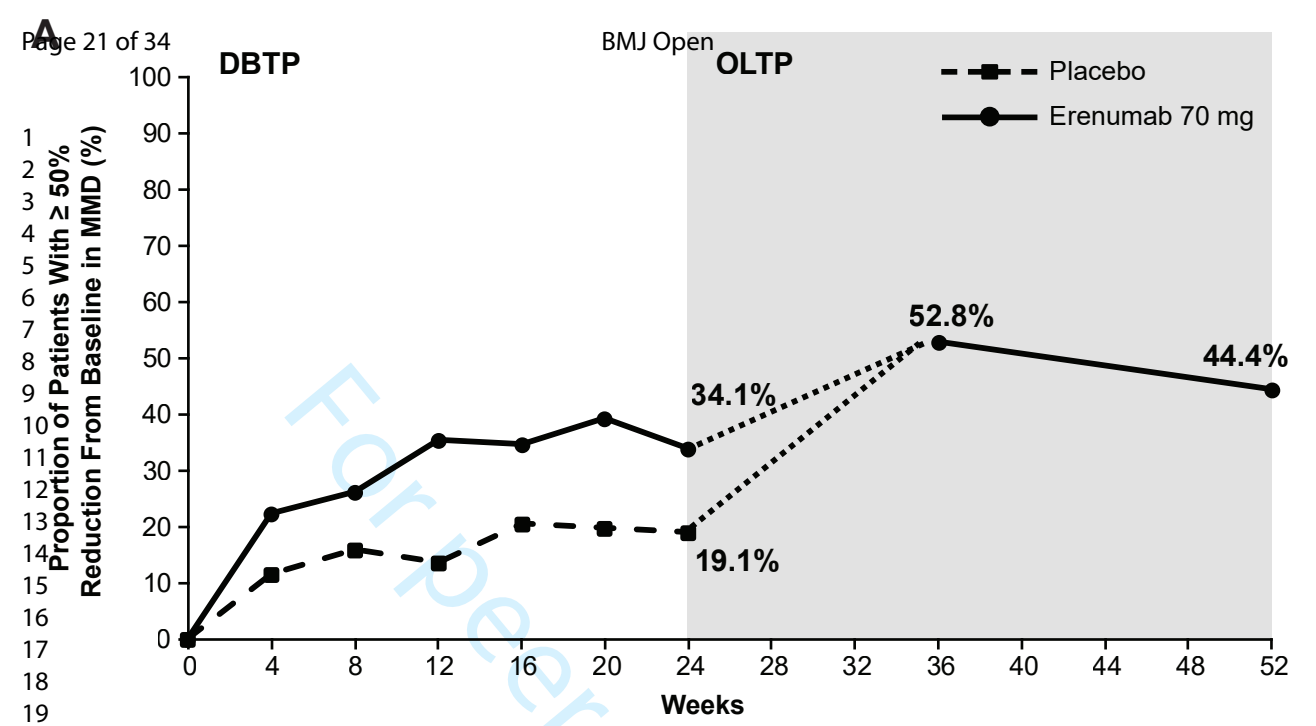
Figure 2. Patients achieving a (A) ≥50% and (B) ≥75% reduction in MMD from baseline. For the OLTP, data are shown for the total population. The dotted line indicates that patients in the placebo group during the DBTP received erenumab 70 mg during the OLTP starting at week 24. *The number of patients in the efficacy analysis set during the DBTP. n = number of patients with observed data. DBTP, double-blind treatment period; MMD, monthly migraine days; OLTP, open-label treatment period.

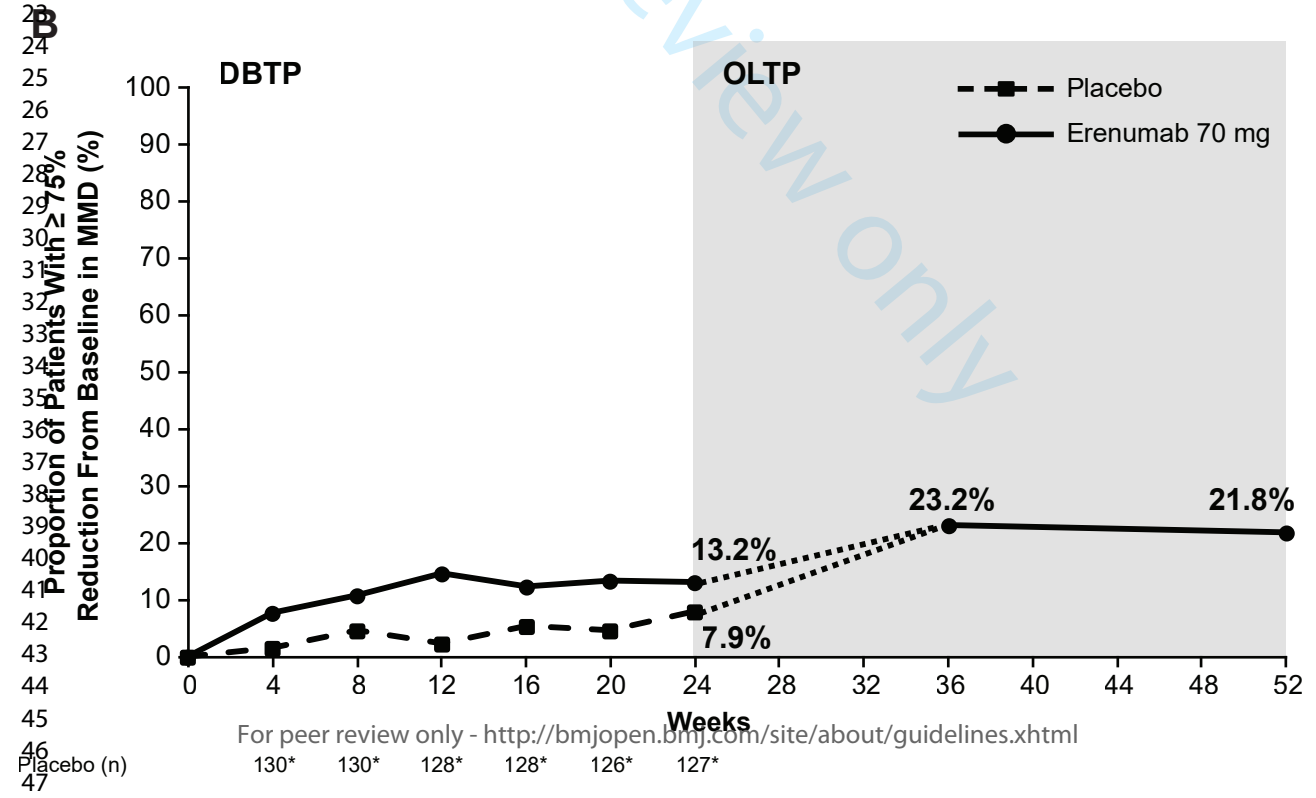


Placebo (n)	130*	130*	128*	128*	126*	127*	
Erenumab 70 mg (n)	130*	129*	128*	128*	128*	129*	246	243



Placebo (n)	130*	130*	128*	128*	126*	127*	
Erenumab 70 mg (n)	130*	129*	128*	128*	128*	129*	246	243





SUPPLEMENTARY APPENDIX

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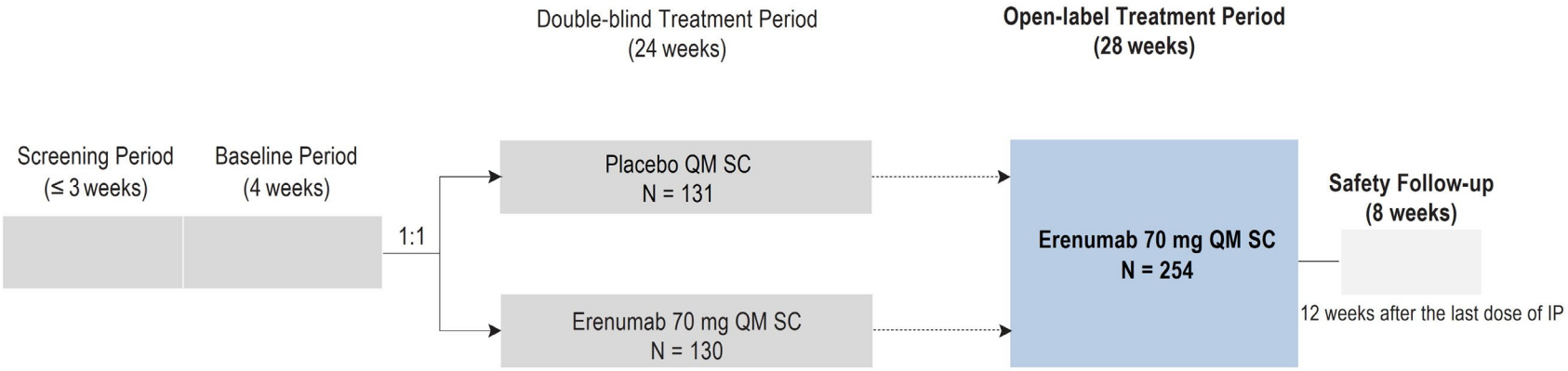
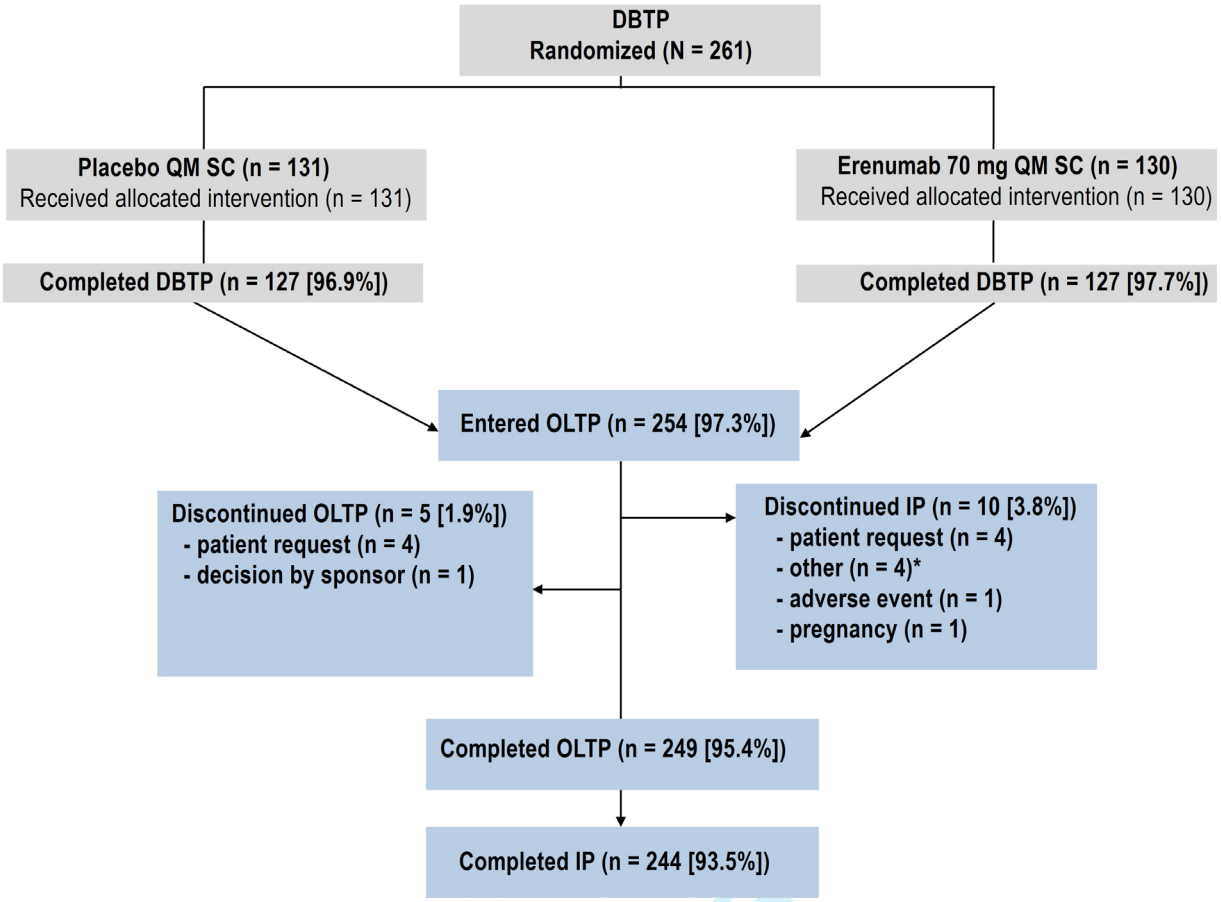
Figure S1



Study design. IP, investigational product; QM, once monthly; SC, subcutaneous.

Figure S2



Patient disposition. *Other refers to COVID-19 control measures. COVID-19, coronavirus disease 2019; DBTP, double-blind treatment period; IP, investigational product; OLTP, open-label treatment period; QM, once monthly; SC, subcutaneous.

Table S1

Study Number	Site Number	Site Name	IRB/IEC Name	IRB/IEC Address
20170609	34001	Saitama Neuropsychiatric Institute	Saitama Medical University Hospital Institutional Review Board	38 Moroyamamachi Morohongo, Iruma-gun, Saitama, 350-0495, Japan
20170609	34002	Fukuuchi Pain Clinic	Tokyo-Eki Center-Building Clinic Institutional Review Board	3-3-14 Nihombashi, Chuo-ku, Tokyo, 103-0027, Japan
20170609	34003	Kumamoto City Hospital	Kumamoto City Hospital Institutional Review Board	4-1-60 Higashimachi Higashi-ku, Kumamoto-shi, Kumamoto, 862-8505, Japan
20170609	34005	Dokkyo Medical University Hospital	Dokkyo Medical University Hospital Institutional Review Board	880 Kitakobayashi Mibumachi, Shimotsuga-gun, Tochigi, 321-0293, Japan
20170609	34006	Iwate Medical University Uchimaru Medical Center	Iwate Medical University Hospital Institutional Review Board	19-1 Uchimaru, Morioka-shi, Iwate, 020-8505, Japan
20170609	34007	Niwa Family Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan
20170609	34008	Osoegawa Neurology Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan
20170609	34009	Tanaka Neurosurgical Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan
20170609	34010	Tokyo Headache Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan

20170609	34011	Fujitsu Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan
20170609	34012	Sendai Headache and Neurology Clinic	Goshozuka Clinic Institutional Review Board	1-21-4 Goshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34013	Nagamitsu Clinic	Goshozuka Clinic Institutional Review Board	1-21-4 Goshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34014	Nagaseki Headache Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan
20170609	34015	Negoro Neurology Clinic	Goshozuka Clinic Institutional Review Board	1-21-4 Goshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34016	Saino Clinic	Goshozuka Clinic Institutional Review Board	1-21-4 Goshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34017	St Marianna University School of Medicine Hospital	St Marianna University Group Institutional Review Board	2-16-1 Sugao Miyamae-ku, Kawasaki-shi, Kanagawa, 216-8511, Japan
20170609	34018	Sakura Clinic	Goshozuka Clinic Institutional Review Board	1-21-4 Goshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34019	Tatsuoka Neurology Clinic	Tatsuoka Neurology Clinic Institutional Review Board	35-3 Chudojibojyocho Shimogyo-ku, Kyoto-shi, Kyoto, 600-8811, Japan
20170609	34020	Kitasato University Kitasato Institute Hospital	The IRB of Kitasato University Shirokane Campus	5-9-1 Shirokane, Minato-ku, Tokyo, 108-8642, Japan

20170609	34021	Tokai University Hachioji Hospital	Tokai University Hospitals Institutional Review Board	1-2-5 Yoyogi, Shibuya-ku, Tokyo, 151-0053, Japan

20170609	34021	Tokai University Hachioji Hospital	Tokai University Hospitals Institutional Review Board	143 Shimokasuya, Isehara-shi, Kanagawa, 259-1193, Japan
20170609	34021	Tokai University Hachioji Hospital	Tokai University Hospitals Institutional Review Board	21-1 Gakkyo Oiso-machi, Naka-gun, Kanagawa, 259-0198, Japan
20170609	34021	Tokai University Hachioji Hospital	Tokai University Hospitals Institutional Review Board	1838 Ishikawamachi, Hachioji-shi, Tokyo, 192-0032, Japan
20170609	34022	Takase Internal Medicine Clinic	Goshozuka Clinic Institutional Review Board	1-21-4 Goshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34023	Tominaga Hospital	Tominaga Hospital Institutional Review Board	1-4-48 Minatomachi Naniwa-ku, Osaka-shi, Osaka, 556-0017, Japan
20170609	34024	Konan Medical Center	Konan Medical Center IRB	1-5-16 Kamokogahara Higashinada-ku, Kobe-shi, Hyogo, 658-0064, Japan
20170609	34025	Japanese Red Cross Shizuoka Hospital	Japanese Red Cross Shizuoka Hospital IRB	8-2 Otemachi Aoi-ku, Shizuoka-shi, Shizuoka, 420-0853, Japan

20170609	34026	Nakamura Memorial Hospital	Nakamura Memorial Hospital Nakamura Memorial Hospital Institutional Review Board	14-291 Minami 1-jo Nishi, Chuo-ku, Sapporo-shi, Hokkaido, 060-8570, Japan
20170609	34027	Saitama Medical University Hospital	Saitama Medical University Hospital Institutional Review Board	38 Moroyamamachi Morohongo, Iruma-gun, Saitama, 350-0495, Japan
20170609	34028	Sakuragi Headache Clinic	Saga Memorial Hospital Institutional Review Board	1240-1 Nagase Takakise-machi, Saga-shi, Saga, 849-0917, Japan
20170609	34029	Sapporo Isobe Headache and Memory Clinic	Sapporo Medical Associations Institutional Review Board	19-1-1 Odorinishi Chuo-ku, Sapporo-shi, Hokkaido, 060-8581, Japan
20170609	34030	Kokubu Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan
20170609	34031	Umenotsuji Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan
20170609	34032	Sanno Clinic Shinagawa	Shinagawa East One Medical Clinic Institutional Review Board	2-16-1 Kounan, Shinagawa East One 3F, Minato-ku, Tokyo, 108-0075, Japan

20170609	34033	Ooba Clinic for Neurosurgery and Headache	Nihonbashi Sakura Clinic Institutional Review Board	1-9-2 Nihonbashikayabacho, Inamura Building 5F, Chuo- ku, Tokyo, 103-0025, Japan
20170609	34034	Doi Internal Medicine Neurology	Goshozuka Clinic Institutional Review Board	1-21-4 Goshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34035	Ikeda Neurosurgical Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan
20170609	34036	Jinnouchi Neurosurgery Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan
20170609	34037	Kijima Neurosurgery Clinic	Goshozuka Clinic Institutional Review Board	1-21-4 Goshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34038	Medical Corporation Yufukai Shimoda Neurology Clinic	Goshozuka Clinic Institutional Review Board	1-21-4 Goshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan

20170609	34039	Medical Corporation Seikokai Takanoko Hospital	Medical Corporation Seikokai Takanoko Hospital Institutional Review Board	525-1 Takanokomachi, Matsuyama-shi, Ehime, 790-0925, Japan
20170609	34040	Medical Corporation Inoue Neurology Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan
20170609	34041	Sakuma Neurological Clinic	Goshozuka Clinic Institutional Review Board	1-21-4 Goshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34042	Higashi Sapporo Neurology and Neurosurgery Clinic	Nihonbashi Sakura Clinic Institutional Review Board	1-9-2 Nihonbashikayabacho, Inamura Building 5F, Chuo- ku, Tokyo, 103-0025, Japan

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2,3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	5,6
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	NA; sample size was based on the number of patients who completed the DBTP and received at least one dose of erenumab 70

			mg in the OLTP
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence	8a	Method used to generate the random allocation sequence	5
generation	8b	Type of randomisation; details of any restriction (such as blocking and block size)	NA
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	NA
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	NA
	11b	If relevant, description of the similarity of interventions	NA; this is a single-arm open-label extension
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7, Figure S2
	13b	For each group, losses and exclusions after randomisation, together with reasons	7, Figure S2
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	5
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	8
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8,9, Figure 1, Figure 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	

		pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	10-12
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	3
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12-13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	Protocol will be provided during submission
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	3

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Items to include when reporting a randomized trial in a journal or conference abstract

Item	Description	Reported on line number
Title	Identification of the study as randomized	2
Authors *	Contact details for the corresponding author	15,16
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	27
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	28-31
Interventions	Interventions intended for each group	32
Objective	Specific objective or hypothesis	24-26
Outcome	Clearly defined primary outcome for this report	33-36
Randomization	How participants were allocated to interventions	NA
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	NA
Results		
Numbers randomized	Number of participants randomized to each group	30
Recruitment	Trial status	NA
Numbers analysed	Number of participants analysed in each group	30-31
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	37-42
Harms	Important adverse events or side effects	43-45
Conclusions	General interpretation of the results	46-48
Trial registration	Registration number and name of trial register	49
Funding	Source of funding	50

**this item is specific to conference abstracts*

BMJ Open

Long-term efficacy and safety of erenumab in Japanese patients with episodic and chronic migraine: Results from a 28-week open-label treatment period of a randomized trial

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Manuscript ID	bmjopen-2022-068616.R1
Article Type:	Original research
Date Submitted by the Author:	30-Jun-2023
Complete List of Authors:	Hirata, Koichi; Dokkyo Ika Daigaku, Department of Neurology Takeshima, Takao ; Tominaga Hospital, Headache Center, Department of Neurology Sakai, Fumihiko ; Saitama Neuropsychiatric Institute, Saitama International Headache Center Numachi, Yotaro ; Amgen KK, Research & Development Yoshida, Ryuji ; Amgen KK, Research & Development Koukakis, Reija ; Amgen Ltd Uxbridge, Biostatistics Hasebe, Miki; Amgen KK, Research & Development Yui, Daishi ; Amgen KK, Research & Development da Silva Lima, Gabriel Paiva ; Amgen Inc, Global Development Cheng, Sunfa; Amgen Inc, Global Development
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Neurology, Pharmacology and therapeutics
Keywords:	NEUROLOGY, Adult neurology < NEUROLOGY, Migraine < NEUROLOGY, Neurological pain < NEUROLOGY, Clinical trials < THERAPEUTICS

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Long-term efficacy and safety of erenumab in Japanese patients with episodic and chronic migraine: Results from a 28-week open-label treatment period of a randomized trial

Koichi Hirata, MD, PhD,[1] Takao Takeshima, MD, PhD,[2] Fumihiko Sakai, MD, PhD,[3] Yotaro Numachi, MD, PhD,[4] Ryuji Yoshida, PhD,[4] Reija Koukakis,[5] Miki Hasebe, PhD,[4] Daishi Yui, PhD,[4] Gabriel Paiva da Silva Lima, MD,[6] Sunfa Cheng, MD[6]

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Keywords: Erenumab, CGRP, Episodic migraine, Chronic migraine, Japanese patients

Article type: Original Research

Word Count: 2511 (limit 4000)

ABSTRACT

Objectives: To evaluate the 1-year efficacy and safety of once-monthly erenumab 70 mg following a 24-week double-blind treatment period (DBTP) of a phase 3 randomized study of Japanese patients with episodic migraine (EM) or chronic migraine (CM).

Design: Multicenter open-label study.

Setting: A total of 41 centers in Japan.

Participants: Patients completing the DBTP continued into the 28-week open-label treatment period (OLTP). 254 of 261 (97.3%) randomized patients continued into the OLTP; 244 (93.5%) completed treatment.

Interventions: Once monthly subcutaneous erenumab 70 mg.

Main Outcome measures: Changes from baseline in monthly migraine days (MMD) and monthly acute migraine-specific medication treatment days (MSMD) reported via patient eDiary; proportion of ≥50% and ≥75% responders in MMD reduction from baseline; incidence and exposure-adjusted incidence of treatment-emergent adverse events (TEAEs).

Results: At week 24 of the DBTP, the mean (SE) change from baseline in MMD for the erenumab group was –3.8 (0.4) days (EM, –3.0 [0.4]; CM, –5.2 [0.8]); in MSMD, –2.6 (0.4) days (EM, –2.1 [0.4]; CM, –3.4 [0.7]). At the end of the OLTP (52 weeks postbaseline), the mean (SE) change from baseline in MMD was –4.7 (0.3) days (EM, –3.4 [0.3]; CM, –6.9 [0.6]); in MSMD, –3.3 (0.3) days (EM, –2.4 [0.3]; CM, –4.6 [0.5]). The proportion of ≥50% responders for MMD reduction in the erenumab group was 34.1% at week 24; 44.4% at week 52. The exposure-adjusted incidence of TEAEs was 219.7 per 100 patient-years during the OLTP (DBTP, 251.0 for the erenumab group). The most common TEAEs during the OLTP were nasopharyngitis, constipation, and influenza. No new safety concerns were identified.

Conclusions: Erenumab treatment was associated with reduced migraine frequency in Japanese patients with EM or CM for up to 1 year. Overall safety results from the OLTP were consistent with DBTP results.

Clinical Trials Registration Number: NCT03812224

Funding: This study was funded by Amgen.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- While the 28-week OLTP was short relative to other studies in non-Japanese patients, this study represents the longest follow-up time with erenumab in Japanese patients with CM
- Patients and study staff remained blinded to assignment (placebo or erenumab) in DBTP during OLTP
- Reporting exposure-adjusted rates normalizes the rates of adverse events occurring during the DBTP and OLTP to equal exposure periods (ie, events per 100 patient-years), and thus allow for proper comparison between the DBTP and OLTP
- The OLTP of this study lacked a comparator arm

INTRODUCTION

Migraine is a common neurological disease worldwide and a leading cause of disability associated with significant personal and societal effects.(1-3) In Japan, 6% to 8% of the population is affected by migraine, which places a substantial burden on patients and society related to quality of life, work productivity, and costs.(4-7) Because of concerns related to inadequate efficacy and poor tolerability, the use of standard of care oral preventive medications is low and is associated with high rates of discontinuation.(6, 8-11) Therefore, there is an unmet need for new migraine preventive medications.

Erenumab (erenumab-aooe in the United States), a fully human monoclonal antibody against the calcitonin gene-related peptide (CGRP) receptor, has been approved for the preventive treatment of adult migraine in over 70 countries worldwide, including the United States (2018), Europe (2018), and Japan (2021).(12, 13) The sustained efficacy and safety of erenumab in the preventive treatment of episodic migraine (EM) and chronic migraine (CM) have been demonstrated in several global clinical studies.(14-18) In Japan, approval was based on two clinical studies in adult patients with EM or CM, which demonstrated erenumab to be safe and efficacious.(19, 20) Sustained efficacy and safety of erenumab for up to 2 years in Japanese patients with EM have also been demonstrated.(21)

Here, we report on the long-term (up to 1 year) efficacy, safety, and tolerability of once-monthly erenumab 70 mg during a 28-week open-label treatment period (OLTP) after a 24-week double-blind treatment period (DBTP) of a phase 3 study, which demonstrated favorable efficacy and safety results for erenumab 70 mg in EM and CM.(20)

METHODS

Study design

This multicenter (41 centers across Japan), 28-week OLTP followed a 24-week, randomized, double-blind, placebo-controlled, phase 3 study of once-monthly erenumab 70 mg in patients with EM or CM in Japan (ClinicalTrials.gov identifier NCT03812224) (Figure S1). Patients who completed the DBTP in each treatment group were eligible to participate in the OLTP and receive once-monthly erenumab 70 mg. The first patient entered the OLTP on October 2, 2019, and the last patient ended the OLTP on November 20, 2020. Randomization was stratified by migraine status (EM or CM) and migraine preventive treatment status (ever used or never used) and was assigned by the sponsor using an interactive response technology system. During the DBTP, patients received once-monthly erenumab 70 mg or placebo in a 1:1 ratio; in the OLTP, all patients received once-monthly erenumab 70 mg. Independent ethics committee or institutional review boards at each site (Table S1) reviewed and approved the protocol and signed the informed patient consent forms before study initiation. The study conforms to the guidelines set by the International Council for Harmonisation for Good Clinical Practice and by the Pharmaceuticals and Medical Devices Agency (PMDA). The study was designed according to the European Medicines Agency (EMA) guideline on Clinical Investigation of Medicinal Products for the Treatment of Migraine, the International Headache Society (IHS) Guidelines for Controlled Trials of Drugs in Migraine, and advice given by the PMDA.(22, 23)

Patient and Public Involvement Statement

No patients or public representatives were involved in the design, conduct, reporting, or dissemination efforts of the study results.

Patients

Patients who completed the DBTP (parent study) in each treatment group were eligible to participate in the OLTP and receive once-monthly erenumab 70 mg. Japanese patients aged 20 through 65 years with a history of migraine with or without aura (based on medical records or patient self-report) for at least 12 months before screening, as defined in the third edition of the *International Classification of Headache Disorders* (ICHD-3) of the IHS, and a diagnosis of EM (<15 headache days/month, ≥4 monthly migraine days [MMD]) or CM (≥15 headache days/month, ≥8 MMD) over the 3 months before screening, were included. Patients had to demonstrate at least 80% compliance with the eDiary during the baseline period prior to the DBTP. A detailed description of the eligibility criteria in the parent study has been described previously.(20)

Endpoints and assessments

Efficacy outcomes during the OLTP included changes from baseline in MMD and monthly acute migraine-specific medication treatment days (MSMD), and the proportion of patients who achieved at least a 50% or 75% reduction in MMD from baseline.

Patients used an eDiary to report clinical outcome assessments daily during weeks 33 to 36 and weeks 49 to 52. 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. A migraine day was defined as a migraine (with or without aura) that lasted for at least 4 hours and had at least two of the following pain features: unilateral, throbbing, moderate to severe, or exacerbated with exercise or physical activity; or was associated with nausea, vomiting, or photophobia and phonophobia. A migraine day also included a day in which a patient took a migraine-specific medication during aura or to treat a headache regardless of the duration and associated symptoms. A qualified headache day was a day characterized by onset, continuation, or

recurrence of a headache and met one of the following criteria: a migraine headache treated with acute migraine-specific medication, a non-migraine headache that lasted for at least 4 hours, or a headache for which acute headache treatment was used. An acute migraine-specific medication treatment day was defined as any day during which migraine-specific medication was used.

Safety endpoints included the incidence and exposure-adjusted incidence of treatment-emergent adverse events (TEAEs), clinical laboratory values and vital signs, and the incidence of anti-erenumab antibodies. Exposure-adjusted rates (per 100 patient-years) were calculated by dividing the number of patients with at least one reported occurrence of the TEAE of interest by the total time at risk for reporting the TEAE (patient-year) multiplied by 100. The time at risk was defined as the time from the first dose of erenumab to the onset of the TEAE or the end of study date. Reporting exposure-adjusted rates normalizes the rates of adverse events occurring during the DBTP and OLTP to equal exposure periods (ie, events per 100 patient-years), and thus allows for a proper comparison between the DBTP and OLTP.

Statistical analysis

Analysis was performed after all patients had completed safety follow-up at the end of the study and included patients who received at least one dose of erenumab 70 mg in the OLTP. Efficacy and safety data were tabulated by the double-blind treatment group. Efficacy endpoints were analyzed by using descriptive statistics based on observed data without imputation and were tabulated by visit. No formal testing was conducted. Patient incidence and exposure-adjusted incidence of TEAEs were tabulated by treatment group and by system organ class and preferred term. All analyses were performed using SAS System 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patients

Of the 261 patients enrolled and randomized in the parent study (erenumab 70 mg, n = 130; placebo, n = 131), 254 (97.3%) entered the OLTP and received at least one dose of the investigational product (IP) and 244 (93.5%) completed the IP. Ten patients (3.8%) discontinued the IP for the following reasons: patient request (n = 4; 1.5%), COVID-19 control measures (n = 4; 1.5%), adverse event (n = 1; 0.4%), and pregnancy (n = 1; 0.4%) (Figure S2). In the OLTP population, the mean age of patients was 44.3 years, 86.6% were female, and the majority (77.6%) had used or were using migraine preventive treatment at baseline (Table 1).

Table 1. Baseline demographics and characteristics of the OLTP population

	Total (N = 254)
Age, mean (SD), years	44.3 (9.0)
Sex, female, n (%)	220 (86.6)
Migraine type*, n (%)	
EM	155 (61.0)
CM	99 (39.0)
Migraine preventive treatment use, n (%)	
Ever used (including prior and/or current users)	197 (77.6)
Never used	57 (22.4)
MMD, mean (SE)	12.2 (0.4)
MSMD, mean (SE)	9.4 (0.4)
MHD, mean (SE)	13.8 (0.4)

*Based on actual data collected instead of randomization stratification. N = number of patients in the analysis set. n = number of patients with observed data. CM, chronic migraine; EM, episodic migraine; MHD, monthly headache days; MMD, monthly migraine days; MSMD, monthly acute migraine-specific medication treatment days; OLTP, open-label treatment period; SD, standard deviation; SE, standard error of the mean.

Efficacy

In the OLTP population (N = 254; EM, n = 155; CM, n = 99), the mean (standard error of the mean [SE]) MMD at baseline was 12.2 (0.4) days (EM, 8.3 [0.2] days; CM, 18.2 [0.4] days) and the mean (SE) MSMD was 9.4 (0.4) days (EM, 6.8 [0.3] days; CM, 13.6 [0.6] days) (Table 1). At the end of the DBTP at week 24, the mean (SE) change from baseline in MMD for the erenumab 70 mg group was –3.8 (0.4) days (EM, –3.0 [0.4] days; CM, –5.2 [0.8] days]) and –1.7 (0.5) days for the placebo group; at the end of the OLTP at week 52, the mean (SE) change was –4.7 (0.3) days (EM, –3.4 [0.3]; CM, –6.9 [0.6]) (Figure 1, Table 2).

At the end of the DBTP at week 24, the mean (SE) change from baseline in MSMD for the erenumab 70 mg group was –2.6 (0.4) days (EM, –2.1 [0.4]; CM, –3.4 [0.7]) and –0.7 (0.4) days for the placebo group; at the end of the OLTP at week 52, the mean (SE) change was –3.3 (0.3) days (EM, –2.4 [0.3] days; CM, –4.6 [0.5] days) (Figure 1, Table 2). Throughout the 28-week OLTP, erenumab 70 mg demonstrated persistent efficacy in MMD and MSMD reduction in patients with EM or CM.

At week 24 of the DBTP, the proportion of patients who achieved at least a 50% reduction in MMD from baseline was 34.1% with erenumab 70 mg (EM, 39.7%; CM, 25.5%) and 19.1% with placebo (Figure 2, Table 2). The response was maintained and numerically higher throughout the OLTP than it was during the DBTP. At week 36 of the OLTP, 52.8% of the patients achieved the 50% threshold for MMD reduction (EM, 58.8%; CM, 43.0%); at week 52, it was 44.4% (EM, 46.3%; CM, 41.7%). The results were similar for patients responding at the 75% threshold for MMD reduction (Figure 2).

Table 2. Efficacy results during the OLTP

	EM (N = 155)	**CM (N = 99)**	**Total (N = 254)**
Change from baseline in MMD, mean (SE)			
	n = 78	n = 51	n = 129
Week 24*	–3.0 (0.4)	–5.2 (0.8)	–3.8 (0.4)

	n = 153	n = 93	n = 246
Week 36	–3.7 (0.3)	–8.0 (0.6)	–5.3 (0.3)
	n = 147	n = 96	n = 243
Week 52	–3.4 (0.3)	–6.9 (0.6)	–4.7 (0.3)
Change from baseline in MSMD, mean (SE)			
	n = 78	n = 51	n = 129
Week 24*	–2.1 (0.4)	–3.4 (0.7)	–2.6 (0.4)
	n = 153	n = 93	n = 246
Week 36	–2.8 (0.3)	–5.2 (0.5)	–3.7 (0.3)
	n = 147	n = 96	n = 243
Week 52	–2.4 (0.3)	–4.6 (0.5)	–3.3 (0.3)
Achievement of ≥50% MMD response, n (%)			
	n = 78	n = 51	n = 129
Week 24*	31 (39.7)	13 (25.5)	44 (34.1)
	n = 153	n = 93	n = 246
Week 36	90 (58.8)	40 (43.0)	130 (52.8)
	n = 147	n = 96	n = 243
Week 52	68 (46.3)	40 (41.7)	108 (44.4)

Efficacy by EM and CM subgroups at week 24 of the DBTP and during the OLTP. *Data are shown for patients in the erenumab 70 mg group at week 24 of the DBTP in the efficacy analysis set. N = number of patients in the open-label analysis set; n = number of patients with observed data. CM, chronic migraine; DBTP, double-blind treatment period; EM, episodic migraine; MMD, monthly migraine days; MSMD, monthly acute migraine-specific medication treatment days; OLTP, open-label treatment period; SE, standard error of the mean.

Safety

The mean (standard deviation) exposure to erenumab 70 mg during the OLTP was 192.6 (20.0) days (total exposure to open-label treatment, 133.9 patient-years). The majority of patients (92.1%) received all seven doses of erenumab 70 mg during the OLTP.

During the OLTP, the incidence of TEAEs was 71.3% (181/254) (Table 3). The exposure-adjusted incidence of TEAEs during the OLTP was 219.7 per 100 patient-years, which is similar to that in the erenumab group (251.0 per 100 patient-years) and in the placebo group (197.7 per 100 patient-years) during the DBTP. The majority of patients (62.2% [158/254]) experienced TEAEs of grade 2 or less. The most common (≥5 per 100 patient-years) TEAEs reported with erenumab (OLTP vs DBTP) were nasopharyngitis (32.8 vs 67.2 per 100 patient-years), constipation (7.8 vs 10.3 per 100 patient-years), influenza (6.6 vs 1.7 per 100 patient-years), gastroenteritis (6.5 vs 6.8 per 100 patient-years), and urticaria (5.9 vs 1.7 per 100 patient-years). Seven patients (2.8%) reported serious adverse events with erenumab during the OLTP, corresponding to an exposure-adjusted rate of 4.1 per 100 patient-years, which is similar to the rate reported during the DBTP in each treatment group (3.4 per 100 patient-years). During the OLTP, one patient with a serious adverse event discontinued treatment because of a grade 3 serious adverse event of drug eruption, which was considered by the investigator to be unrelated to erenumab treatment. No deaths were reported during the study. No clinically significant changes in laboratory values or vital signs were observed throughout the OLTP.

Of the 254 patients in the OLTP, nine (3.5%) developed anti-erenumab binding antibodies for the first time (negative or no result before the first OLTP dose), which is consistent with that observed during the DBTP (5.4%) (Table 3). Of the nine patients who were positive for binding antibodies during the OLTP, six received placebo during the DBTP and three received erenumab during the DBTP and the OLTP. During the entire study, 16 patients (6.3%) developed anti-erenumab binding antibodies after erenumab treatment, of which 6 (37.5%) had transient antibodies (negative result at the last assessment). No patients developed anti-erenumab neutralizing antibodies.

Table 3. Safety results during the DBTP and OLTP

	DBTP	OLTP

	Placebo (N = 131)	Erenumab 70 mg (N = 130)	Total (N = 254)
All TEAEs, n (%) [r]	78 (59.5) [197.7]	86 (66.2) [251.0]	181 (71.3) [219.7]
Grade ≥2	67 (51.1) [159.2]	72 (55.4) [180.6]	158 (62.2) [159.9]
Grade ≥3	2 (1.5) [3.4]	4 (3.1) [6.8]	12 (4.7) [7.1]
Serious AEs	2 (1.5) [3.4]	2 (1.5) [3.4]	7 (2.8) [4.1]
Leading to IP discontinuation	0 (0.0) [0.0]	0 (0.0) [0.0]	1 (0.4) [0.6]
Fatal AEs	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]
Most common TEAEs, n (%) [r]*			
Nasopharyngitis	37 (28.2) [74.4]	35 (26.9) [67.2]	49 (19.3) [32.8]
Constipation	1 (0.8) [1.7]	6 (4.6) [10.3]	13 (5.1) [7.8]
Influenza	2 (1.5) [3.4]	1 (0.8) [1.7]	11 (4.3) [6.6]
Gastroenteritis	4 (3.1) [6.7]	4 (3.1) [6.8]	11 (4.3) [6.5]
Urticaria	0 (0.0) [0.0]	1 (0.8) [1.7]	10 (3.9) [5.9]
Developed anti-erenumab antibodies, n (%)			
Developed binding anti-erenumab antibodies	NA	n' = 129 7 (5.4)	n' = 254 9 (3.5)
Transient†	NA	2 (28.6)	4 (44.4)
Developed neutralizing anti-erenumab antibodies	NA	NA	NA

*Exposure-adjusted rates of TEAEs of at least 5 per 100 patient-years during the OLTP. †A negative result was reported at the patient's last time point within the study period. N = number of patients in the analysis set; n = number of patients with at least one occurrence of a TEAE or number of patients who developed anti-erenumab antibodies; n' = patients with a postbaseline result during the DBTP or OLTP; r = exposure-adjusted patient incidence rate per 100 patient-years. AE, adverse event; DBTP, double-blind treatment period; IP, investigational product; NA, not applicable; OLTP, open-label treatment period; TEAE, treatment-emergent adverse event.

DISCUSSION

The results of this 28-week OLTP study of erenumab 70 mg in Japanese patients with EM or CM demonstrated a persistence of efficacy for up to 1 year and a safety profile similar to that reported during the DBTP. From week 24 of the DBTP to the end of the OLTP at week 52, the reduction from baseline in MMD and MSMD, and the proportion of ≥50% and ≥75% responders in MMD reduction were maintained.

The incidence and exposure-adjusted incidence of TEAEs during the OLTP were consistent with those from the DBTP and previous studies,(18, 20, 21) except for influenza and urticaria, which were numerically higher during the OLTP than they were during the DBTP. Furthermore, although the exposure-adjusted rates of constipation during the OLTP (7.8 per 100 patient-years) were consistent with those during the DBTP (10.0 per 100 patient-years), they were higher than those reported during the OLTP of the phase 2 study in Japanese patients with EM (2.6 per 100 patient-years).(21) The development of anti-erenumab antibodies in 6.3% patients over the entire study was consistent with the 5.8% seen in the global CM OLE study and was lower than the 13.1% in the global EM OLE study.(24, 25) Neutralizing antibodies were uncommon in the global studies and were not observed in this study. In addition, no new safety concerns regarding clinically relevant changes in laboratory assessments and vital signs were identified throughout the OLTP. Of the patients who entered the OLTP, 3.9% discontinued IP including 1 for an AE. The high proportion of patients completing erenumab treatment through both DBTP and OLTP (93.5%) reflects the excellent tolerability and sustained efficacy. In the pivotal topiramate trials, 28.7% of participants withdrew during the 8-month OLE, more than 40% of these due to AEs.(26) The high retention rate also reduces the potential for bias that may be seen in open-label extension studies where patients may drop out for diminished efficacy, thus skewing the efficacy results over time.

The OLTP of this study was non-randomized and lacked a comparator arm, thus limiting the ability to distinguish study drug specific effects on efficacy and safety from other factors. In addition, the duration of the 28-week OLTP was short relative to some other studies in non-Japanese patients.(18) However, the study does represent the longest follow-up experience with erenumab in Japanese patients with CM and shows long-term efficacy and safety that are comparable to that seen in a global long-term study of erenumab in patients with CM.(25) In the global CM study, the reduction in MMD and MSMD after 52 weeks for the erenumab 70 mg group was –7.8 days and –5.8 days, respectively; 47.4% of the patients achieved at least a 50% reduction from baseline in MMD. In the global EM study, the reduction in MMD and MSMD after the 52-week open-label period (study week 64) for the erenumab 70 mg group was –5.0 days and –2.4, respectively; 65% of the patients achieved at least a 50% reduction from baseline in MMD.(24) This is comparable to the reductions in MMD and MSMD in this study at overall week 52 of –4.74 days and –3.26, respectively; 44.4% of the patients achieved at least a 50% reduction from baseline in MMD. These data support long-term treatment with erenumab in Japanese patients with EM and CM.

CONCLUSION

Treatment with erenumab was associated with a reduction in migraine frequency that was maintained for up to 1 year in Japanese patients with EM or CM. Erenumab had a safety profile similar to that observed in the DBTP; no new safety signals were identified during the OLTP.

Ethics Approval

This study involved human patients and was approved by ethics committees and institutional review boards listed in the supplementary appendix (Table S1).

Acknowledgments

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Author contributions

SC and GPL contributed to the conception and design of the study and acquired the data. KH, TT, FS, YN, RY, RK, MH, DY, GPL, and SC analyzed and interpreted the data, drafted the manuscript, critically reviewed and revised the manuscript for intellectual content, and provided final approval of the version to be published.

Conflict of Interest Statement

KH reports royalties from Amgen, Astellas, Daiichi Sankyo, Eisai, Merck Sharp & Dohme, and Pfizer. TT has nothing to disclose. FS reports consulting fees from Amgen. RY, RK, MH, DY, GPL, and SC are employees of and own stock in Amgen. YN owns stock in Amgen.

Institutional review board approval

The Institutional review boards at each study center (Table S1) approved the study protocol, informed consent forms, and any materials provided to the patients.

Data availability statement

Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request.

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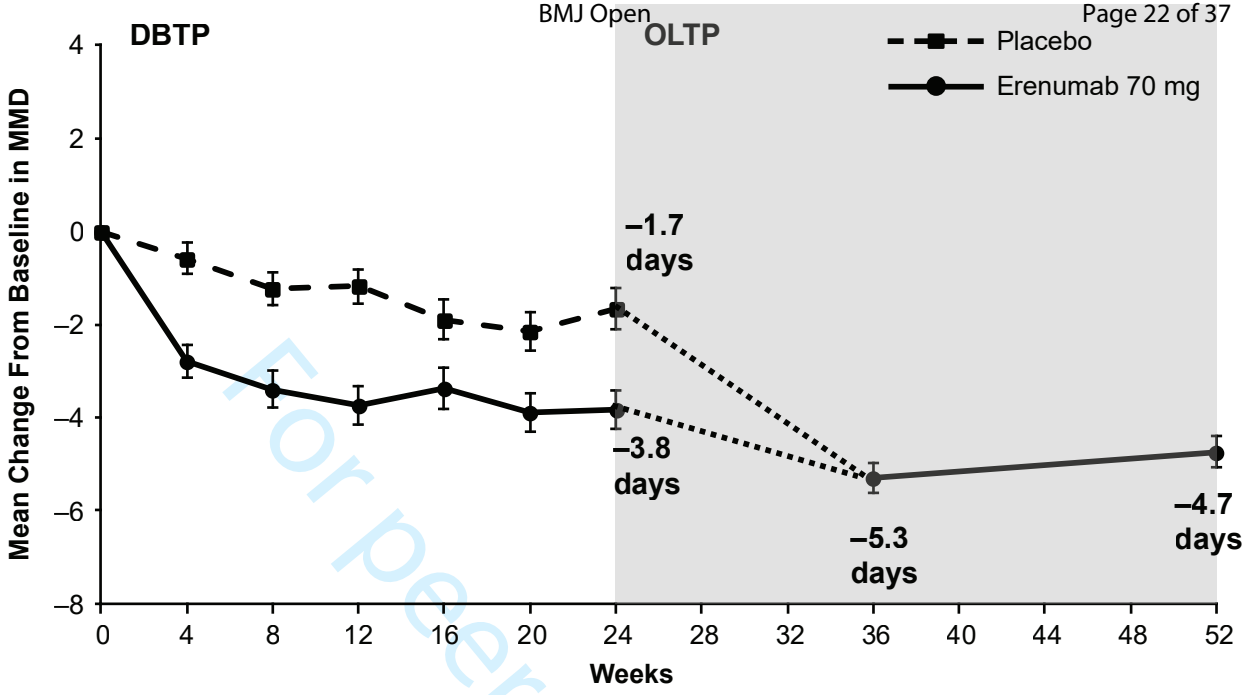
Figure 1. Change in (A) MMD and (B) MSMD from baseline. The mean (SE) change from baseline in MMD and MSMD during the DBTP and OLTP is shown for the treatment groups. For the OLTP, data are shown for the total population. The dotted line indicates that patients in the placebo group during the DBTP received erenumab 70 mg during the OLTP starting at week 24. *The number of patients in the efficacy analysis set during the DBTP. Error bars represent SE. n = number of patients with observed data. DBTP, double-blind treatment period; MMD, monthly migraine days; MSMD, monthly acute migraine-specific medication treatment days; OLTP, open-label treatment period; SE, standard error of the mean.

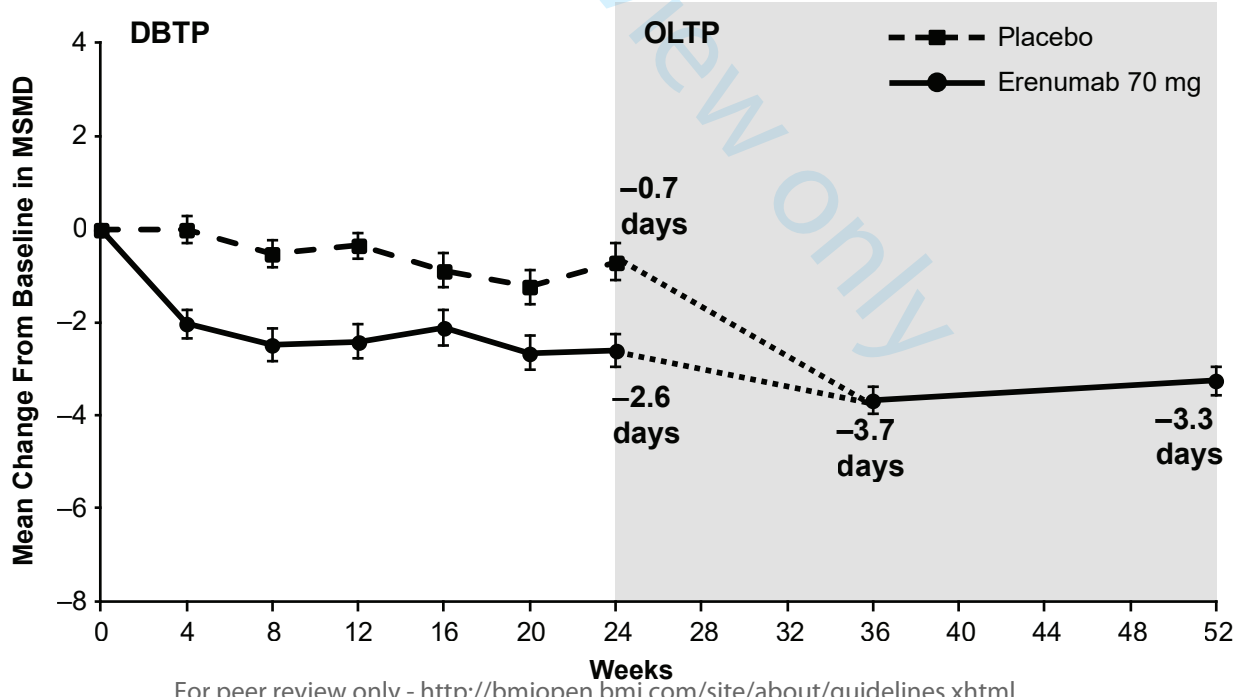
Figure 2. Patients achieving a (A) ≥50% and (B) ≥75% reduction in MMD from baseline. For the OLTP, data are shown for the total population. The dotted line indicates that patients in the placebo group during the DBTP received erenumab 70 mg during the OLTP starting at week 24. *The number of patients in the efficacy analysis set during the DBTP. n = number of patients with observed data. DBTP, double-blind treatment period; MMD, monthly migraine days; OLTP, open-label treatment period.

A



Placebo (n)	130*	130*	128*	128*	126*	127*	
Erenumab 70 mg (n)	130*	129*	128*	128*	128*	129*	246	243

B



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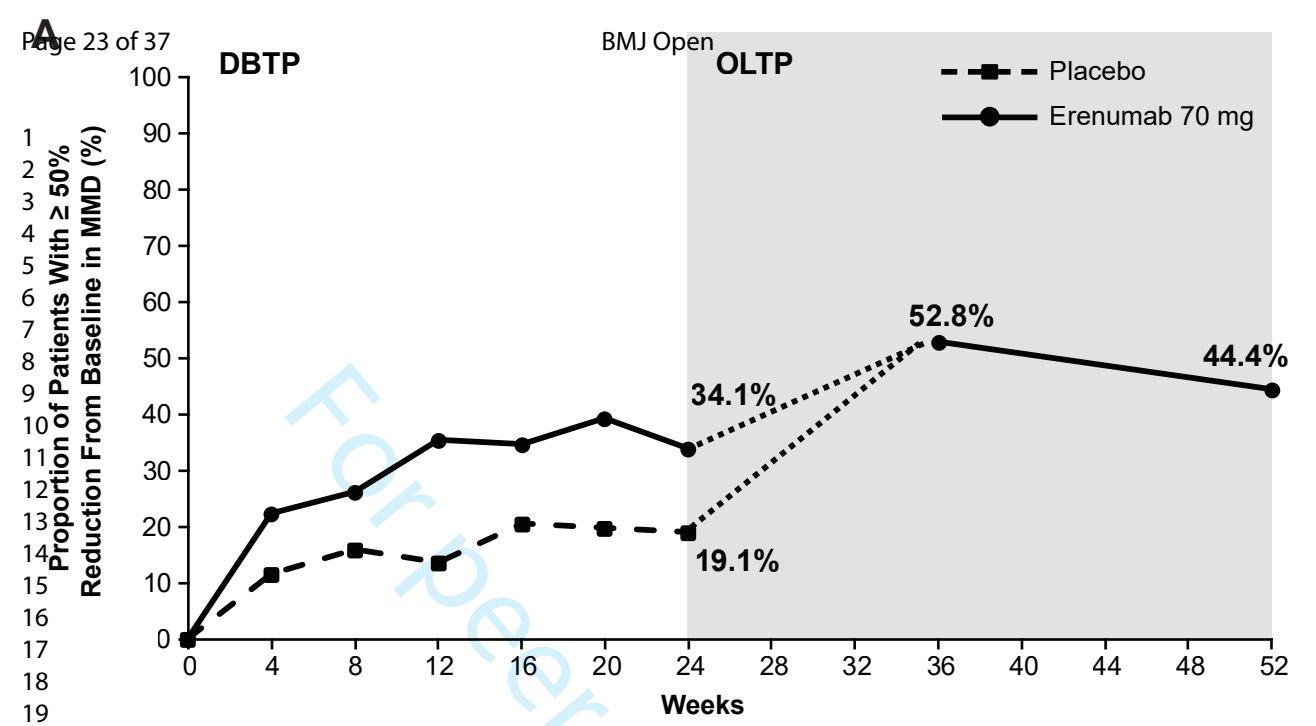
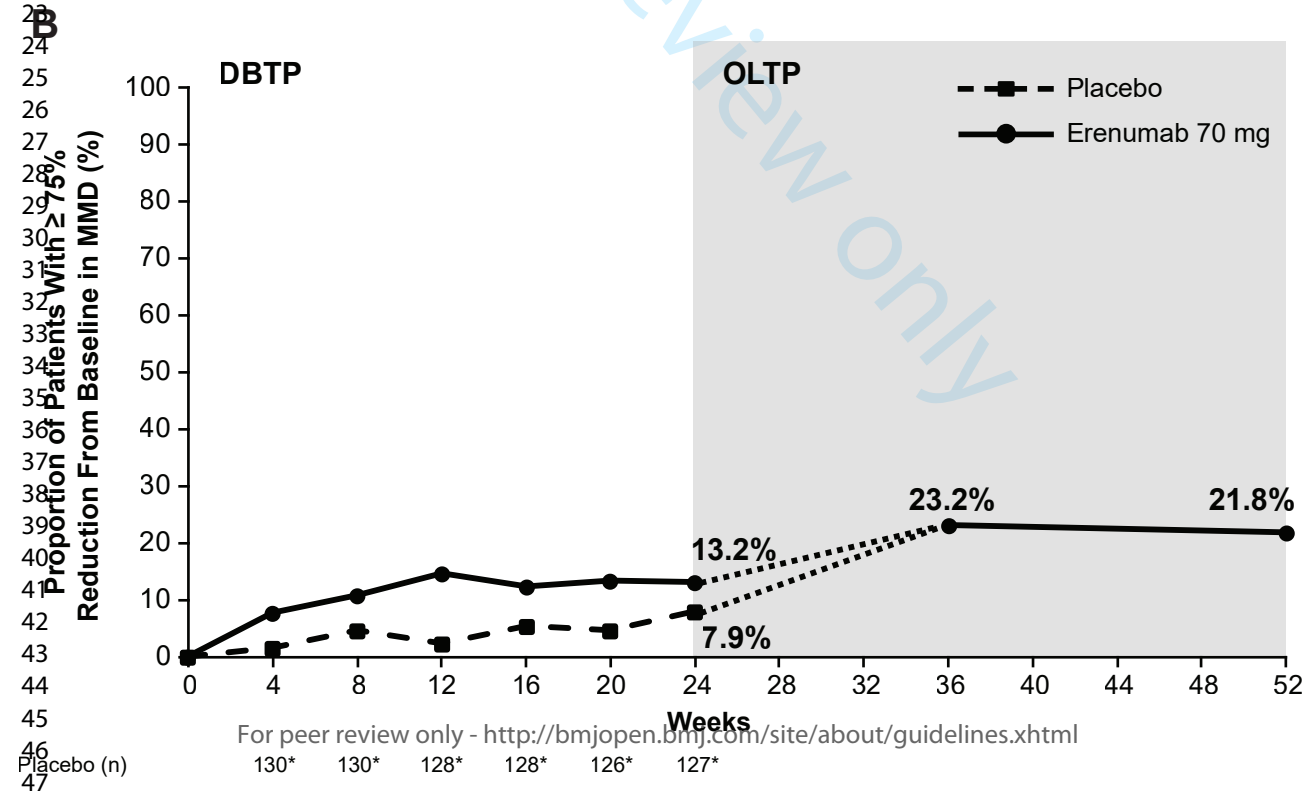
Erenumab 70 mg (n)	130*	129*	128*	128*	128*	129*	246	243





SUPPLEMENTARY APPENDIX

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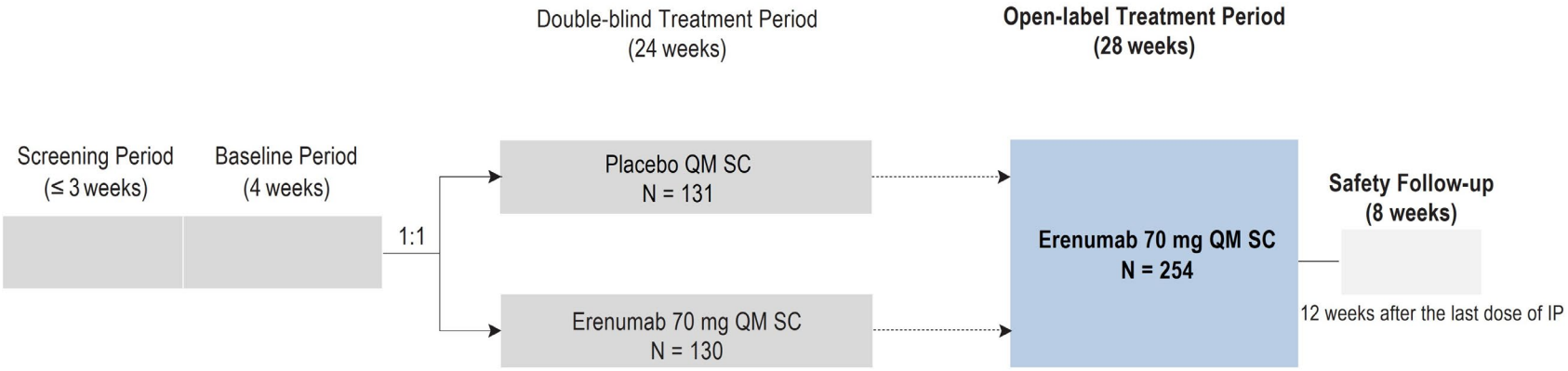
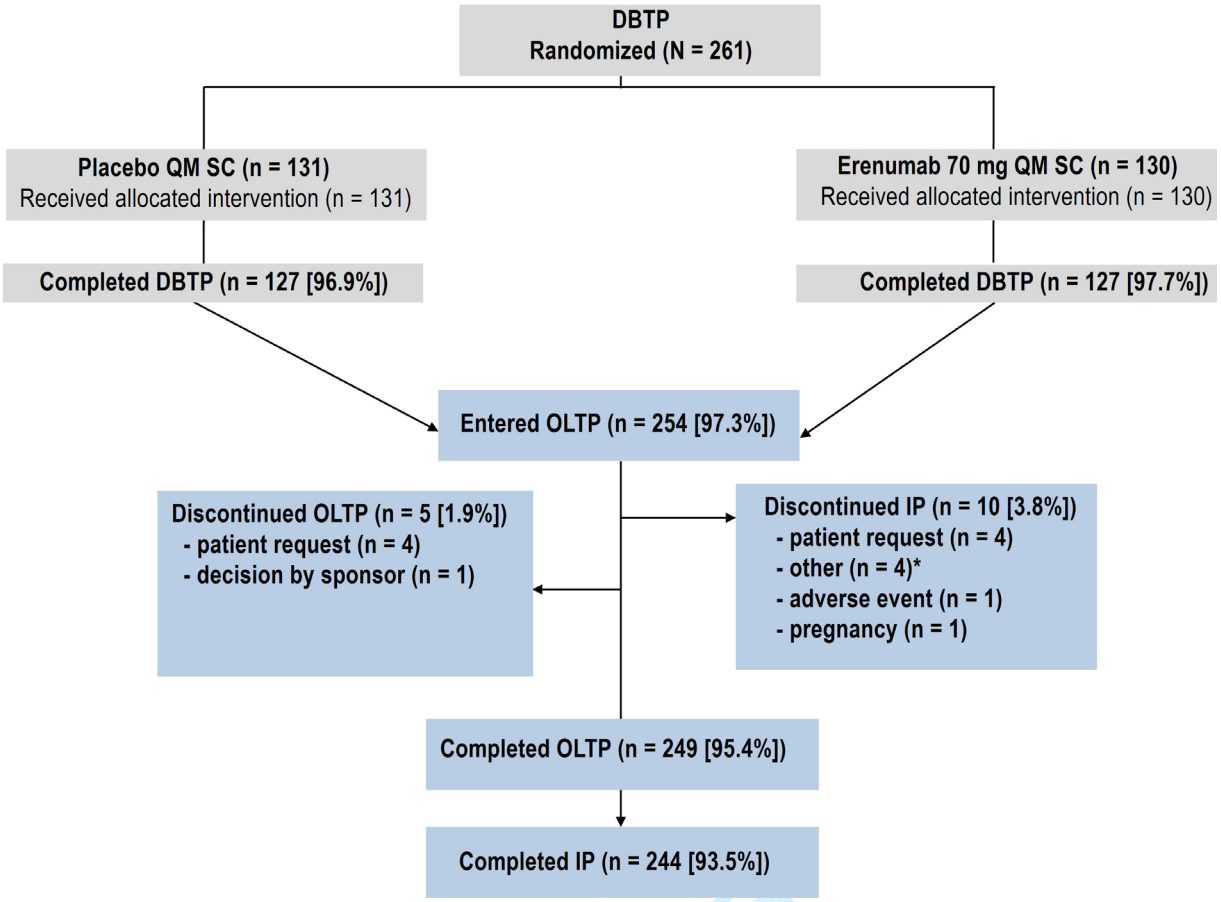
Figure S1



Study design. IP, investigational product; QM, once monthly; SC, subcutaneous.

Figure S2



Patient disposition. *Other refers to COVID-19 control measures. COVID-19, coronavirus disease 2019; DBTP, double-blind treatment period; IP, investigational product; OLTP, open-label treatment period; QM, once monthly; SC, subcutaneous.

Table S1

Study Number	Site Number	Site Name	IRB/IEC Name	IRB/IEC Address
20170609	34001	Saitama Neuropsychiatric Institute	Saitama Medical University Hospital Institutional Review Board	38 Moroyamamachi Morohongo, Iruma-gun, Saitama, 350-0495, Japan
20170609	34002	Fukuuchi Pain Clinic	Tokyo-Eki Center-Building Clinic Institutional Review Board	3-3-14 Nihombashi, Chuo-ku, Tokyo, 103-0027, Japan
20170609	34003	Kumamoto City Hospital	Kumamoto City Hospital Institutional Review Board	4-1-60 Higashimachi Higashi-ku, Kumamoto-shi, Kumamoto, 862-8505, Japan
20170609	34005	Dokkyo Medical University Hospital	Dokkyo Medical University Hospital Institutional Review Board	880 Kitakobayashi Mibumachi, Shimotsuga-gun, Tochigi, 321-0293, Japan
20170609	34006	Iwate Medical University Uchimaru Medical Center	Iwate Medical University Hospital Institutional Review Board	19-1 Uchimaru, Morioka-shi, Iwate, 020-8505, Japan
20170609	34007	Niwa Family Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan
20170609	34008	Osoegawa Neurology Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan
20170609	34009	Tanaka Neurosurgical Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan
20170609	34010	Tokyo Headache Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan

20170609	34011	Fujitsu Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan
20170609	34012	Sendai Headache and Neurology Clinic	Goshozuka Clinic Institutional Review Board	1-21-4 Goshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34013	Nagamitsu Clinic	Goshozuka Clinic Institutional Review Board	1-21-4 Goshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34014	Nagaseki Headache Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan
20170609	34015	Negoro Neurology Clinic	Goshozuka Clinic Institutional Review Board	1-21-4 Goshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34016	Saino Clinic	Goshozuka Clinic Institutional Review Board	1-21-4 Goshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34017	St Marianna University School of Medicine Hospital	St Marianna University Group Institutional Review Board	2-16-1 Sugao Miyamae-ku, Kawasaki-shi, Kanagawa, 216-8511, Japan
20170609	34018	Sakura Clinic	Goshozuka Clinic Institutional Review Board	1-21-4 Goshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34019	Tatsuoka Neurology Clinic	Tatsuoka Neurology Clinic Institutional Review Board	35-3 Chudojibojyocho Shimogyo-ku, Kyoto-shi, Kyoto, 600-8811, Japan
20170609	34020	Kitasato University Kitasato Institute Hospital	The IRB of Kitasato University Shirokane Campus	5-9-1 Shirokane, Minato-ku, Tokyo, 108-8642, Japan

20170609	34021	Tokai University Hachioji Hospital	Tokai University Hospitals Institutional Review Board	1-2-5 Yoyogi, Shibuya-ku, Tokyo, 151-0053, Japan

20170609	34021	Tokai University Hachioji Hospital	Tokai University Hospitals Institutional Review Board	143 Shimokasuya, Isehara-shi, Kanagawa, 259-1193, Japan
20170609	34021	Tokai University Hachioji Hospital	Tokai University Hospitals Institutional Review Board	21-1 Gakkyo Oiso-machi, Naka-gun, Kanagawa, 259-0198, Japan
20170609	34021	Tokai University Hachioji Hospital	Tokai University Hospitals Institutional Review Board	1838 Ishikawamachi, Hachioji-shi, Tokyo, 192-0032, Japan
20170609	34022	Takase Internal Medicine Clinic	Goshozuka Clinic Institutional Review Board	1-21-4 Goshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34023	Tominaga Hospital	Tominaga Hospital Institutional Review Board	1-4-48 Minatomachi Naniwa-ku, Osaka-shi, Osaka, 556-0017, Japan
20170609	34024	Konan Medical Center	Konan Medical Center IRB	1-5-16 Kamokogahara Higashinada-ku, Kobe-shi, Hyogo, 658-0064, Japan
20170609	34025	Japanese Red Cross Shizuoka Hospital	Japanese Red Cross Shizuoka Hospital IRB	8-2 Otemachi Aoi-ku, Shizuoka-shi, Shizuoka, 420-0853, Japan

20170609	34026	Nakamura Memorial Hospital	Nakamura Memorial Hospital Nakamura Memorial Hospital Institutional Review Board	14-291 Minami 1-jo Nishi, Chuo-ku, Sapporo-shi, Hokkaido, 060-8570, Japan
20170609	34027	Saitama Medical University Hospital	Saitama Medical University Hospital Institutional Review Board	38 Moroyamamachi Morohongo, Iruma-gun, Saitama, 350-0495, Japan
20170609	34028	Sakuragi Headache Clinic	Saga Memorial Hospital Institutional Review Board	1240-1 Nagase Takakise-machi, Saga-shi, Saga, 849-0917, Japan
20170609	34029	Sapporo Isobe Headache and Memory Clinic	Sapporo Medical Associations Institutional Review Board	19-1-1 Odorinishi Chuo-ku, Sapporo-shi, Hokkaido, 060-8581, Japan
20170609	34030	Kokubu Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan
20170609	34031	Umenotsuji Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan
20170609	34032	Sanno Clinic Shinagawa	Shinagawa East One Medical Clinic Institutional Review Board	2-16-1 Kounan, Shinagawa East One 3F, Minato-ku, Tokyo, 108-0075, Japan

20170609	34033	Ooba Clinic for Neurosurgery and Headache	Nihonbashi Sakura Clinic Institutional Review Board	1-9-2 Nihonbashikayabacho, Inamura Building 5F, Chuo- ku, Tokyo, 103-0025, Japan
20170609	34034	Doi Internal Medicine Neurology	Goshozuka Clinic Institutional Review Board	1-21-4 Goshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34035	Ikeda Neurosurgical Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan
20170609	34036	Jinnouchi Neurosurgery Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan
20170609	34037	Kijima Neurosurgery Clinic	Goshozuka Clinic Institutional Review Board	1-21-4 Goshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34038	Medical Corporation Yufukai Shimoda Neurology Clinic	Goshozuka Clinic Institutional Review Board	1-21-4 Goshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan

20170609	34039	Medical Corporation Seikokai Takanoko Hospital	Medical Corporation Seikokai Takanoko Hospital Institutional Review Board	525-1 Takanokomachi, Matsuyama-shi, Ehime, 790-0925, Japan
20170609	34040	Medical Corporation Inoue Neurology Clinic	Medical Corporation Shintokai Yokohama Minoru Clinic Institutional Review Board	1-13-8 Bessho Minami-ku, Yokohama-shi, Kanagawa, 232-0064, Japan
20170609	34041	Sakuma Neurological Clinic	Goshozuka Clinic Institutional Review Board	1-21-4 Goshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34042	Higashi Sapporo Neurology and Neurosurgery Clinic	Nihonbashi Sakura Clinic Institutional Review Board	1-9-2 Nihonbashikayabacho, Inamura Building 5F, Chuo- ku, Tokyo, 103-0025, Japan

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2,3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	5,6
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6,7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	NA; sample size was based on the number of patients who completed the DBTP and received at least one dose of erenumab 70

			mg in the OLTP
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence	8a	Method used to generate the random allocation sequence	5
generation	8b	Type of randomisation; details of any restriction (such as blocking and block size)	NA
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	NA
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	NA
	11b	If relevant, description of the similarity of interventions	NA; this is a single-arm open-label extension
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8, Figure S2
	13b	For each group, losses and exclusions after randomisation, together with reasons	8, Figure S2
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	5
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	8
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8-10, Figure 1, Figure 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	

		pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	10-12
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	3, 14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13-14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	Protocol will be provided during submission
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	3

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Items to include when reporting a randomized trial in a journal or conference abstract

Item	Description	Reported on line number
Title	Identification of the study as randomized	2
Authors *	Contact details for the corresponding author	15,16
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	27
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	28-31
Interventions	Interventions intended for each group	32
Objective	Specific objective or hypothesis	24-26
Outcome	Clearly defined primary outcome for this report	33-36
Randomization	How participants were allocated to interventions	NA
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	NA
Results		
Numbers randomized	Number of participants randomized to each group	30
Recruitment	Trial status	NA
Numbers analysed	Number of participants analysed in each group	30-31
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	37-42
Harms	Important adverse events or side effects	42-45
Conclusions	General interpretation of the results	46-48
Trial registration	Registration number and name of trial register	49
Funding	Source of funding	50

**this item is specific to conference abstracts*

The CONSORT-PRO Reporting Guidance Checklist

Section/Topic	CONSORT-PRO Item	Recommended Content	Page Addressed
Title and Abstract			
	P1b	The PRO should be identified in the abstract as a primary or secondary outcome.	2
Introduction			
Background and objectives	2a	The scientific background and explanation of rationale of PRO assessment should be included.	NA
	P2b	The PRO hypothesis should be stated, and relevant domains identified, if applicable.	NA
Methods			
Participants	4a	PRO-specific criteria are required only if PROs were used for eligibility or stratification.	6
Outcomes	P6a	Evidence of PRO instrument validity and reliability should be provided or cited if available including the person completing the PRO and methods of data collection (paper, telephone, electronic).	NA
Sample size	7a	Sample size determination is required only if PRO is a primary study outcome.	NA
Randomization			
Statistical methods	P12a	Statistical approaches for dealing with missing data are explicitly stated.	NA
Results			
Participant flow	13a	The number of PRO outcome data at baseline and at subsequent time points should be transparent.	Figure S2
Baseline data	15	PRO data in the table showing baseline demographic and clinical characteristics for each group should be included.	8 (Table 1)
Numbers analyzed	16	For each group, the number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups) is required for PRO results.	9-10 (Table 2)
Outcomes and estimation	17a	The estimated effect size and its precision such as 95% confidence interval should be presented for multidimensional PROs from each domain and time point.	NA
Ancillary analyses	18	Results of any other PRO analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory should be presented, where relevant.	NA
Discussion			
Limitation	P20/21	PRO-specific limitations and implications for generalizability and clinical practice should be presented.	NA
Interpretation	22	PRO data should be interpreted in relation to clinical outcomes including survival data, where relevant.	NA

Calvert M, Blazeby J, Altman DG, et al. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA*. 2013;309(8):814-822. doi:10.1001/jama.2013.879

Note: The CONSORT-PRO Extension should be used with the CONSORT 2010 Statement and any other relevant CONSORT Extensions, found at consort-statement.org