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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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4 1 **Long-term efficacy and safety of erenumab in Japanese patients with episodic and**
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6 2 **chronic migraine: Results from a 28-week open-label treatment period of a randomized**
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8 3 **trial**
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3 22 **ABSTRACT**
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6 24 **Objectives:** To evaluate the 1-year efficacy and safety of once-monthly erenumab 70 mg
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8 25 following a 24-week double-blind treatment period (DBTP) of a phase 3 randomized study of
9
10 26 Japanese patients with episodic migraine (EM) or chronic migraine (CM).

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13 27 **Design:** Multicenter open-label study.
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16 28 **Setting:** A total of 41 centers in Japan.
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19 29 **Participants:** Patients completing the DBTP continued into the 28-week open-label treatment
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21 30 period (OLTP). 254 of 261 (97.3%) randomized patients continued into the OLTP; 244 (93.5%)
22
23 31 completed treatment.
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25
26 32 **Interventions:** Once monthly subcutaneous erenumab 70 mg.
27

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29 33 **Main Outcome measures:** Changes from baseline in monthly migraine days (MMD), monthly
30
31 34 acute migraine-specific medication treatment days (MSMD), proportion of $\geq 50\%$ and $\geq 75\%$
32
33 35 responders in MMD reduction from baseline, and the incidence and exposure-adjusted
34
35 36 incidence of treatment-emergent adverse events (TEAEs).
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37
38 37 **Results:** At week 24 of the DBTP, the mean (SE) change from baseline in MMD for the
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40 38 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
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42 39 (EM, -2.1 [0.4]; CM, -3.4 [0.7]). At the end of the OLTP (52 weeks postbaseline), the mean
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44 40 (SE) change from baseline in MMD was -4.7 (0.3) days (EM, -3.4 [0.3]; CM, -6.9 [0.6]); in
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46 41 MSMD, -3.3 (0.3) days (EM, -2.4 [0.3]; CM, -4.6 [0.5]). The proportion of $\geq 50\%$ responders for
47
48 42 MMD reduction in the erenumab group was 34.1% at week 24; 44.4% at week 52. The
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50 43 exposure-adjusted incidence of TEAEs was 219.7 per 100 patient-years during the OLTP
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52 44 (DBTP, 251.0 for the erenumab group). The most common TEAEs during the OLTP were
53
54 45 nasopharyngitis, constipation, and influenza. No new safety concerns were identified.
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3 46 **Conclusions:** Erenumab demonstrated a persistent efficacy in Japanese patients with EM or
4
5 47 CM for up to 1 year. Overall safety results from the OLTP were consistent with those from the
6
7 48 DBTP.
8
9

10 49 **Clinical Trials Registration Number:** NCT03812224
11
12

13 50 **Funding:** This study was funded by Amgen.
14
15

16 51 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 17 52 • This study represents the longest follow-up experience with erenumab in Japanese
18 53 patients with CM
- 19 54
- 20 54
- 21 55 • The duration of the 28-week OLTP was short
22 56
- 23 57
- 24 58 • This study lacked a comparator arm
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61 INTRODUCTION

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

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

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

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84 **METHODS**

86 **Study design**

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

103 **Patient and Public Involvement Statement**

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

106 **Patients**

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

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3 109 parent study included Japanese patients aged 20 through 65 years with a history of migraine
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5 110 with or without aura (based on medical records or patient self-report) for at least 12 months
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7 111 before screening, as defined in the third edition of the *International Classification of Headache*
8
9 112 *Disorders* (ICHD-3) of the IHS, and a diagnosis of EM (<15 headache days/month, ≥4 monthly
10
11 113 migraine days [MMD]) or CM (≥15 headache days/month, ≥8 MMD) over the 3 months before
12
13 114 screening. A detailed description of the eligibility criteria in the parent study has been described
14
15 115 previously.[20]

18 116 **Endpoints and assessments**

19 117 Efficacy outcomes during the OLTP included changes from baseline in MMD and monthly acute
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21 118 migraine-specific medication treatment days (MSMD), and the proportion of patients who
22
23 119 achieved at least a 50% or 75% reduction in MMD from baseline.

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27 120 A migraine day was defined as a migraine (with or without aura) that lasted for at least 4 hours
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29 121 and had at least two of the following pain features: unilateral, throbbing, moderate to severe, or
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31 122 exacerbated with exercise or physical activity; or was associated with nausea, vomiting, or
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33 123 photophobia and phonophobia. A migraine day also included a day in which a patient took a
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35 124 migraine-specific medication during aura or to treat a headache regardless of the duration and
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37 125 associated symptoms. A qualified headache day was a day characterized by onset,
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39 126 continuation, or recurrence of a headache and met one of the following criteria: a migraine
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41 127 headache treated with acute migraine-specific medication, a non-migraine headache that lasted
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43 128 for at least 4 hours, or a headache for which acute headache treatment was used. An acute
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45 129 migraine-specific medication treatment day was defined as any day during which migraine-
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47 130 specific medication was used.

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51 131 Safety endpoints included the incidence and exposure-adjusted incidence of treatment-
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53 132 emergent adverse events (TEAEs), clinical laboratory values and vital signs, and the incidence
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55 133 of anti-erenumab antibodies. Exposure-adjusted rates (per 100 patient-years) were calculated

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3 134 by dividing the number of patients with at least one reported occurrence of the TEAE of interest
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5 135 by the total time at risk for reporting the TEAE (patient-year) multiplied by 100. The time at risk
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7 136 was defined as the time from the first dose of erenumab to the onset of the TEAE or the end of
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9 137 study date. Reporting exposure-adjusted rates normalizes the rates of adverse events occurring
10
11 138 during the DBTP and OLTP to equal exposure periods (ie, events per 100 patient-years), and
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13 139 thus allows for a proper comparison between the DBTP and OLTP.
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16 140 **Statistical analysis**

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18 141 Analysis was performed after all patients had completed safety follow-up at the end of the study
19
20 142 and included patients who received at least one dose of erenumab 70 mg in the OLTP. Efficacy
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22 143 and safety data were tabulated by the double-blind treatment group. Efficacy endpoints were
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24 144 analyzed by using descriptive statistics based on observed data without imputation and were
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26 145 tabulated by visit. No formal testing was conducted. Patient incidence and exposure-adjusted
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28 146 incidence of TEAEs were tabulated by treatment group and by system organ class and
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30 preferred term. All analyses were performed using SAS System 9.4 (SAS Institute, Cary, NC,
31
32 147 USA).
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36 149 **RESULTS**

37 150 38 39 151 **Patients**

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41 152 Of the 261 patients enrolled and randomized in the parent study (erenumab 70 mg, n = 130;
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43 153 placebo, n = 131), 254 (97.3%) entered the OLTP and received at least one dose of the
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45 154 investigational product (IP) and 244 (93.5%) completed the IP. Ten patients (3.8%) discontinued
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47 155 the IP for the following reasons: patient request (n = 4; 1.5%), COVID-19 control measures (n =
48
49 156 4; 1.5%), adverse event (n = 1; 0.4%), and pregnancy (n = 1; 0.4%) (Figure S2). Overall, the
50
51 157 mean age of patients was 44.4 years, 87% were female, and the majority (76.6%) had used or
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53 158 were using migraine preventive treatment at baseline (Table 1).
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159 **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)

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

165 **Efficacy**

166 In the OLTP population (N = 254; EM, n = 155; CM, n = 99), the mean (standard error of the
 167 mean [SE]) MMD at baseline was 12.2 (0.4) days (EM, 8.3 [0.2] days; CM, 18.2 [0.4] days) and
 168 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
 169 the end of the DBTP at week 24, the mean (SE) change from baseline in MMD for the
 170 erenumab 70 mg group was -3.8 (0.4) days (EM, -3.0 [0.4] days; CM, -5.2 [0.8] days) and -
 171 1.7 (0.5) days for the placebo group; at the end of the OLTP at week 52, the mean (SE) change
 172 was -4.7 (0.3) days (EM, -3.4 [0.3]; CM, -6.9 [0.6]) (Figure 1, Table 2).

173 At the end of the DBTP at week 24, the mean (SE) change from baseline in MSMD for the
 174 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
 175 for the placebo group; at the end of the OLTP at week 52, the mean (SE) change was -3.3 (0.3)
 176 days (EM, -2.4 [0.3] days; CM, -4.6 [0.5] days) (Figure 1, Table 2). Throughout the 28-week
 177 OLTP, erenumab 70 mg demonstrated persistent efficacy in MMD and MSMD reduction in
 178 patients with EM or CM.

179 At week 24 of the DBTP, the proportion of patients who achieved at least a 50% reduction in
 180 MMD from baseline was 34.1% with erenumab 70 mg (EM, 39.7%; CM, 25.5%) and 19.1% with
 181 placebo (Figure 2, Table 2). The response was maintained and numerically higher throughout
 182 the OLTP than it was during the DBTP. At week 36 of the OLTP, 52.8% of the patients achieved
 183 the 50% threshold for MMD reduction (EM, 58.8%; CM, 43.0%); at week 52, it was 44.4% (EM,
 184 46.3%; CM, 41.7%). The results were similar for patients responding at the 75% threshold for
 185 MMD reduction (Figure 2).

186 **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 $\geq 50\%$ 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)

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

193

Safety

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 195 The mean (standard deviation) exposure to erenumab 70 mg during the OLTP was 192.6 (20.0)
 196 days (total exposure to open-label treatment, 133.9 patient-years). The majority of patients
 197 (92.1%) received all seven doses of erenumab 70 mg during the OLTP.

198 During the OLTP, the incidence of TEAEs was 71.3% (181/254) (Table 3). The exposure-
 199 adjusted incidence of TEAEs during the OLTP was 219.7 per 100 patient-years, which is similar
 200 to that in the erenumab group (251.0 per 100 patient-years) and in the placebo group (197.7 per
 201 100 patient-years) during the DBTP. The majority of patients (62.2% [158/254]) experienced
 202 TEAEs of grade 2 or less. The most common (≥ 5 per 100 patient-years) TEAEs reported with
 203 erenumab (OLTP vs DBTP) were nasopharyngitis (32.8 vs 67.2 per 100 patient-years),
 204 constipation (7.8 vs 10.3 per 100 patient-years), influenza (6.6 vs 1.7 per 100 patient-years),
 205 gastroenteritis (6.5 vs 6.8 per 100 patient-years), and urticaria (5.9 vs 1.7 per 100 patient-
 206 years). Seven patients (2.8%) reported serious adverse events with erenumab during the OLTP,

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

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

221 **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 $\geq 50\%$ and $\geq 75\%$ 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

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3 240 higher than those reported during the OLTP of the phase 2 study in Japanese patients with EM
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5 241 (2.6 per 100 patient-years).[21] In addition, no new safety concerns regarding clinically relevant
6
7 242 changes in laboratory assessments and vital signs were identified throughout the OLTP. The
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9 243 high proportion of patients completing erenumab treatment reflects the excellent tolerability and
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11 244 sustained efficacy. The high retention rate prevents the bias that may be seen in open-label
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13 245 extension studies where patients may drop out for diminished efficacy, thus skewing the efficacy
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15 246 results over time.

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18 247 This study represents the longest follow-up experience with erenumab in Japanese patients with
19
20 248 CM and shows long-term efficacy and safety that are comparable to that seen in a global long-
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22 249 term study of erenumab in patients with CM.[24] In the global study, the reduction in MMD and
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24 250 MSMD after 52 weeks for the erenumab 70 mg group was –7.8 days and –5.8 days,
25
26 251 respectively; 47.4% of the patients achieved at least a 50% reduction from baseline in MMD.
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28 252 Nonetheless, these data support long-term treatment with erenumab in Japanese patients with
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30 253 EM and CM.

31 254 **CONCLUSION**

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34 255 Erenumab demonstrated a persistence of efficacy for up to 1 year in Japanese patients with EM
35
36 256 or CM and had a safety profile similar to that observed in the DBTP. No new safety signals were
37
38 257 identified during the OLTP.

39 258 **Ethics Approval**

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41 259 This study involved human patients and was approved by ethics committees and institutional
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43 260 review boards listed in the supplementary appendix (Table S1).

44 261 **Acknowledgments**

45
46 262 Erenumab is codeveloped by Amgen and Novartis. The authors thank the patients and all the
47
48 263 investigators who participated in this study. Medical writing support was provided by Qais Al-

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3 264 Hadid, PhD (Amgen). Editorial support was provided by Sangeeta P.C. (Cactus
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5 265 Communications).

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8 266 **Author contributions**

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11 267 SC and GPL contributed to the conception and design of the study and acquired the data. All
12
13 268 authors analyzed and interpreted the data. All authors drafted the manuscript and critically
14
15 269 reviewed and revised the manuscript for intellectual content. All authors provided final approval
16
17 270 of the version to be published.

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20 271 **Conflict of Interest Statement**

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22
23 272 KH reports royalties from Amgen, Astellas, Daiichi Sankyo, Eisai, Merck Sharp & Dohme, and
24
25 273 Pfizer. TT has nothing to disclose. FS reports consulting fees from Amgen. RY, RK, MH, DY,
26
27 274 GPL, and SC are employees of and own stock in Amgen. YN owns stock in Amgen.

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29
30 275 **Institutional review board approval**

31
32 276 The Institutional review boards at each study center (Table S1) approved the study protocol,
33
34 277 informed consent forms, and any materials provided to the patients.

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36
37 278 **Data availability statement**

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40 279 Qualified researchers may request data from Amgen clinical studies. Complete details are
41
42 280 available at the following: [https://wwwext.amgen.com/science/clinical-trials/clinical-data-](https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request)
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44 281 [transparency-practices/clinical-trial-data-sharing-request](https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request).

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46
47 282 **Funding:** This study was funded by Amgen. No grants or awards were used for funding of this
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49 283 study.

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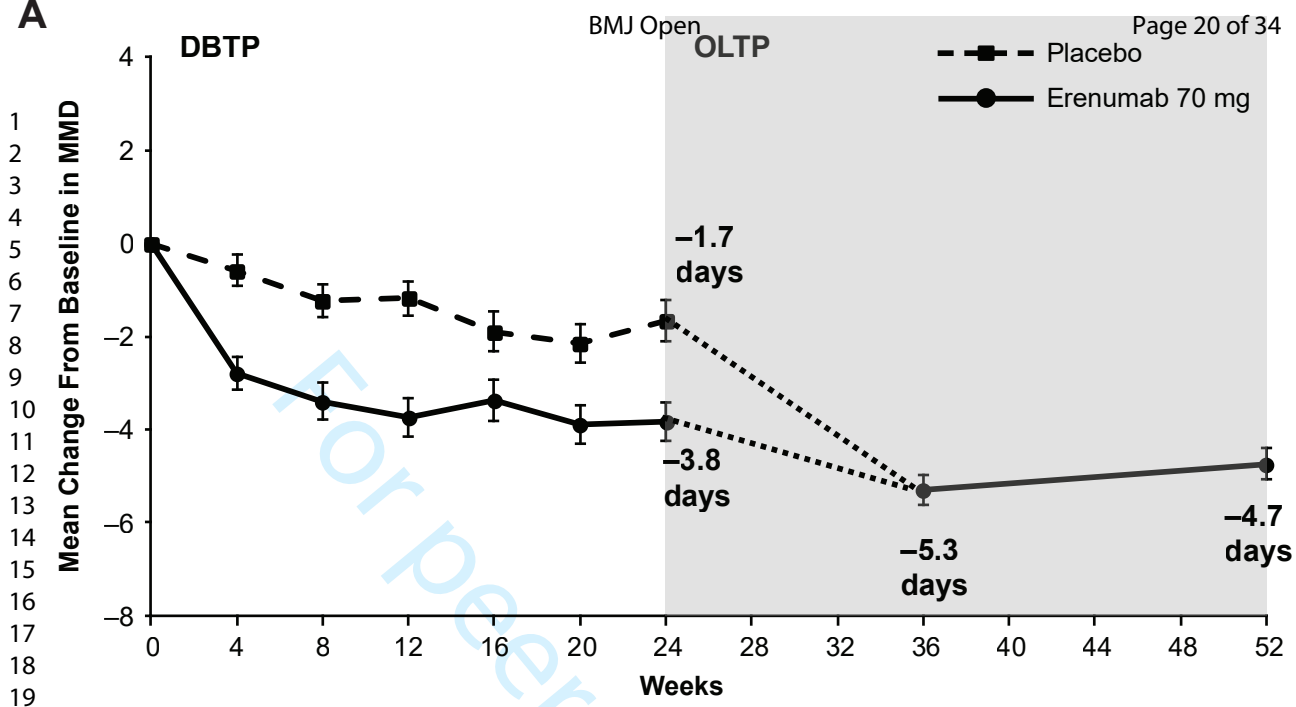
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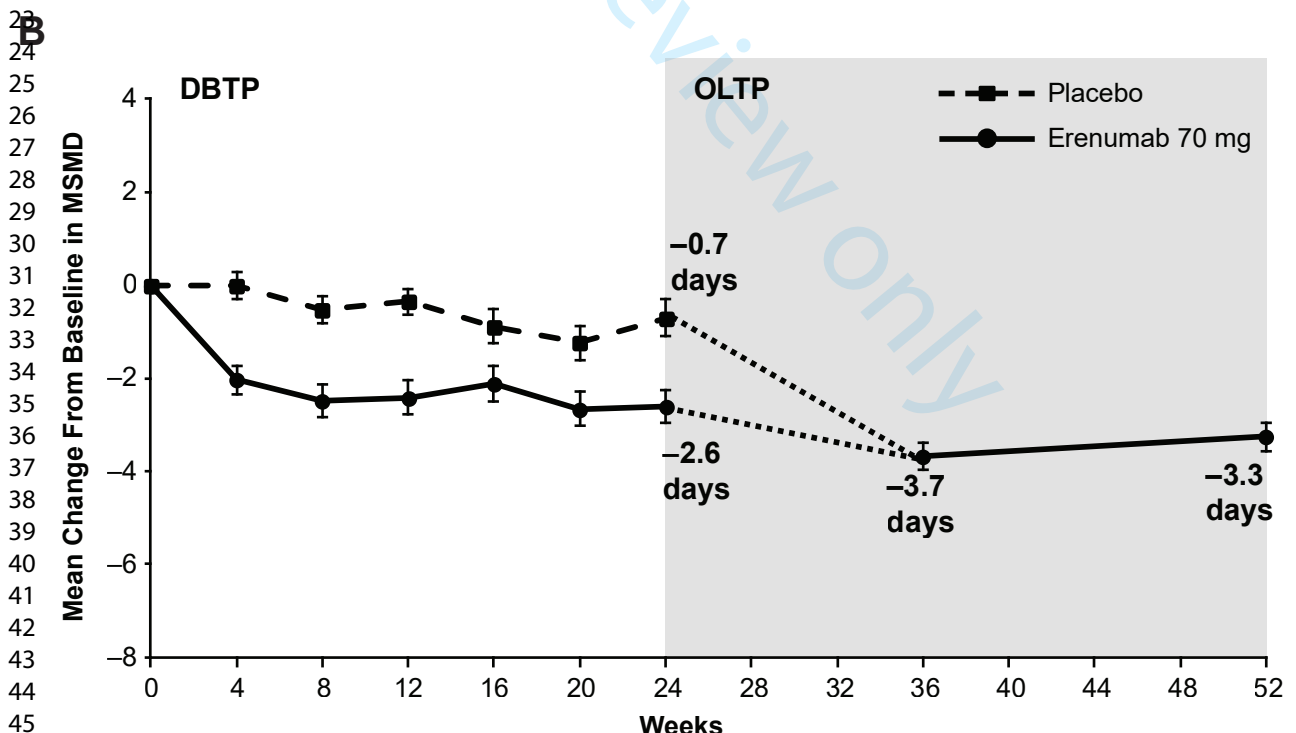
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3 348 **Figure 1.** Change in (A) MMD and (B) MSMD from baseline. The mean (SE) change from
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5 349 baseline in MMD and MSMD during the DBTP and OLTP is shown for the treatment groups. For
6
7 350 the OLTP, data are shown for the total population. The dotted line indicates that patients in the
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9 351 placebo group during the DBTP received erenumab 70 mg during the OLTP starting at week 24.
10
11 352 *The number of patients in the efficacy analysis set during the DBTP. Error bars represent SE. n
12
13 = number of patients with observed data. DBTP, double-blind treatment period; MMD, monthly
14 353 migraine days; MSMD, monthly acute migraine-specific medication treatment days; OLTP,
15
16 354 open-label treatment period; SE, standard error of the mean.
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21 356 **Figure 2.** Patients achieving a (A) $\geq 50\%$ and (B) $\geq 75\%$ reduction in MMD from baseline. For the
22
23 357 OLTP, data are shown for the total population. The dotted line indicates that patients in the
24
25 358 placebo group during the DBTP received erenumab 70 mg during the OLTP starting at week 24.
26
27 359 *The number of patients in the efficacy analysis set during the DBTP. n = number of patients
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29 360 with observed data. DBTP, double-blind treatment period; MMD, monthly migraine days; OLTP,
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31 361 open-label treatment period.
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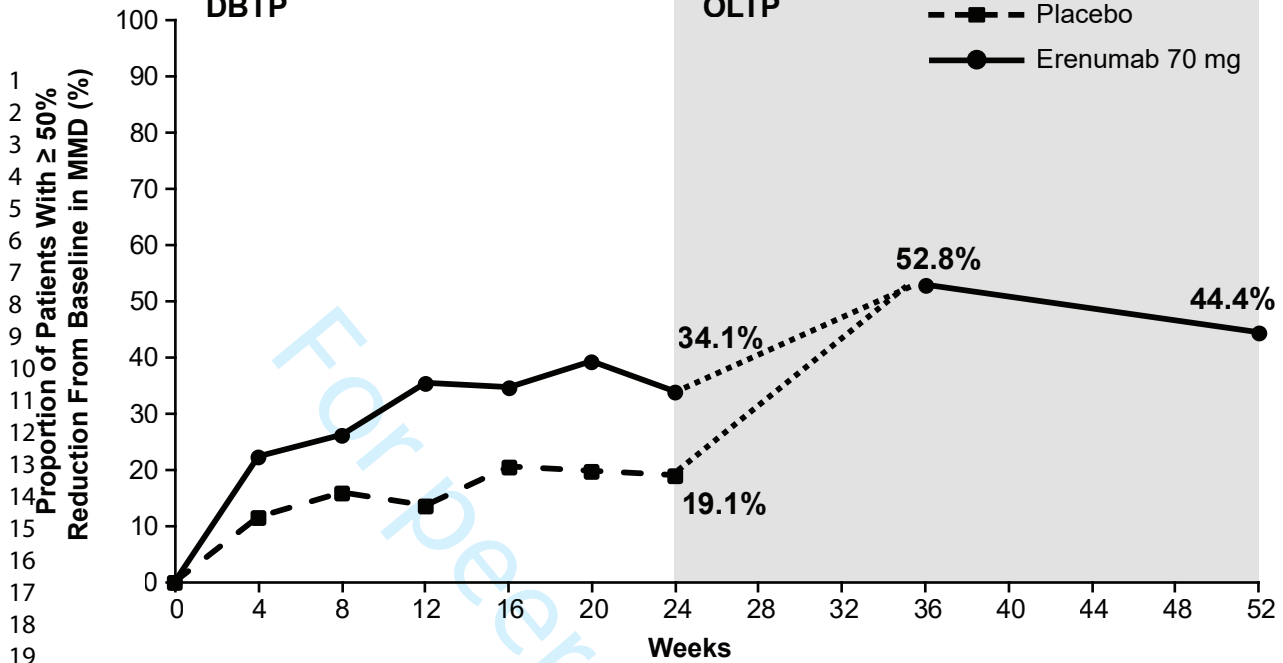


Placebo (n)	130*	130*	128*	128*	126*	127*		
Erenumab 70 mg (n)	130*	129*	128*	128*	128*	129*	246	243

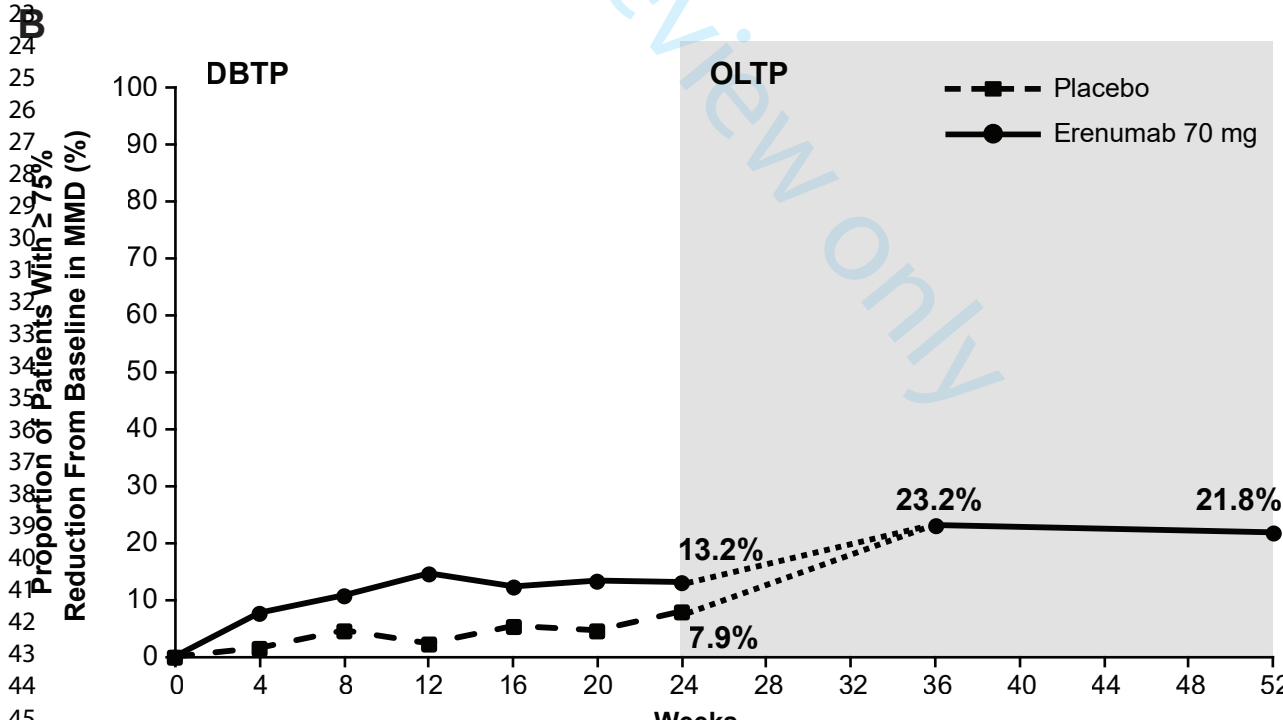


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Placebo (n)	130*	130*	128*	128*	126*	127*		
Erenumab 70 mg (n)	130*	129*	128*	128*	128*	129*	246	243



Placebo (n)	131*	131*	131*	131*	131*	131*		
Erenumab 70 mg (n)	130*	130*	130*	130*	130*	130*	246	243



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

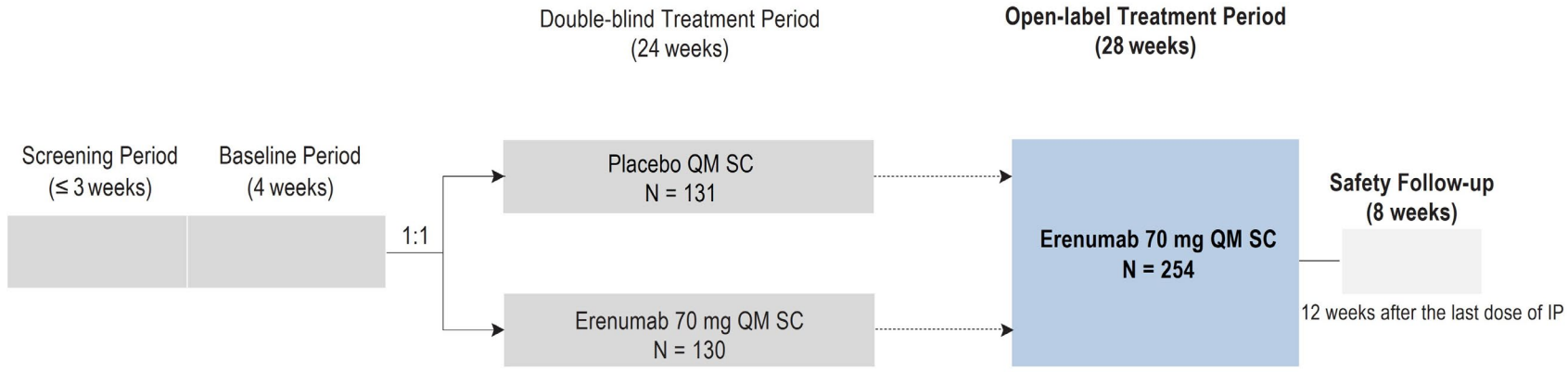
SUPPLEMENTARY APPENDIX

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Table S1 – Ethics Committees/IRBs.....	4

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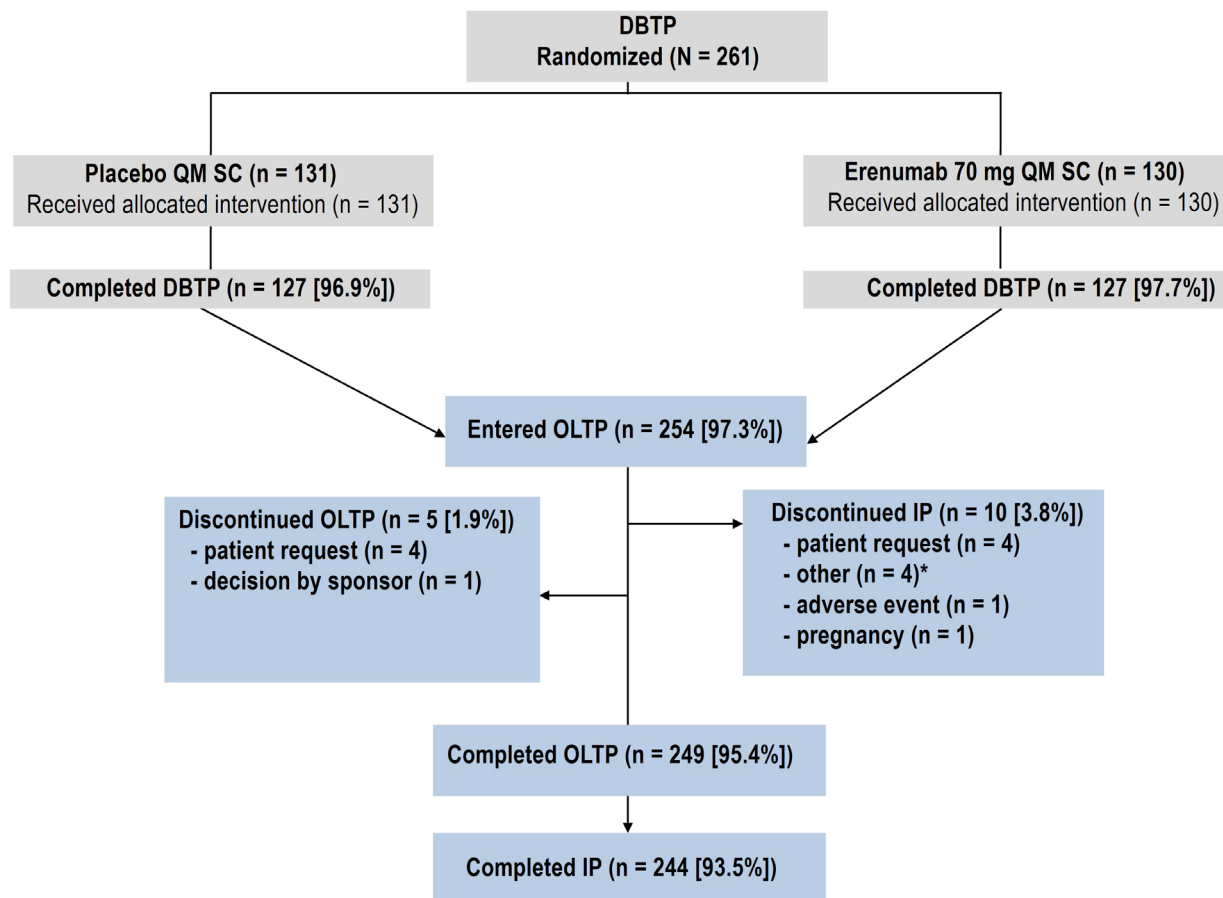
Figure S1



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

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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	Gshozuka Clinic Institutional Review Board	1-21-4 Gshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34013	Nagamitsu Clinic	Gshozuka Clinic Institutional Review Board	1-21-4 Gshozuka 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	Gshozuka Clinic Institutional Review Board	1-21-4 Gshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34016	Saino Clinic	Gshozuka Clinic Institutional Review Board	1-21-4 Gshozuka 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	Gshozuka Clinic Institutional Review Board	1-21-4 Gshozuka 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

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20170609	34021	Tokai University Hachioji Hospital	Tokai University Hospitals Institutional Review Board	1-2-5 Yoyogi, Shibuya-ku, Tokyo, 151-0053, Japan
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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	Gshozuka Clinic Institutional Review Board	1-21-4 Gshozuka 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	Gshozuka Clinic Institutional Review Board	1-21-4 Gshozuka 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	Gshozuka Clinic Institutional Review Board	1-21-4 Gshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34038	Medical Corporation Yufukai Shimoda Neurology Clinic	Gshozuka Clinic Institutional Review Board	1-21-4 Gshozuka 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	Gshozuka Clinic Institutional Review Board	1-21-4 Gshozuka 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

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NA

NA; this is a
single-arm
open-label
extension

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NA

7, Figure S2

7, Figure S2

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8,9, Figure 1,
Figure 2

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Randomisation:

Sequence

generation

Allocation

concealment

mechanism

Implementation

Blinding

Statistical methods

Results

Participant flow (a

diagram is strongly

recommended)

Recruitment

Baseline data

Numbers analysed

Outcomes and

estimation

Ancillary analyses

- 7b When applicable, explanation of any interim analyses and stopping guidelines
- 8a Method used to generate the random allocation sequence
- 8b Type of randomisation; details of any restriction (such as blocking and block size)
- 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
- 10 Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
- 11a If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how
- 11b If relevant, description of the similarity of interventions
- 12a Statistical methods used to compare groups for primary and secondary outcomes
- 12b Methods for additional analyses, such as subgroup analyses and adjusted analyses
- 13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
- 13b For each group, losses and exclusions after randomisation, together with reasons
- 14a Dates defining the periods of recruitment and follow-up
- 14b Why the trial ended or was stopped
- 15 A table showing baseline demographic and clinical characteristics for each group
- 16 For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
- 17a For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
- 17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended
- 18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing

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

18

19 *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

20 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials.

21 Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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

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39 **this item is specific to conference abstracts*
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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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4 1 **Long-term efficacy and safety of erenumab in Japanese patients with episodic and**
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6 2 **chronic migraine: Results from a 28-week open-label treatment period of a randomized**
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8 3 **trial**
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3 22 **ABSTRACT**
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6 24 **Objectives:** To evaluate the 1-year efficacy and safety of once-monthly erenumab 70 mg
7
8 25 following a 24-week double-blind treatment period (DBTP) of a phase 3 randomized study of
9
10 26 Japanese patients with episodic migraine (EM) or chronic migraine (CM).

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13 27 **Design:** Multicenter open-label study.
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16 28 **Setting:** A total of 41 centers in Japan.
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18
19 29 **Participants:** Patients completing the DBTP continued into the 28-week open-label treatment
20
21 30 period (OLTP). 254 of 261 (97.3%) randomized patients continued into the OLTP; 244 (93.5%)
22
23 31 completed treatment.
24

25
26 32 **Interventions:** Once monthly subcutaneous erenumab 70 mg.
27

28
29 33 **Main Outcome measures:** Changes from baseline in monthly migraine days (MMD) and
30
31 34 monthly acute migraine-specific medication treatment days (MSMD) reported via patient eDiary;
32
33 35 proportion of $\geq 50\%$ and $\geq 75\%$ responders in MMD reduction from baseline; incidence and
34
35 36 exposure-adjusted incidence of treatment-emergent adverse events (TEAEs).
36

37
38 37 **Results:** At week 24 of the DBTP, the mean (SE) change from baseline in MMD for the
39
40 38 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
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42 39 (EM, -2.1 [0.4]; CM, -3.4 [0.7]). At the end of the OLTP (52 weeks postbaseline), the mean
43
44 40 (SE) change from baseline in MMD was -4.7 (0.3) days (EM, -3.4 [0.3]; CM, -6.9 [0.6]); in
45
46 41 MSMD, -3.3 (0.3) days (EM, -2.4 [0.3]; CM, -4.6 [0.5]). The proportion of $\geq 50\%$ responders for
47
48 42 MMD reduction in the erenumab group was 34.1% at week 24; 44.4% at week 52. The
49
50 43 exposure-adjusted incidence of TEAEs was 219.7 per 100 patient-years during the OLTP
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52 44 (DBTP, 251.0 for the erenumab group). The most common TEAEs during the OLTP were
53
54 45 nasopharyngitis, constipation, and influenza. No new safety concerns were identified.
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3 46 **Conclusions:** Erenumab treatment was associated with reduced migraine frequency in
4
5 47 Japanese patients with EM or CM for up to 1 year. Overall safety results from the OLTP were
6
7 48 consistent with DBTP results.
8
9

10 49 **Clinical Trials Registration Number:** NCT03812224
11
12

13 50 **Funding:** This study was funded by Amgen.
14
15

16 51 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 17 52 • While the 28-week OLTP was short relative to other studies in non-Japanese patients,
18 53 this study represents the longest follow-up time with erenumab in Japanese patients with
19 54 CM
20 54
- 21 55
- 22 56 • Patients and study staff remained blinded to assignment (placebo or erenumab) in DBTP
23 57 during OLTP
24 58
- 25 59 • Reporting exposure-adjusted rates normalizes the rates of adverse events occurring
26 60 during the DBTP and OLTP to equal exposure periods (ie, events per 100 patient-years),
27 61 and thus allow for proper comparison between the DBTP and OLTP
28 61
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- 30 63 • The OLTP of this study lacked a comparator arm
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66 INTRODUCTION

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

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

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

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88

89 **METHODS**

91 **Study design**

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

109 **Patient and Public Involvement Statement**

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

112 **Patients**

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3 113 Patients who completed the DBTP (parent study) in each treatment group were eligible to
4
5 114 participate in the OLTP and receive once-monthly erenumab 70 mg. Japanese patients aged 20
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7 115 through 65 years with a history of migraine with or without aura (based on medical records or
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9 116 patient self-report) for at least 12 months before screening, as defined in the third edition of the
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11 117 *International Classification of Headache Disorders* (ICHD-3) of the IHS, and a diagnosis of EM
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13 118 (<15 headache days/month, ≥ 4 monthly migraine days [MMD]) or CM (≥ 15 headache
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15 119 days/month, ≥ 8 MMD) over the 3 months before screening, were included. Patients had to
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17 120 demonstrate at least 80% compliance with the eDiary during the baseline period prior to the
18
19 121 DBTP. A detailed description of the eligibility criteria in the parent study has been described
20
21 122 previously.⁽²⁰⁾

25 123 **Endpoints and assessments**

26 124 Efficacy outcomes during the OLTP included changes from baseline in MMD and monthly acute
27
28 125 migraine-specific medication treatment days (MSMD), and the proportion of patients who
29
30 126 achieved at least a 50% or 75% reduction in MMD from baseline.

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33 127 Patients used an eDiary to report clinical outcome assessments daily during weeks 33 to 36 and
34
35 128 weeks 49 to 52. Clinical outcome assessments included the date and time of headache start
36
37 129 and end; the worst pain severity of the headache; pain features (e.g., one-sided, throbbing,
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39 130 worsens with exercise/physical activity); associated symptoms (e.g., aura, nausea, vomiting,
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41 131 photophobia, phonophobia), and use of acute headache medications. A migraine day was
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43 132 defined as a migraine (with or without aura) that lasted for at least 4 hours and had at least two
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45 133 of the following pain features: unilateral, throbbing, moderate to severe, or exacerbated with
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47 134 exercise or physical activity; or was associated with nausea, vomiting, or photophobia and
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49 135 phonophobia. A migraine day also included a day in which a patient took a migraine-specific
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51 136 medication during aura or to treat a headache regardless of the duration and associated
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53 137 symptoms. A qualified headache day was a day characterized by onset, continuation, or
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3 138 recurrence of a headache and met one of the following criteria: a migraine headache treated
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5 139 with acute migraine-specific medication, a non-migraine headache that lasted for at least 4
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7 140 hours, or a headache for which acute headache treatment was used. An acute migraine-specific
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9 141 medication treatment day was defined as any day during which migraine-specific medication
10
11 142 was used.

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14 143 Safety endpoints included the incidence and exposure-adjusted incidence of treatment-
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16 144 emergent adverse events (TEAEs), clinical laboratory values and vital signs, and the incidence
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18 145 of anti-erenumab antibodies. Exposure-adjusted rates (per 100 patient-years) were calculated
19
20 146 by dividing the number of patients with at least one reported occurrence of the TEAE of interest
21
22 147 by the total time at risk for reporting the TEAE (patient-year) multiplied by 100. The time at risk
23
24 148 was defined as the time from the first dose of erenumab to the onset of the TEAE or the end of
25
26 149 study date. Reporting exposure-adjusted rates normalizes the rates of adverse events occurring
27
28 150 during the DBTP and OLTP to equal exposure periods (ie, events per 100 patient-years), and
29
30 151 thus allows for a proper comparison between the DBTP and OLTP.

31 152 **Statistical analysis**

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33
34 153 Analysis was performed after all patients had completed safety follow-up at the end of the study
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36 154 and included patients who received at least one dose of erenumab 70 mg in the OLTP. Efficacy
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38 155 and safety data were tabulated by the double-blind treatment group. Efficacy endpoints were
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40 156 analyzed by using descriptive statistics based on observed data without imputation and were
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42 157 tabulated by visit. No formal testing was conducted. Patient incidence and exposure-adjusted
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44 158 incidence of TEAEs were tabulated by treatment group and by system organ class and
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46 159 preferred term. All analyses were performed using SAS System 9.4 (SAS Institute, Cary, NC,
47
48 160 USA).

49 161 **RESULTS**

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163 Patients

164 Of the 261 patients enrolled and randomized in the parent study (erenumab 70 mg, n = 130;
 165 placebo, n = 131), 254 (97.3%) entered the OLTP and received at least one dose of the
 166 investigational product (IP) and 244 (93.5%) completed the IP. Ten patients (3.8%) discontinued
 167 the IP for the following reasons: patient request (n = 4; 1.5%), COVID-19 control measures (n =
 168 4; 1.5%), adverse event (n = 1; 0.4%), and pregnancy (n = 1; 0.4%) (Figure S2). In the OLTP
 169 population, the mean age of patients was 44.3 years, 86.6% were female, and the majority
 170 (77.6%) had used or were using migraine preventive treatment at baseline (Table 1).

171 **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)

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

177 Efficacy

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3 178 In the OLTP population (N = 254; EM, n = 155; CM, n = 99), the mean (standard error of the
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5 179 mean [SE]) MMD at baseline was 12.2 (0.4) days (EM, 8.3 [0.2] days; CM, 18.2 [0.4] days) and
6
7 180 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
8
9 181 the end of the DBTP at week 24, the mean (SE) change from baseline in MMD for the
10
11 182 erenumab 70 mg group was -3.8 (0.4) days (EM, -3.0 [0.4] days; CM, -5.2 [0.8] days) and -
12
13 183 1.7 (0.5) days for the placebo group; at the end of the OLTP at week 52, the mean (SE) change
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15 184 was -4.7 (0.3) days (EM, -3.4 [0.3]; CM, -6.9 [0.6]) (Figure 1, Table 2).

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17
18 185 At the end of the DBTP at week 24, the mean (SE) change from baseline in MSMD for the
19
20 186 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
21
22 187 for the placebo group; at the end of the OLTP at week 52, the mean (SE) change was -3.3 (0.3)
23
24 188 days (EM, -2.4 [0.3] days; CM, -4.6 [0.5] days) (Figure 1, Table 2). Throughout the 28-week
25
26 189 OLTP, erenumab 70 mg demonstrated persistent efficacy in MMD and MSMD reduction in
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28 190 patients with EM or CM.

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30
31 191 At week 24 of the DBTP, the proportion of patients who achieved at least a 50% reduction in
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33 192 MMD from baseline was 34.1% with erenumab 70 mg (EM, 39.7%; CM, 25.5%) and 19.1% with
34
35 193 placebo (Figure 2, Table 2). The response was maintained and numerically higher throughout
36
37 194 the OLTP than it was during the DBTP. At week 36 of the OLTP, 52.8% of the patients achieved
38
39 195 the 50% threshold for MMD reduction (EM, 58.8%; CM, 43.0%); at week 52, it was 44.4% (EM,
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41 196 46.3%; CM, 41.7%). The results were similar for patients responding at the 75% threshold for
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43 197 MMD reduction (Figure 2).

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48 198 **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 $\geq 50\%$ 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)

199 Efficacy by EM and CM subgroups at week 24 of the DBTP and during the OLTP. *Data are

200 shown for patients in the erenumab 70 mg group at week 24 of the DBTP in the efficacy

201 analysis set. N = number of patients in the open-label analysis set; n = number of patients with

202 observed data. CM, chronic migraine; DBTP, double-blind treatment period; EM, episodic

203 migraine; MMD, monthly migraine days; MSMD, monthly acute migraine-specific medication

204 treatment days; OLTP, open-label treatment period; SE, standard error of the mean.

205

206 Safety

207 The mean (standard deviation) exposure to erenumab 70 mg during the OLTP was 192.6 (20.0)

208 days (total exposure to open-label treatment, 133.9 patient-years). The majority of patients

209 (92.1%) received all seven doses of erenumab 70 mg during the OLTP.

210 During the OLTP, the incidence of TEAEs was 71.3% (181/254) (Table 3). The exposure-
 211 adjusted incidence of TEAEs during the OLTP was 219.7 per 100 patient-years, which is similar
 212 to that in the erenumab group (251.0 per 100 patient-years) and in the placebo group (197.7 per
 213 100 patient-years) during the DBTP. The majority of patients (62.2% [158/254]) experienced
 214 TEAEs of grade 2 or less. The most common (≥ 5 per 100 patient-years) TEAEs reported with
 215 erenumab (OLTP vs DBTP) were nasopharyngitis (32.8 vs 67.2 per 100 patient-years),
 216 constipation (7.8 vs 10.3 per 100 patient-years), influenza (6.6 vs 1.7 per 100 patient-years),
 217 gastroenteritis (6.5 vs 6.8 per 100 patient-years), and urticaria (5.9 vs 1.7 per 100 patient-
 218 years). Seven patients (2.8%) reported serious adverse events with erenumab during the OLTP,
 219 corresponding to an exposure-adjusted rate of 4.1 per 100 patient-years, which is similar to the
 220 rate reported during the DBTP in each treatment group (3.4 per 100 patient-years). During the
 221 OLTP, one patient with a serious adverse event discontinued treatment because of a grade 3
 222 serious adverse event of drug eruption, which was considered by the investigator to be
 223 unrelated to erenumab treatment. No deaths were reported during the study. No clinically
 224 significant changes in laboratory values or vital signs were observed throughout the OLTP.

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

233 **Table 3.** Safety results during the DBTP and OLTP

	DBTP	OLTP
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	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

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

241 **DISCUSSION**

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

247 The incidence and exposure-adjusted incidence of TEAEs during the OLTP were consistent
248 with those from the DBTP and previous studies,(18, 20, 21) except for influenza and urticaria,
249 which were numerically higher during the OLTP than they were during the DBTP. Furthermore,
250 although the exposure-adjusted rates of constipation during the OLTP (7.8 per 100 patient-
251 years) were consistent with those during the DBTP (10.0 per 100 patient-years), they were
252 higher than those reported during the OLTP of the phase 2 study in Japanese patients with EM
253 (2.6 per 100 patient-years).(21) The development of anti-erenumab antibodies in 6.3% patients
254 over the entire study was consistent with the 5.8% seen in the global CM OLE study and was
255 lower than the 13.1% in the global EM OLE study.(24, 25) Neutralizing antibodies were
256 uncommon in the global studies and were not observed in this study. In addition, no new safety
257 concerns regarding clinically relevant changes in laboratory assessments and vital signs were
258 identified throughout the OLTP. Of the patients who entered the OLTP, 3.9% discontinued IP
259 including 1 for an AE. The high proportion of patients completing erenumab treatment through
260 both DBTP and OLTP (93.5%) reflects the excellent tolerability and sustained efficacy. In the
261 pivotal topiramate trials, 28.7% of participants withdrew during the 8-month OLE, more than
262 40% of these due to AEs.(26) The high retention rate also reduces the potential for bias that
263 may be seen in open-label extension studies where patients may drop out for diminished
264 efficacy, thus skewing the efficacy results over time.

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3 265 The OLTP of this study was non-randomized and lacked a comparator arm, thus limiting the
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5 266 ability to distinguish study drug specific effects on efficacy and safety from other factors. In
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7 267 addition, the duration of the 28-week OLTP was short relative to some other studies in non-
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9 268 Japanese patients.(18) However, the study does represent the longest follow-up experience
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11 269 with erenumab in Japanese patients with CM and shows long-term efficacy and safety that are
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13 270 comparable to that seen in a global long-term study of erenumab in patients with CM.(25) In the
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15 271 global CM study, the reduction in MMD and MSMD after 52 weeks for the erenumab 70 mg
16
17 272 group was -7.8 days and -5.8 days, respectively; 47.4% of the patients achieved at least a 50%
18
19 273 reduction from baseline in MMD. In the global EM study, the reduction in MMD and MSMD after
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21 274 the 52-week open-label period (study week 64) for the erenumab 70 mg group was -5.0 days
22
23 275 and -2.4, respectively; 65% of the patients achieved at least a 50% reduction from baseline in
24
25 276 MMD.(24) This is comparable to the reductions in MMD and MSMD in this study at overall week
26
27 277 52 of -4.74 days and -3.26, respectively; 44.4% of the patients achieved at least a 50%
28
29 278 reduction from baseline in MMD. These data support long-term treatment with erenumab in
30
31 279 Japanese patients with EM and CM.
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36 280 **CONCLUSION**

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38 281 Treatment with erenumab was associated with a reduction in migraine frequency that was
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40 282 maintained for up to 1 year in Japanese patients with EM or CM. Erenumab had a safety profile
41
42 283 similar to that observed in the DBTP; no new safety signals were identified during the OLTP.
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45 284 **Ethics Approval**

46
47 285 This study involved human patients and was approved by ethics committees and institutional
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49 286 review boards listed in the supplementary appendix (Table S1).
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287 **Acknowledgments**

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289 investigators who participated in this study. Medical writing support was provided by Qais Al-
290 Hadid, PhD (Amgen). Editorial support was provided by Sangeeta P.C. (Cactus
291 Communications).

292 **Author contributions**

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

297 **Conflict of Interest Statement**

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

301 **Institutional review board approval**

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

304 **Data availability statement**

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

308 **Funding:** This study was funded by Amgen. No grants or awards were used for funding of this
309 study.

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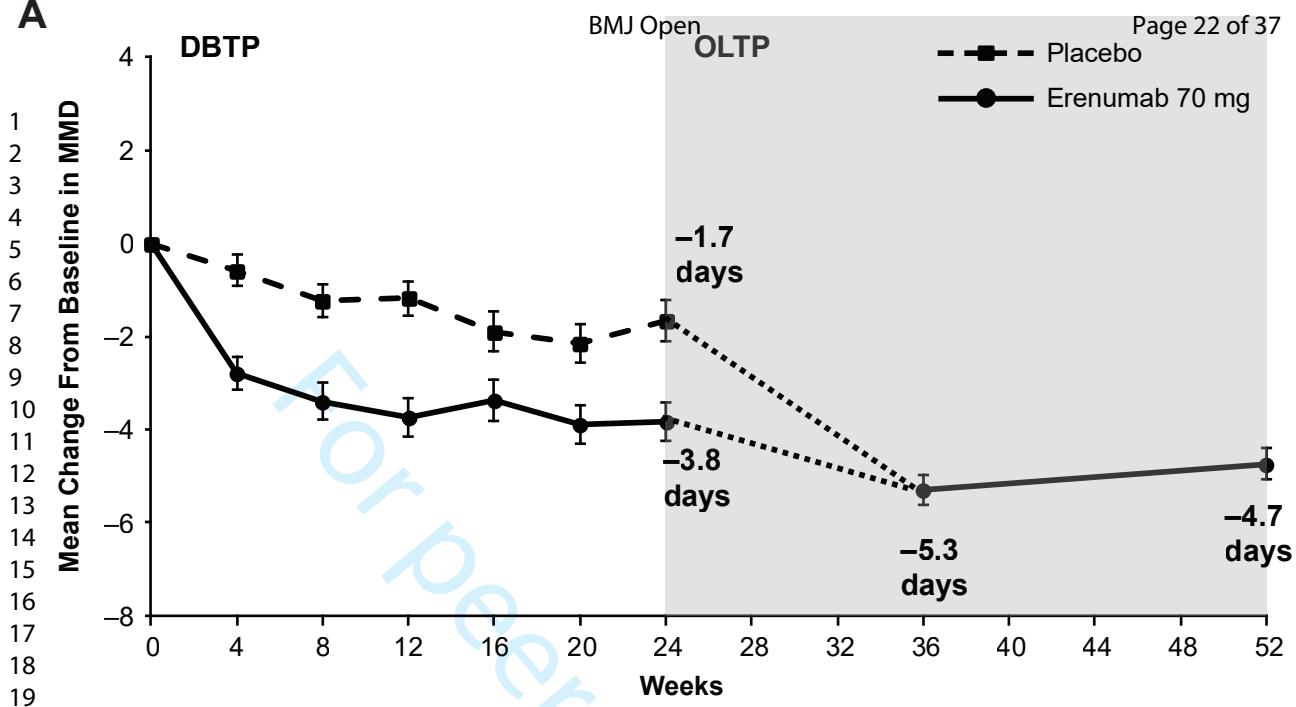
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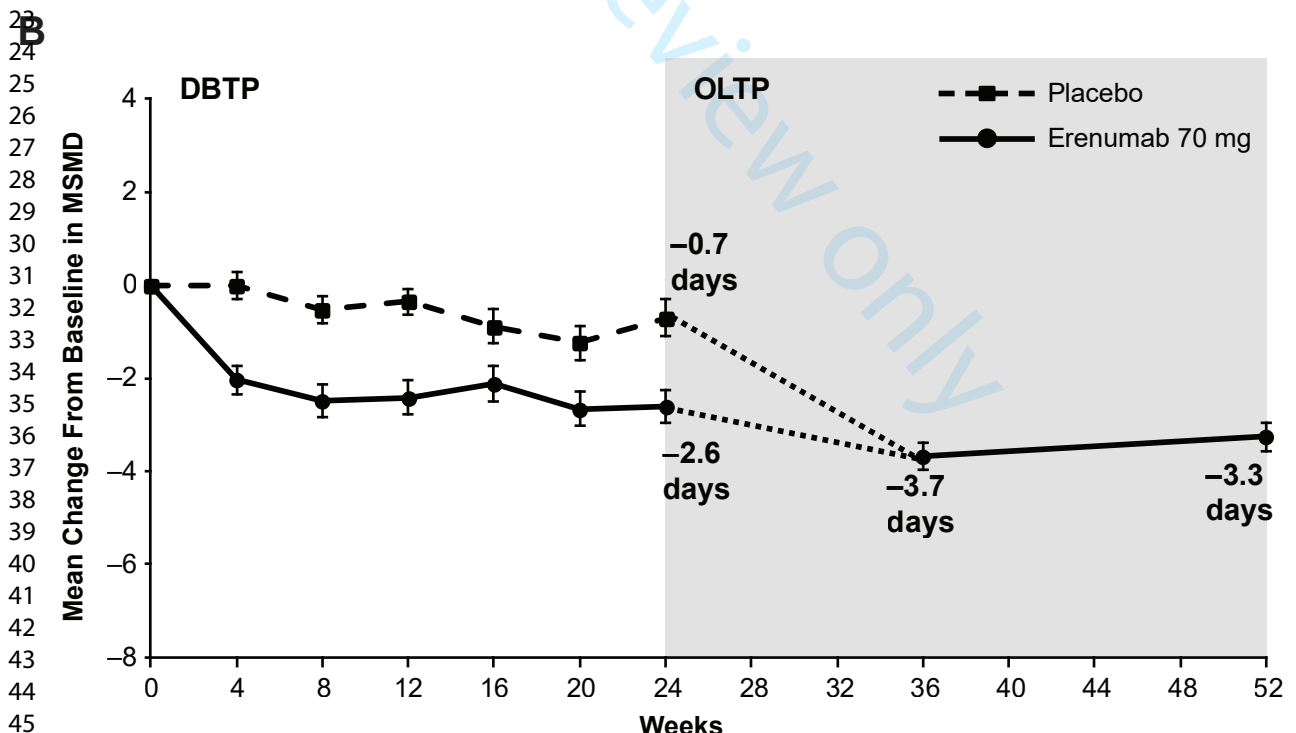
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3 386 **Figure 1.** Change in (A) MMD and (B) MSMD from baseline. The mean (SE) change from
4
5 387 baseline in MMD and MSMD during the DBTP and OLTP is shown for the treatment groups. For
6
7 388 the OLTP, data are shown for the total population. The dotted line indicates that patients in the
8
9 389 placebo group during the DBTP received erenumab 70 mg during the OLTP starting at week 24.
10
11 390 *The number of patients in the efficacy analysis set during the DBTP. Error bars represent SE. n
12
13 = number of patients with observed data. DBTP, double-blind treatment period; MMD, monthly
14 391 migraine days; MSMD, monthly acute migraine-specific medication treatment days; OLTP,
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16 392 open-label treatment period; SE, standard error of the mean.
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21 394 **Figure 2.** Patients achieving a (A) $\geq 50\%$ and (B) $\geq 75\%$ reduction in MMD from baseline. For the
22
23 395 OLTP, data are shown for the total population. The dotted line indicates that patients in the
24
25 396 placebo group during the DBTP received erenumab 70 mg during the OLTP starting at week 24.
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27 397 *The number of patients in the efficacy analysis set during the DBTP. n = number of patients
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29 398 with observed data. DBTP, double-blind treatment period; MMD, monthly migraine days; OLTP,
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31 399 open-label treatment period.
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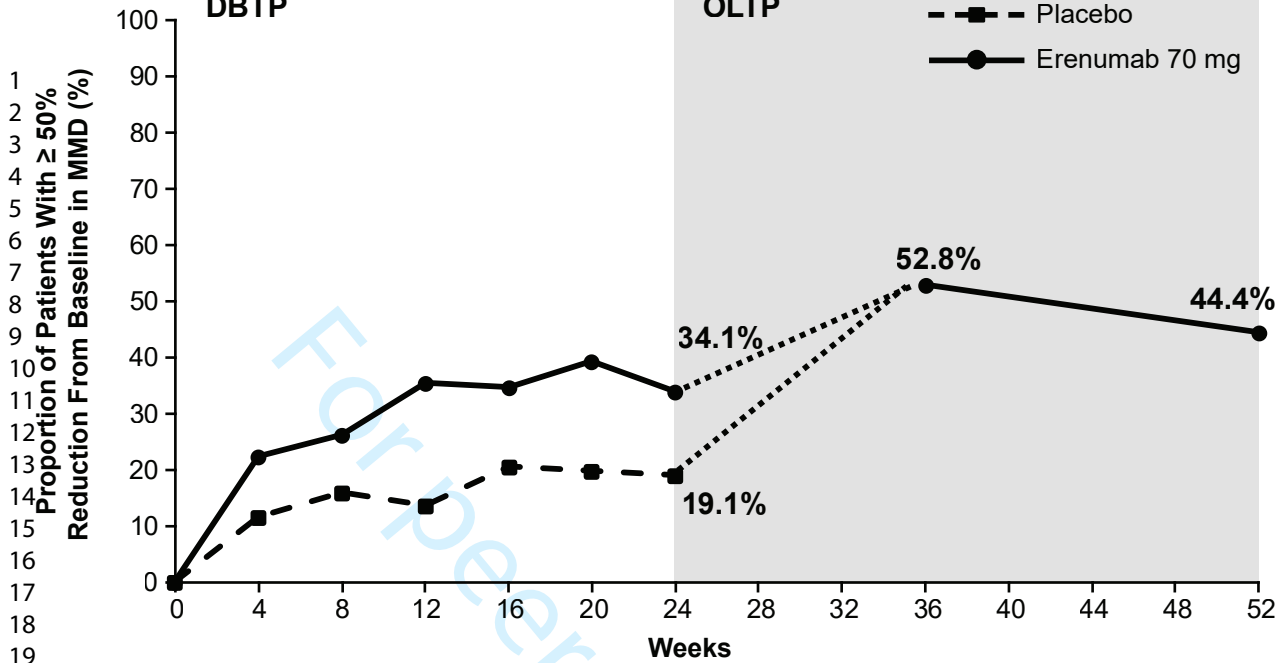


Placebo (n)	130*	130*	128*	128*	126*	127*		
Erenumab 70 mg (n)	130*	129*	128*	128*	128*	129*	246	243

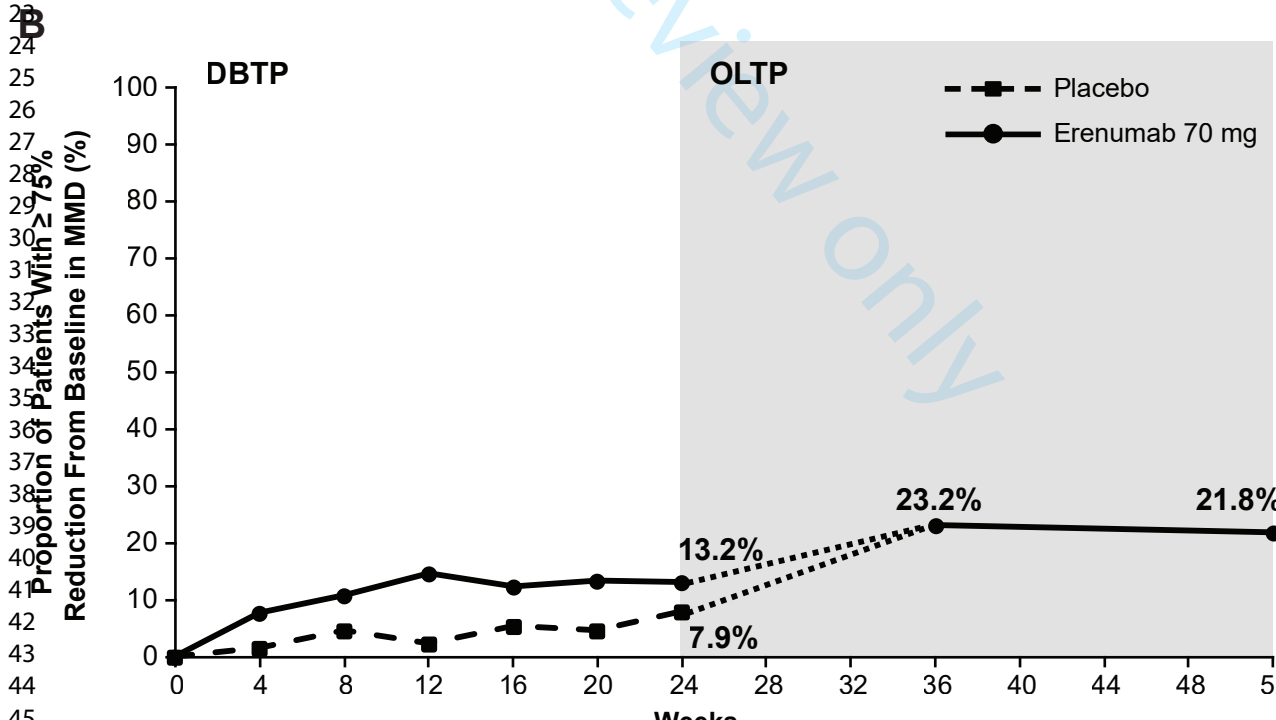


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Placebo (n)	130*	130*	128*	128*	126*	127*		
Erenumab 70 mg (n)	130*	129*	128*	128*	128*	129*	246	243



Placebo (n)	131*	131*	131*	131*	131*	131*		
Erenumab 70 mg (n)	130*	130*	130*	130*	130*	130*	246	243



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

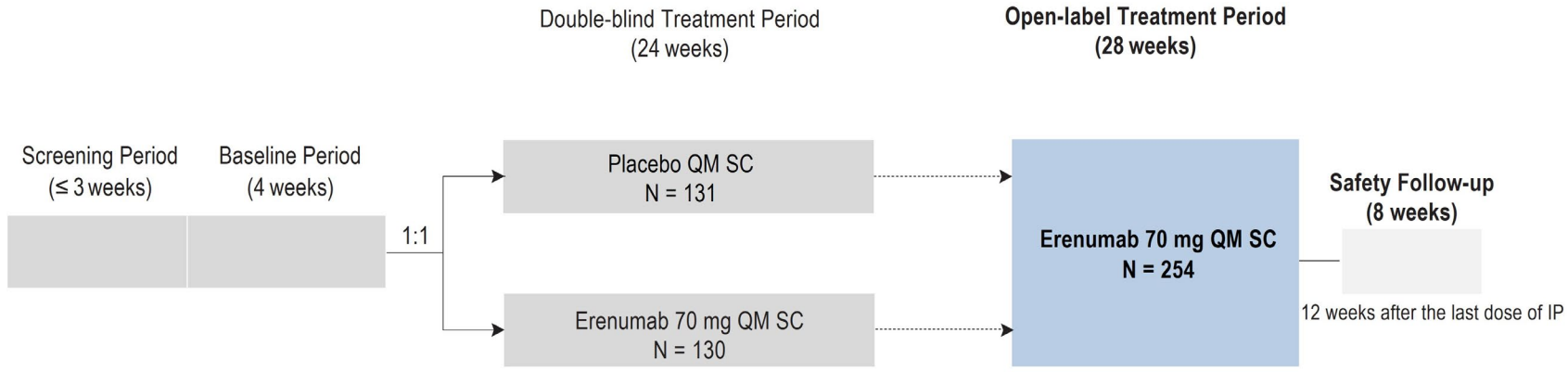
SUPPLEMENTARY APPENDIX

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Table S1 – Ethics Committees/IRBs.....	4

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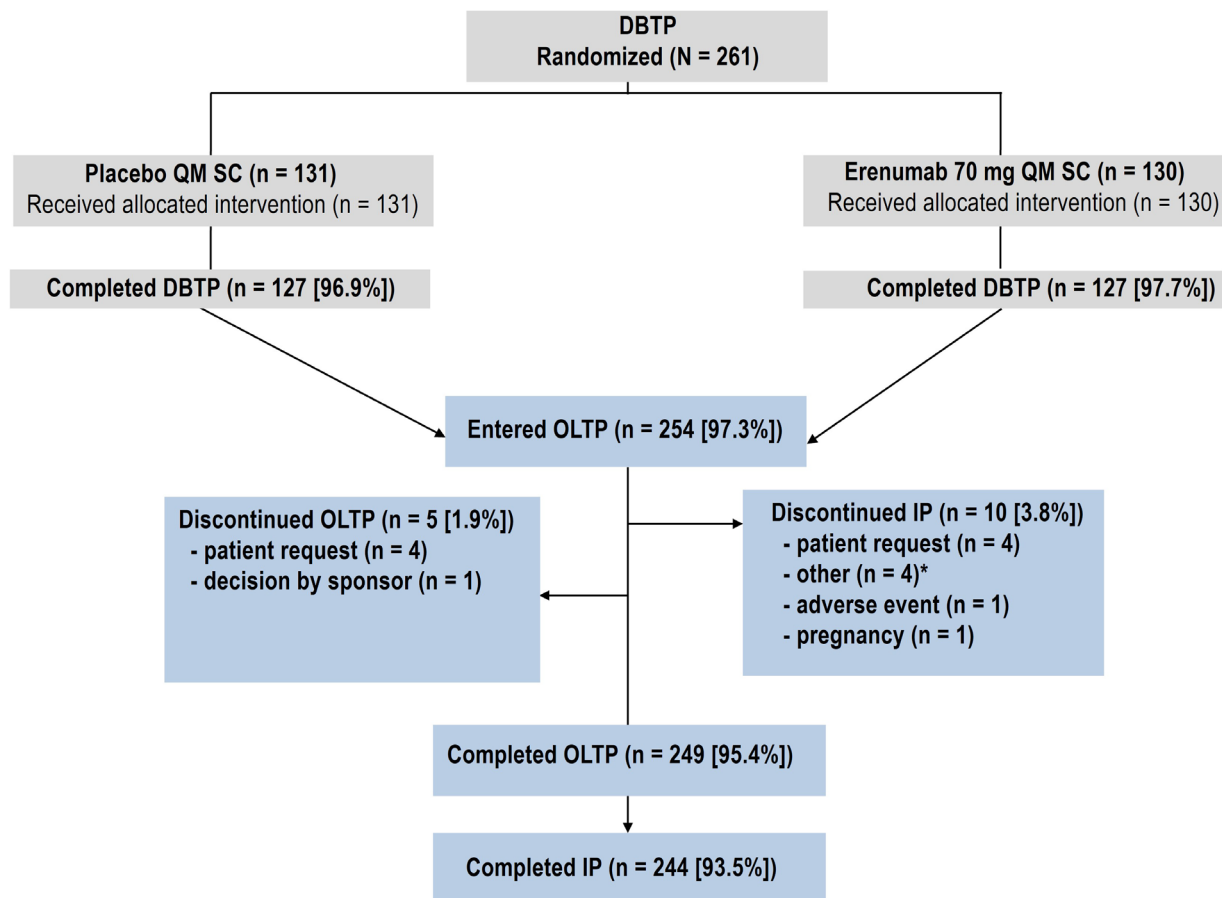
1 **Figure S1**



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

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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	Gshozuka Clinic Institutional Review Board	1-21-4 Gshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34013	Nagamitsu Clinic	Gshozuka Clinic Institutional Review Board	1-21-4 Gshozuka 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	Gshozuka Clinic Institutional Review Board	1-21-4 Gshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34016	Saino Clinic	Gshozuka Clinic Institutional Review Board	1-21-4 Gshozuka 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	Gshozuka Clinic Institutional Review Board	1-21-4 Gshozuka 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

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20170609	34021	Tokai University Hachioji Hospital	Tokai University Hospitals Institutional Review Board	1-2-5 Yoyogi, Shibuya-ku, Tokyo, 151-0053, Japan
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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	Gshozuka Clinic Institutional Review Board	1-21-4 Gshozuka 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	Gshozuka Clinic Institutional Review Board	1-21-4 Gshozuka 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	Gshozuka Clinic Institutional Review Board	1-21-4 Gshozuka Miyamae-ku, Kawasaki-shi, Kanagawa, 216-0021, Japan
20170609	34038	Medical Corporation Yufukai Shimoda Neurology Clinic	Gshozuka Clinic Institutional Review Board	1-21-4 Gshozuka 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	Gshozuka Clinic Institutional Review Board	1-21-4 Gshozuka 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

1			mg in the
2			OLTP
3		7b	When applicable, explanation of any interim analyses and stopping guidelines
4	Randomisation:		NA
5	Sequence	8a	Method used to generate the random allocation sequence
6	generation	8b	Type of randomisation; details of any restriction (such as blocking and block size)
7	Allocation	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers),
8	concealment		describing any steps taken to conceal the sequence until interventions were assigned
9	mechanism		NA
10	Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to
11			interventions
12			5
13	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those
14			assessing outcomes) and how
15		11b	If relevant, description of the similarity of interventions
16			NA
17			NA; this is a
18			single-arm
19			open-label
20			extension
21			7
22	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
23		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
24			NA
25	Results		
26	Participant flow (a	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and
27	diagram is strongly		were analysed for the primary outcome
28	recommended)	13b	For each group, losses and exclusions after randomisation, together with reasons
29	Recruitment	14a	Dates defining the periods of recruitment and follow-up
30		14b	Why the trial ended or was stopped
31			5
32	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
33	Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was
34			by original assigned groups
35			8
36	Outcomes and	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its
37	estimation		precision (such as 95% confidence interval)
38			8-10, Figure
39			1, Figure 2
40		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
41	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing
42			NA

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

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19 *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

20 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials.

21 Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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

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39 **this item is specific to conference abstracts*
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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

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>