Received: 12 August 2021 | Accepted: 4 April 2022

DOI: 10.1111/head.14313

RESEARCH SUBMISSIONS

Long-term efficacy and safety of erenumab in patients with chronic migraine in whom prior preventive treatments had failed: A subgroup analysis

Messoud Ashina MD, PhD[1] | Stewart J. Tepper MD[2] | Jan Lewis Brandes MD[3] | Uwe Reuter MD[4,5] | Guy P. Boudreau MD[6] | Mark Weatherall FRCP, PhD[7] | Andreas R. Gantenbein MD[8,9] | David Doležil MD, PhD[10] | Jan Klatt MD[11] | Andrea Wang MA[12] | Ananda Krishna Karanam PhD[13] | Sunfa Cheng MD[12] | Daniel D. Mikol MD, PhD[12]

[1]Department of Neurology, Danish Headache Center, Rigshospitalet Glostrup, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[2]Geisel School of Medicine at Dartmouth, Hanover, New Hampshire, USA

[3]Department of Neurology, Vanderbilt University School of Medicine, Nashville Neuroscience Group, Nashville, Tennessee, USA

[4]Department of Neurology, Charité Universitätsmedizin, Berlin, Germany

[5]Universitätsmedizin Greifswald, Greifswald, Germany

[6]Centre de Traitement Neurologique, Montreal, Québec, Canada

[7]Department of Neurology, Stoke Mandeville Hospital, Aylesbury, UK

[8]Department for Neurology and Neurorehabilitation, ZURZACH Care, Bad Zurzach, Switzerland

[9]Department of Neurology, University Hospital Zurich, Zürich, Switzerland

[10]Prague Headache Center, DADO MEDICAL sro, Prague, Czech Republic

[11]Novartis Pharma AG, Basel, Switzerland

[12]Amgen Inc., Thousand Oaks, California, USA

[13]Novartis Healthcare Private Limited, Hyderabad, India

Abstract

Objective: To assess the long-term efficacy and safety of erenumab in the subgroup of patients with chronic migraine (CM) in whom prior preventive treatments had failed (TF) (≥1, ≥2, and ≥3 TF medication categories) and never failed (preventive naïve or prior preventive treatments had not failed), using the data from a 52-week, open-label treatment period (OLTP) of the parent study.

Background: Erenumab is a fully human monoclonal antibody that selectively binds to and inhibits the canonical calcitonin gene-related peptide receptor. There are limited long-term data evaluating the efficacy and safety of erenumab in patients with CM in whom prior preventive treatments had failed.

Methods: Patients who had completed the 12-week double-blind treatment period (DBTP) in the parent study were eligible to participate in the 52-week OLTP, during which they received erenumab every 4 weeks. The TF subgroups (≥1, ≥2, and ≥3 TF medication categories) were not mutually exclusive; patients in whom prior preventive treatments from ≥3 medication categories had failed were also counted in the ≥2 and ≥1 medication categories. Endpoints included monthly migraine days (MMD), monthly acute migraine-specific medication days (MSMD), achievement of ≥50%, ≥75%, and 100% reduction from baseline in MMD, and exposure-adjusted patient incidence rates of adverse events (AEs; per 100 patient-years).

Results: Erenumab treatment provided sustained mean reductions in MMD and MSMD relative to the parent study baseline throughout the 52 weeks of the OLTP across all TF subgroups. At Week 52, the mean MMD change was −8.6 (SD 6.6) (baseline: 18.4 [SD 4.5] days) in the ≥1 TF subgroup. A post hoc completer analysis (52 weeks [OLTP]

Abbreviations: AEs, adverse events; CI, confidence interval; CM, chronic migraine; DBTP, double-blind treatment period; EM, episodic migraine; MMD, monthly migraine days; MSMD, monthly acute migraine-specific medication days; OLTP, open-label treatment period; TEAE, treatment-emergent AEs; TF, prior preventive treatments failed.

Correspondence
Messoud Ashina, Department of Neurology, Danish Headache Center, Rigshospitalet Glostrup, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
Email: ashina@dadlnet.dk

Funding information
This study was fully funded by Amgen Inc., Thousand Oaks, CA. Erenumab is co-developed in partnership with Amgen and Novartis.

erenumab) showed that compared with erenumab 70 mg, the 140 mg dose was associated with numerically greater reductions in the mean MMD (Week 40: −8.6 and −7.2 days; Week 52: −9.7 and −7.9 days [≥1 TF subgroup]) and a higher proportion of patients achieved ≥50%, ≥75%, and 100% response thresholds across all subgroups at Weeks 40 and 52. Overall the exposure-adjusted patient incidence rates of AEs did not increase during the OLTP versus the DBTP (≥1 TF subgroup: 141.9/100 versus 317.9/100 patient-years), and no new safety signals occurred.

Conclusion: The long-term treatment with erenumab was well tolerated and showed sustained efficacy in patients with CM in whom prior preventive treatments had failed, with numerically greater treatment effects for 140 mg versus 70 mg.

KEYWORDS
chronic migraine, erenumab, erenumab-aooe, migraine, preventive treatment

INTRODUCTION

Chronic migraine (CM) is a disabling and complex neurological disease requiring acute and preventive treatment.[1] The goals of preventive treatment in CM management include reductions in attack frequency, severity, duration of migraine, acute medication use, and disability, as well as improvements in function and health-related quality-of-life.[2] For patients with migraine, the standard of care oral migraine preventive medications are associated with low persistence[3] and adherence[4] due to insufficient efficacy and/or poor tolerability, resulting in frequent treatment discontinuations, thereby limiting achievement of treatment goals. Frequent switching or re-initiation of preventive treatment is common following discontinuations; however, discontinuation rates increase as patients cycle through additional oral migraine preventive medications.[3] There is an unmet need to improve medical care for patients with CM, particularly for those in whom prior preventive treatments had failed.

Erenumab (erenumab-aooe in U.S.) is a fully human monoclonal antibody that selectively binds to and inhibits the canonical calcitonin gene-related peptide receptor.[5] Erenumab is approved for the preventive treatment of migraine in adults in the United States,[6] the European Union,[7] and elsewhere.[8] Clinical studies have demonstrated the efficacy and safety of erenumab for migraine prevention.[9,10] However, there are limited long-term data evaluating the efficacy and safety of erenumab in patients with CM in whom prior preventive treatments had failed.

Here, we present 52-week efficacy and safety data for erenumab (70 and 140 mg) from a post hoc subgroup analysis of patients with CM in whom prior preventive treatments had failed (TF) (≥1, ≥2, and ≥3 TF medication categories) and never failed (preventive naïve or prior preventive treatments had not failed), where *failure* is defined as discontinuation of prior preventive treatment due to lack of efficacy and/or poor tolerability.

METHODS

Study design

The study design schema and methods for the parent study[9] and its open-label treatment period (OLTP)[11] were published previously. In brief, the parent study was a randomized, 12-week, double-blind, placebo-controlled trial that evaluated the efficacy and safety of erenumab in patients with CM at 69 sites across North America and Europe.[9] After completing 12 weeks of the parent study double-blind treatment period (DBTP), eligible patients were enrolled in the 52-week OLTP. Week 12 DBTP visit assessments were conducted on the same day as the Week 0 OLTP visit. An overview of the study flowchart showing patient disposition is provided in Figure S1 in the Supporting Information.

Patients received subcutaneous erenumab once per month (i.e., every 4 weeks) during the 52-week OLTP. Patients who were enrolled in the OLTP under the original protocol initially received erenumab 70 mg. Following an amendment to the protocol, patients receiving erenumab 70 mg who had not completed the Week 28 visit (i.e., midpoint of the OLTP) had their dose increased to 140 mg, allowing patients to reach the steady state by Week 40. Patients who had completed the Week 28 visit remained on erenumab 70 mg for the remainder of the OLTP. Those enrolling after the protocol amendment received erenumab 140 mg throughout the OLTP.

During the parent study[9] and the OLTP[11] patients used an electronic diary (eDiary) to record information regarding migraine and non-migraine headaches, and acute migraine-specific medication use. In the parent study[9] patients used the eDiary daily between Week 4 and Day 1 (pre-randomization) during the 1-month baseline period and daily through the 12-week DBTP. During the OLTP, patients used the eDiary daily between Day 1 and the Week 12 visit, between Week 20 and the Week 24 visit, between Week 36 and the Week 40 visit, and between Week 48 and the Week 52 visit.

Study patients

The parent study[9] enrolled adult patients (aged 18–65 years) with CM who had a history of ≥15 headache days/month for >3 months, of which ≥8 were migraine days (with or without aura). Other eligibility criteria for enrollment in the parent study and its OLTP study have been reported previously.[9,11] Briefly, exclusion criteria in the parent study DBTP included no therapeutic response to >3 migraine preventive medication categories, following an adequate therapeutic trial. *No therapeutic response* was strictly defined as no reduction in headache frequency, duration, or severity following administration of the medication for ≥6 weeks at the generally accepted therapeutic dose(s) (based on the investigator's assessment). Previous preventive migraine medication categories included the following: topiramate, β-blockers (e.g., propranolol or metoprolol), tricyclic antidepressants (e.g., amitriptyline or nortriptyline), calcium channel blockers (e.g., flunarizine or verapamil), divalproex sodium or sodium valproate, serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine or desvenlafaxine, duloxetine or milnacipran), botulinum toxin, antihypertensives (e.g., lisinopril or candesartan), and other medications. Failure of a preventive medication category as a result of insufficient efficacy or poor tolerability, according to the clinical judgment of the investigator, did not equate with no therapeutic response, unless the definition for no therapeutic response was also met.

Furthermore, the key eligibility criteria for the OLTP were a stipulation that patients must have completed the Week 12 DBTP study visit and must not have discontinued the investigational product during the parent study. Patients were excluded from the OLTP if any of the following had occurred during the parent study: an unstable or clinically significant medical condition or a laboratory or ECG abnormality that could pose a safety risk or interfere with study procedures; any treatment-related serious adverse event (AE); or poorly controlled hypertension.

Standard protocol approvals, registrations, and patient consents

The parent study and its OLTP are registered with ClinicalTrials.gov (NCT02066415 and NCT02174861, respectively). Protocols for the parent study[9] and its OLTP[11] were approved by independent ethics committee or local institutional review board at each participating site.

Both studies were conducted in accordance with the International Conference on Harmonisation Guideline on Good Clinical Practice. All patients provided written informed consent.

Subgroups

Subgroups were defined based on the number of prior migraine preventive medication categories that had failed for the reasons of "lack of efficacy" or "unacceptable tolerability," or both, as recorded by the investigator before enrollment into the parent study. The never failed subgroup included preventive-naïve patients and those who had prior use of preventive medication, but the treatment did not fail for reasons of "lack of efficacy" and/or "unacceptable tolerability."

Endpoints

Endpoints were change from the parent study baseline to specified assessment time points during the OLTP in monthly migraine days (MMD), monthly acute migraine-specific medication days (MSMD), and MSMD in the subgroup of patients who used migraine-specific medications (MSM) during the parent study baseline. The proportions of patients achieving ≥50%, ≥75%, and 100% reduction from the parent study baseline in MMD (≥50%, ≥75% and 100% response thresholds) were also evaluated. Safety analyses included reporting of AEs using exposure-adjusted patient incidence rates per 100 patient-years.

Statistical analysis

The details of sample size calculations of the parent study are available in the Supporting Information (Appendix S1) and published elsewhere.[9] This study was not designed or powered to make formal comparison between the two dose groups (erenumab 70 mg vs. erenumab 140 mg) or between the TF versus never failed subgroups. The descriptive statistics performed here were consistent with the descriptive nature of the long-term efficacy assessment in the OLTP[11] of the parent study.[9] For continuous endpoints, the descriptive statistics included number of observations, mean, median, standard deviation, standard error, first and third quartile, minimum and maximum, and two-sided 95% confidence interval (CI) of the means. For categorical endpoints, the number and percentage of patients were reported for each category.

Missing diary data were handled using the proration approach; monthly measurements, for instance MMD, were calculated if patients completed at least 50% of their daily diary reporting each month. If patients had low diary compliance, defined as completed <50% of daily diary reporting, the monthly measurements were set as missing. Missing monthly measurements could be due to discontinuation from the study (dropout rate 25.9%) or low diary compliance. The number of patients with observed monthly measurements are presented within the figures as the sample size (*n*) at each time point.

In the current subgroup analysis, patients were analyzed based on the number of migraine preventive medication categories failed (0 [never failed]; ≥1, ≥2, or ≥3 TF) due to lack of efficacy and/or poor tolerability before patient enrollment into the parent study. The efficacy analysis set included patients who had received at least one dose of the investigational product and completed at least one post-baseline monthly eDiary measurement. Patient demographics and

baseline disease characteristics were analyzed using descriptive statistics. Efficacy data were summarized by visit (Weeks 4, 8, 12, 24, 40, and 52) during the OLTP in a combined erenumab dose groups (70 mg only, 140 mg only, and 70 to 140 mg switchers).

As patients with erenumab dose increase to 140 mg at or before Week 28 received the higher dose for ≥12 weeks (i.e., reached steady state of 140 mg) by Week 40, the efficacy of erenumab between the 70 and 140 mg dose groups could be evaluated among completers because they have received either 70 or 140 mg for at least 12 and 24 weeks at Weeks 40 and 52, respectively. Safety was assessed by monitoring of AEs throughout the study. To account for the different study duration of the 12-week parent study[9] and the 52-week OLTP,[11] the AEs were summarized by treatment period as exposure-adjusted patient incidence rates of treatment-emergent AEs (TEAE) by the dose level at which the AE occurred. An AE which started in the parent study was considered a TEAE during the OLTP only if it worsened. Furthermore, an AE was not considered treatment-emergent if it was ongoing during the OLTP with no change in severity. The exposure-adjusted patient incidence of a TEAE for either dose of erenumab (presented per 100 patient-years) was the number of patients with at least one reported occurrence of the event at that dose level divided by the total time (patient-years) at risk, and multiplied by 100, for reporting the TEAE. For patients with AEs, only the time until the first event contributed to the total patient-years. If a patient had multiple occurrences of the same AE both within a dose level, or at a different dose level, only the first occurrence within each dose level was presented.

AEs were coded using the Medical Dictionary for Regulatory Activities Version 20.0. AE grading was according to Common Terminology Criteria for Adverse Eventsversion 4.03.

All statistical analyses were performed using SAS system version 9.4 (SAS Institute Inc., Cary, NC, USA).

Primary research question

Is erenumab associated with evidence of long-term efficacy and safety in patients with CM who have previously failed preventive treatment(s)? This study provides evidence that efficacy was sustained with erenumab treatment in patients with CM in whom prior preventive treatments had failed, and that the 140 mg monthly dose had a greater effect than 70 mg in the completer subset of the TF subgroup.

RESULTS

Patient demographics, baseline disease characteristics, and preventive treatments

A total of 609 patients were enrolled in the OLTP. There was a majority of 69.0% ($n = 419$) patients in whom ≥1 prior preventive treatment had failed, whereas in 31.0% ($n = 190$) the prior preventive treatments had never failed (preventive naïve [$n = 155$] or prior preventive treatments had not failed [$n = 35$]) (Figure S1). The proportion of patients who discontinued from the study medication was similar across all four subgroups (0 [never failed], ≥1, ≥2, and ≥3 TF medication categories) (Figure S1). Patients across all subgroups had a similar median age (43.0–45.0 years), and the majority were women (80.0%–85.2%) (Table 1). Patients in whom prior preventive treatments had failed had a longer mean duration of migraine at baseline (23–24 years) than those who had never failed (19 years) (Table 1). At the parent study baseline, both MMD and the proportion of patients with acute MSM use increased with increasing numbers of TF (MMD: 17.4–19.0 days; acute MSM: 61.6%–91.7%) (Table 1). Across all subgroups patients had high monthly acute headache medication treatment days at the parent study baseline (15.1–15.7 days), consistent with a more severe, difficult-to-treat population. Topiramate was the most frequently reported prior treatment category; followed by β-blockers and tricyclic antidepressants across all subgroups (Table 1).

MMD and MSMD

At each assessment point (Weeks 4, 8, and 12) during the DBTP, treatment with erenumab (70 and 140 mg) showed greater mean reductions in MMD and MSMD across all subgroups compared with placebo (Figures 1 and 2 [≥1 TF medication category]; Figures S2 and S3 [never failed, ≥2, and ≥3 TF medication categories]). During the 52-week OLTP, in the combined dose group, treatment with erenumab provided sustained mean reductions in MMD and MSMD relative to the parent study baseline across all subgroups (Figures 1 and 2 [≥1 TF medication category]; Figures S2 and S3 [never failed, ≥2, and ≥3 TF medication categories]). At Week 52 of the OLTP, the mean MMD changes were −10.8 (to 6.6 days; baseline 17.4 days) in the never failed subgroup, −8.6 (to 9.8 days from baseline 18.4 days) in the ≥1 TF subgroup, −8.0 (to 10.5 days from baseline 18.5 days) in the ≥2 TF subgroup, and −7.9 (to 11.0 days from baseline 18.9 days) in the ≥3 TF subgroup. The mean MSMD changes were −3.7 days (baseline 6.7), −5.6 days (baseline 10.8), −5.5 days (baseline 11.6), and −5.5 days (baseline 11.8) at Week 52 in the respective subgroups.

Among completers, numerically greater reductions in the mean MMD and MSMD were observed at Weeks 40 and 52 with erenumab 140 mg versus 70 mg across all subgroups (except for the never failed subgroup for MSMD) (Figures 1 and 2 [≥1 TF medication category]; Figures S2 and S3 [never failed, ≥2, and ≥3 TF medication categories]). The differences in MSMD at Weeks 40 and 52 across subgroups were even greater with erenumab 140 mg versus 70 mg in patients who used MSM at baseline (Figure 2 [≥1 TF medication category]; Figure S3 [never failed, ≥2, and ≥3 TF medication categories]).

MMD response

The proportion of patients achieving ≥50% reduction from baseline in MMD was higher in those treated with erenumab 70 and 140 mg

TABLE 1 Patient demographics, baseline disease characteristics and prior migraine preventive treatments (FAS)[a]

	Never failed *N* = 190	≥1 TF *N* = 419	≥2 TF *N* = 308	≥3 TF *N* = 218
Women, *n* (%)	152 (80.0)	357 (85.2)	262 (85.1)	181 (83.0)
Median age (range), years	43 (19 – 64)	44 (18 – 66)	45 (18 – 66)	44.5 (18 – 66)
Race, *n* (%)				
White	169 (88.9)	405 (96.7)	297 (96.4)	211 (96.8)
Black or African American	17 (8.9)	8 (1.9)	5 (1.6)	4 (1.8)
Asian	3 (1.6)	4 (1.0)	4 (1.3)	3 (1.4)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.5)	2 (0.5)	2 (0.6)	0 (0.0)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, *n* (%)				
Not Hispanic/Latino	170 (89.5)	414 (98.8)	305 (99.0)	215 (98.6)
Hispanic/Latino	20 (10.5)	5 (1.2)	3 (1.0)	3 (1.4)
Age at onset of migraine, years	23.2 (10.7)	19.8 (10.0)	19.2 (9.8)	18.9 (9.9)
Disease duration of migraine with or without aura, years	18.6 (12.1)	23.3 (12.2)	24.4 (12.5)	24.4 (12.7)
MMD	17.4 (4.5)	18.5 (4.5)	18.5 (4.3)	19.0 (4.3)
Monthly headache days	20.7 (4.0)	21.1 (3.7)	21.0 (3.6)	21.2 (3.7)
Acute headache medication use, *n* (%)				
Acute MSM use, *n* (%)	117 (61.6)	359 (85.7)	276 (89.6)	200 (91.7)
MSMD	6.7 (6.8)	10.9 (7.2)	11.6 (7.0)	11.9 (7.0)
Monthly acute headache medication treatment days	15.1 (5.9)	15.5 (6.1)	15.6 (6.1)	15.7 (6.1)
Number of patients reporting any prior migraine preventive medication				
	N1 = 35	**N1 = 419**	**N1 = 308**	**N1 = 218**
Medication category, *n* (%)[b,c]				
Topiramate	11 (31.4)	300 (71.6)	247 (80.2)	191 (87.6)
β-blockers	5 (14.3)	240 (57.3)	210 (68.2)	165 (75.7)
Tricyclic antidepressants	7 (20.0)	215 (51.3)	197 (64.0)	164 (75.2)
Other medications[d]	2 (5.7)	146 (34.8)	134 (43.5)	113 (51.8)
Botulinum toxin	11 (31.4)	135 (32.2)	121 (39.3)	102 (46.8)
Divalproex sodium, sodium valproate	2 (5.7)	99 (23.6)	95 (30.8)	84 (38.5)
Flunarizine or verapamil	2 (5.7)	79 (18.9)	74 (24.0)	68 (31.2)
Lisinopril or candesartan	1 (2.9)	74 (17.7)	68 (22.1)	55 (25.2)
SNRIs	0	45 (10.7)	43 (14.0)	39 (17.9)
Reason of migraine preventive treatment failure, *n* (%)[b]				
Lack of efficacy	NA	336 (80.2)	266 (86.4)	193 (88.5)
With therapeutic dose	NA	284 (67.8)	223 (72.4)	167 (76.6)
Without therapeutic dose	NA	116 (27.7)	107 (34.7)	83 (38.1)
Adverse reaction/unacceptable tolerability	NA	301 (71.8)	249 (80.8)	194 (89.0)
Reason other than treatment failure	35 (100)	132 (31.5)	107 (34.7)	80 (36.7)
Preventive medication no longer clinically necessary	6 (17.1)	40 (9.5)	34 (11.0)	25 (11.5)
Other	31 (88.6)	106 (25.3)	86 (27.9)	65 (29.8)

Note: Data are mean (SD) values unless otherwise indicated. *N*1 = number of subjects receiving any prior preventive medication. *N* = Number of subjects in the analysis set. % = *n*/*N* * 100. Prior preventive treatments never failed includes preventive-naïve patients and patients who had prior use of preventive medication, but the treatment did not fail for the reasons of "lack of efficacy" and/or "adverse reaction." FAS included patients who were enrolled in the study and received at least one dose of the investigational product.

Abbreviations: FAS, full analysis set; MMD, monthly migraine days; MSM, migraine-specific medication; MSMD, monthly acute migraine–specific medication treatment days; OLTP, open-label treatment period; TF, prior preventive treatments failed; SD, standard deviation; SNRIs, serotonin-norepinephrine reuptake inhibitor.

[a]Assessed at the parent study baseline.

[b]% = *n*/*N*1 * 100.

[c]Subjects may contribute to more than one category.

[d]Other medications may include butterbur/feverfew/magnesium (≥600 mg/day)/riboflavin (≥100 mg/day), clonidine/guanfacine, cyproheptadine, methysergide, pizotifen, carbamazepine and gabapentin.

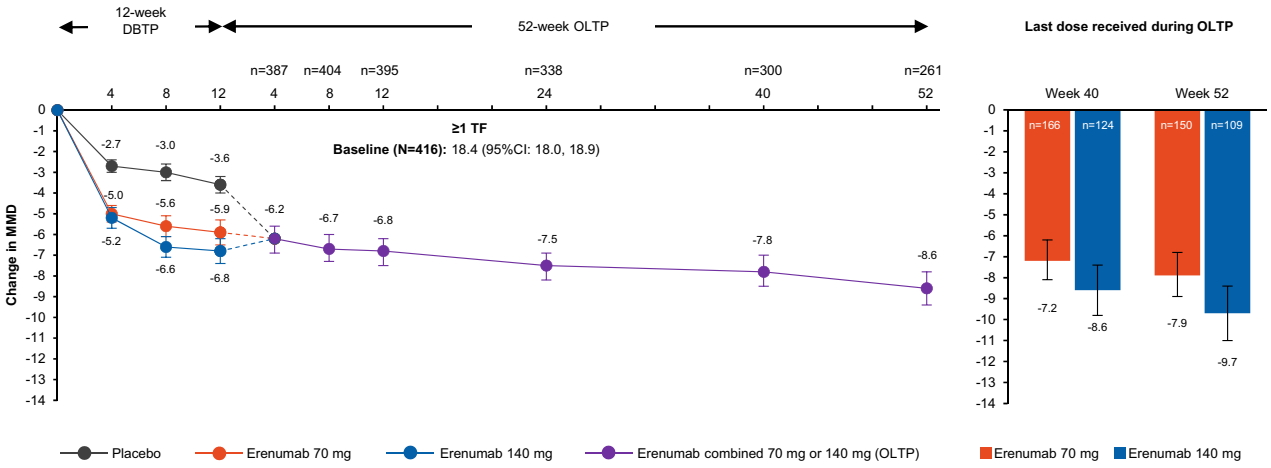

FIGURE 1 The change from the parent study baseline in the number of MMD (≥1 TF medication category). During the OLTP, subjects in the erenumab 140 mg treatment group had received ≥3 months of 140 mg erenumab at Week 40 and ≥6 months of 140 mg erenumab at Week 52. Error bars are SEM for the parent study and 95% CI for the OLTP. Dashed lines indicate transition from end of the parent study to Week 4 of the OLTP. CI, confidence interval; DBTP, double-blind treatment period; MMD, monthly migraine days; OLTP, open-label treatment period; SEM, standard error of the mean; TF, prior preventive treatments failed. [Color figure can be viewed at wileyonlinelibrary.com]

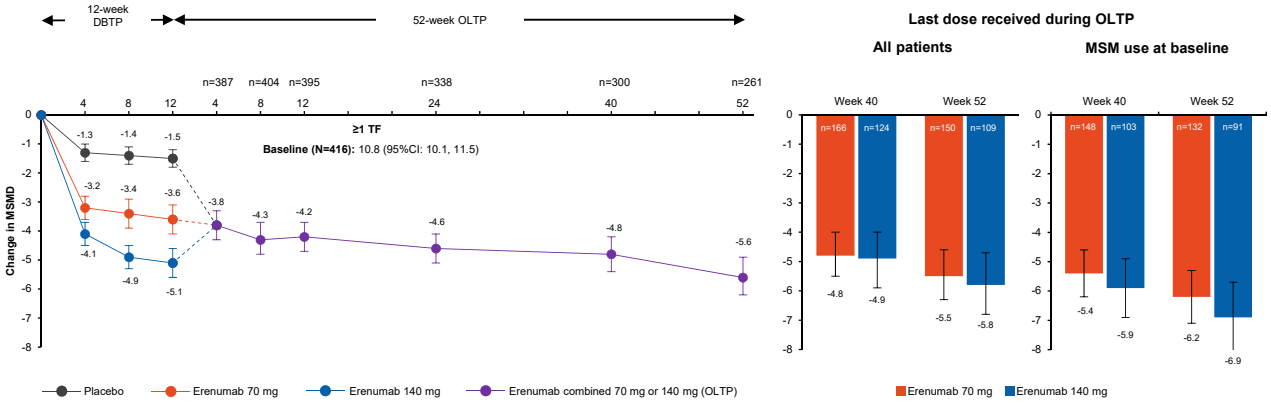

FIGURE 2 Change from the parent study baseline in the number of MSMD (≥1 TF medication category). During the OLTP, patients in the erenumab 140 mg group received ≥3 months of 140 mg erenumab at Week 40 and ≥6 months of 140 mg erenumab at Week 52. Error bars are SEM for the parent study and 95% CI for the OLTP. Dashed lines indicate transition from end of the parent study to Week 4 of the OLTP. CI, confidence interval; DBTP, double-blind treatment period; MSM, migraine-specific medication; MSMD, monthly acute migraine-specific medication days; OLTP, open-label treatment period; SEM, standard error of the mean; TF, prior preventive treatments failed. [Color figure can be viewed at wileyonlinelibrary.com]

compared with placebo at each specified assessment time point during the DBTP (Figure 3 [≥1 TF medication category]; Figure S4 [never failed, ≥2, and ≥3 TF medication categories]). The proportion of patients in the combined dose group who achieved a ≥50% MMD response at Week 52 of the OLTP was 68.0% in the never failed subgroup, 54.8% in the ≥1 TF subgroup, 50.3% in the ≥2 TF subgroup, and 46.6% in the ≥3 TF subgroup. Among completers the proportion of patients who achieved a ≥50% MMD response was higher at Weeks 40 and 52 in those who received erenumab 140 mg versus 70 mg across all subgroups (Figure 3 [≥1 TF medication category]; Figure S4 [never failed, ≥2, and ≥3 TF medication categories]). A similar pattern of results was observed for ≥75% and 100% reduction from baseline in MMD (Figures 4 and 5 [≥1 TF medication category]; Figures S5 and S6 [never failed, ≥2, and ≥3 TF medication categories]).

Adverse events

Overall, the exposure-adjusted patient incidence rates of any AEs were 98.1/100 patient-years in the never failed subgroup, 141.9/100 patient-years in the ≥1 TF subgroup, 152.2/100 patient-years in the ≥2 TF subgroup, and 162.2/100 patient-years in the ≥3 TF subgroup during the OLTP (Table 2 [≥1 TF medication category]; Table S1 [never failed, ≥2, and ≥3 TF medication categories]). In the OLTP, the overall rate of AEs (Grade ≥2 or Grade

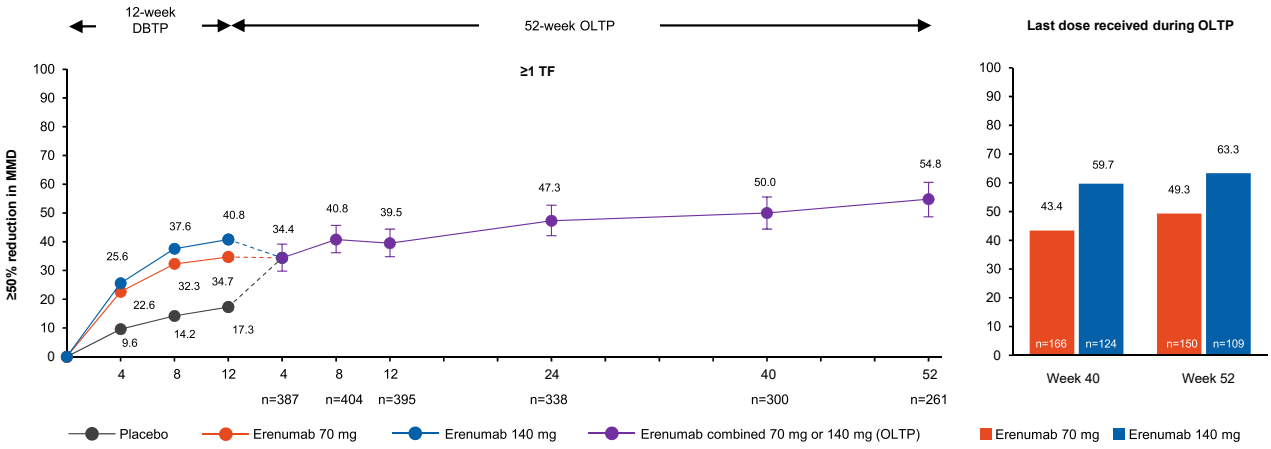

FIGURE 3 Proportion of patients achieving ≥50% reduction from the parent study baseline in MMD (≥1 TF medication category). During the OLTP, patients in the erenumab 140 mg treatment group received ≥3 months of 140 mg erenumab at Week 40 and ≥6 months of 140 mg erenumab at Week 52. Dashed lines indicate transition from end of the parent study to Week 4 of the OLTP. DBTP, double-blind treatment period; MMD, monthly migraine days; OLTP, open-label treatment period; TF, prior preventive treatments failed. [Color figure can be viewed at wileyonlinelibrary.com]

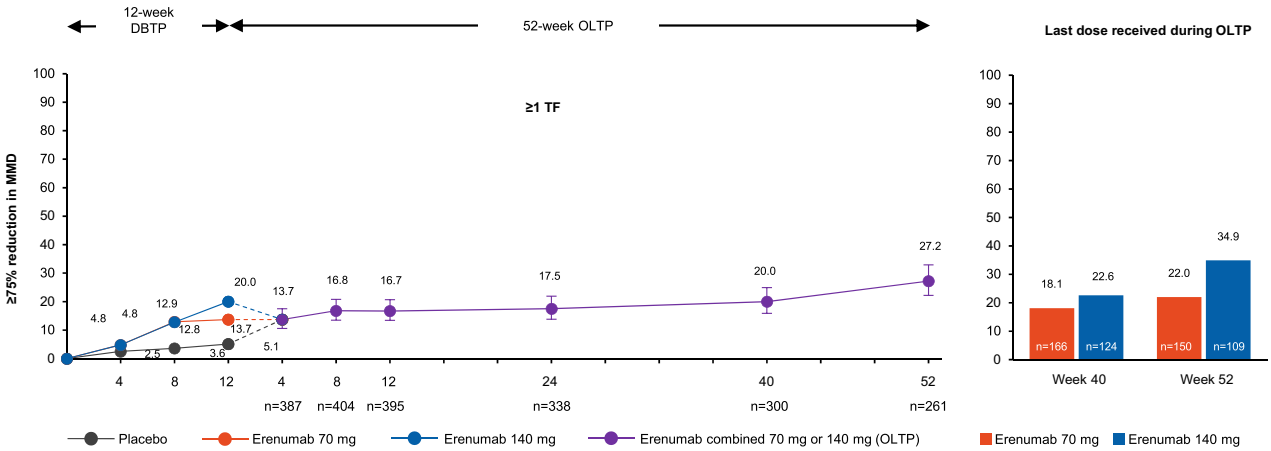

FIGURE 4 Proportion of patients achieving ≥75% reduction from the parent study baseline in MMD (≥1 TF medication category). During the OLTP, patients in the erenumab 140 mg treatment group received ≥3 months of 140 mg erenumab at Week 40 and ≥6 months of 140 mg erenumab at Week 52. Dashed lines indicate transition from end of the parent study to Week 4 of the OLTP. DBTP, double-blind treatment period; MMD, monthly migraine days; OLTP, open-label treatment period; TF, prior preventive treatments failed. [Color figure can be viewed at wileyonlinelibrary.com]

≥3) was greater in the subgroups of patients in whom prior preventive treatments had failed than in the never failed subgroup (preventive naïve and prior preventive treatments had not failed) (Table 2 [≥1 TF medication category]; Table S1 [never failed, ≥2, and ≥3 TF medication categories]). There were no fatal adverse events reported during the DBTP and the OLTP. While the incidence rates of AEs during the OLTP were higher in patients with more TF versus those with fewer or no TF, the respective rate in each TF subgroup was lower than the rates in both treated and placebo groups in the DBTP (Table 2 [≥1 TF medication category]; Table S1 [never failed, ≥2, and ≥3 TF medication categories]). No new safety signals were observed in the OLTP versus the DBTP in each of the TF subgroups.

DISCUSSION

The findings of this long-term study provide insights into the efficacy of erenumab in patients with CM in whom prior preventive treatments had failed, and the results of this subgroup analysis are in line with previous publications. In the combined erenumab dose group, treatment with erenumab resulted in sustained efficacy throughout the 52-week OLTP, with ~50% reduction from the parent study baseline in mean MMD and MSMD at Week 52 in patients for whom ≥1 and ≥2 prior preventive treatments had failed. In the parent study of patients with CM, treatment with erenumab (70 and 140 mg) was associated with a reduction in the mean MMD and MSMD compared with placebo, and increased odds of achieving ≥50% reduction from

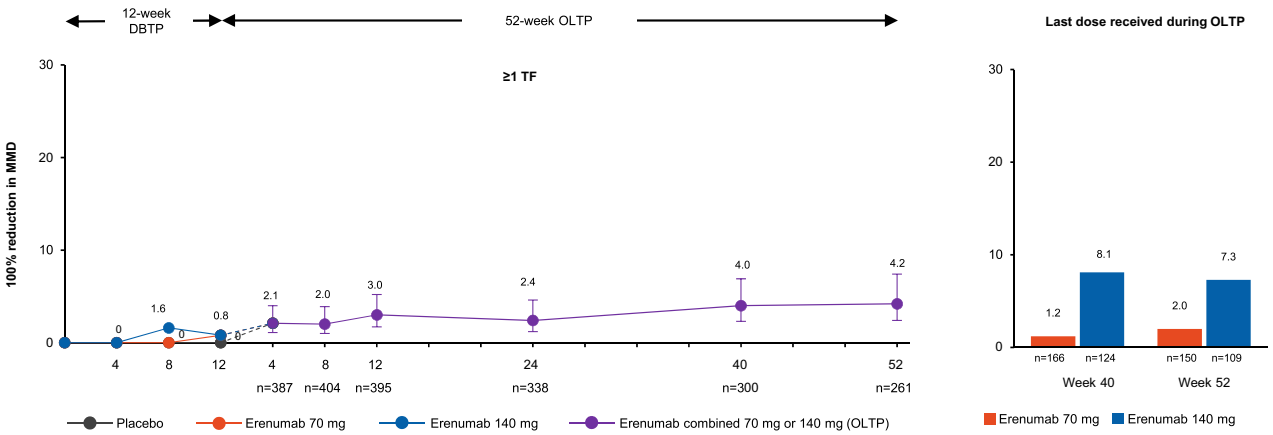

FIGURE 5 Proportion of patients achieving a 100% reduction from the parent study baseline in MMD (≥1 TF medication category). During the OLTP, patients in the erenumab 140 mg treatment group received ≥3 months of 140 mg erenumab at Week 40 and ≥6 months of 140 mg erenumab at Week 52. Dashed lines indicate transition from end of the parent study to Week 4 of the OLTP. DBTP, double-blind treatment period; MMD, monthly migraine days; OLTP, open-label treatment period; TF, prior preventive treatments failed. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Exposure-adjusted patient incidence rates of TEAEs (summarized according to dose received when AE occurred) (≥1 TF medication category)

	DBTP		OLTP		
	Placebo *n*(%)/*e*[*r*]	Erenumab 70/140 mg *n*(%)/*e*[*r*]	Erenumab 70 mg *n*(%)/*e*[*r*]	Erenumab 140 mg *n*(%)/*e*[*r*]	Erenumab 70/140 mg *n*(%)/*e*[*r*]
≥1 TF	*N* = 197	*N* = 251	(*N* = 385)[a]	(*N* = 174)[a]	(*N* = 419)[a]
Any AE	84(42.6)/35.9[233.9]	126(50.2)/39.6[317.9]	232(60.3)/155.7[149.0]	116(66.7)/65.5[177.0]	288(68.7)/203.0[141.9]
Grade ≥2	52(26.4)/41.8[124.5]	64(25.5)/54.5[117.3]	183(47.5)/193.8[94.4]	85(48.9)/92.1[92.3]	238(56.8)/262.3[90.7]
Grade ≥3	11(5.6)/49.5[22.2]	11(4.4)/64.1[17.2]	24(6.2)/299.1[8.0]	6(3.4)/142.3[4.2]	28(6.7)/437.3[6.4]
Grade ≥4	0(0.0)/51.8[0.0]	1(0.4)/65.6[1.5]	0(0.0)/308.7[0.0]	0(0.0)/145.1[0.0]	0(0.0)/453.8[0.0]
TEAEs	21(10.7)/47.0[44.6]	48(19.1)/54.0[88.9]	66(17.1)/265.1[24.9]	32(18.4)/124.1[25.8]	90(21.5)/378.0[23.8]
SAEs	5(2.5)/51.0[9.8]	5(2.0)/65.0[7.7]	12(3.1)/302.6[4.0]	9(5.2)/141.1[6.4]	21(5.0)/442.3[4.7]
Discontinuation[b]	2(1.0)/51.1[3.9]	1(0.4)/65.5[1.5]	6(1.6)/306.9[2.0]	5(2.9)/143.1[3.5]	11(2.6)/450.0[2.4]
Fatal AEs	0(0.0)/51.8[0.0]	0(0.0)/65.6[0.0]	0(0.0)/308.7[0.0]	0(0.0)/145.1[0.0]	0(0.0)/453.8[0.0]

Note: *N* = number of subjects in the analysis set. *n* = number of subjects reporting at least one occurrence of an AE. % = *n*/*N* * 100. *e* = Sum across all subjects, the total time at risk in the study in years. Time at risk during the study is the time from the first dose of investigational product through to onset of first event or the min (end of study date, last IP dose +112). *r* = Exposure-adjusted patient rate per 100 subject years (*n*/*e**100). Grading categories determined using Common Terminology Criteria for Adverse Events version 4.03.

Abbreviations: AE, adverse event; DBTP, double-blind treatment period; OLTP, open-label treatment period; SAEs, serious adverse events; TEAEs, treatment emergent adverse events; TF, prior preventive treatments failed.

[a]Numbers of subjects in the 70 and 140 mg groups represent subjects exposed to both doses of erenumab.

[b]AEs leading to study drug discontinuation.

baseline in MMD (≥50% MMD response) with erenumab compared with placebo.[9] During the OLTP,[11] sustained efficacy of erenumab was observed throughout 52 weeks (with greater clinical benefit at 140 mg versus 70 mg). Recently, subgroup analysis[12] of the parent study based on TF also showed that erenumab (70 and 140 mg) resulted in greater mean reductions in MMD, MSMD, and a higher proportion of patients with ≥50% MMD response compared with placebo. The average reductions in MMD observed suggest that many of these patients would likely no longer be classified as having CM. A post hoc analysis[13] of the pivotal CM study and subsequent OLTP showed that overall 66.3% (*n* = 120/181) patients who completed receiving 64 weeks of erenumab attained long-term reversion to episodic migraine (EM) and remained as EM throughout the OLTP (regardless of reversion status after 12 weeks of erenumab treatment). In our analysis, >50% of patients achieved ≥50% MMD response at Week 52. At this time point, 27.0% of patients in the ≥1 TF subgroup had achieved ≥75% response threshold. In addition, 19.0% of patients in the never failed subgroup and 4.0% of patients in the TF subgroups achieved a response threshold of 100% (i.e., migraine-free; a high threshold in CM) with long-term erenumab treatment

(Figure 5 [≥1 TF medication category]; Figure S6 [never failed, ≥2, and ≥3 TF medication categories]). Although the OLTP was not randomized or blinded, a similar number of patients had received 70 or 140 mg for at least 12 weeks at Week 40 and at least 24 weeks at Week 52 of the OLTP, such that assessing relative efficacy between erenumab 70 and 140 mg dose groups at Weeks 40 and 52 was feasible; the results suggest greater efficacy with erenumab 140 mg than 70 mg in patients with CM in whom prior preventive treatments had failed, across the endpoints studied. These data are consistent with the overall results reported for the OLTP of this study.[11]

During the OLTP, *absolute* treatment effect appeared to decline with increasing number of TF (Figures 1 and 3 [≥1 TF medication category]; Figures S2 and S4 [never failed, ≥2, and ≥3 TF medication categories]), which suggests that patients in whom multiple prior preventive treatments had failed are increasingly difficult to treat. Nonetheless, erenumab was effective across all subgroups, and these results are consistent with those from the DBTPs of EM and CM studies.[9,10] The findings are further supported by the results of the LIBERTY study,[14] which enrolled a population consisting entirely of patients with EM in whom 2–4 prior preventive treatments had failed. Furthermore, the results of the LIBERTY study at 64 weeks (52-week OLTP) showed sustained reductions in migraine frequency in patients with EM in whom 2–4 prior preventive treatments had failed.[15]

This was a subgroup analysis of an open-label, non-randomized study, and there is a need to observe how these results translate in the real world. A limitation of the current subgroup analysis is the OLTP design that may introduce bias through unblinding and dose switching at the different time points. The results from the subgroup analyses indicated that the erenumab 140 mg dose may be more beneficial than the 70 mg dose in patients with more advanced, difficult-to-treat CM. These findings may assist healthcare providers' clinical decision-making in treating patients who have experienced lack of success on prior preventive medications.

In this study, there were no reported TEAEs of Grade ≥4 severity and fatal AEs in any patient during the OLTP. In patients for whom prior preventive treatments had failed, the long-term treatment with erenumab did not result in higher exposure-adjusted patient incidence rates of AEs than observed in either the erenumab or the placebo group of the parent study DBTP (Table 2 [≥1 TF medication category]; Table S1 [never failed, ≥2, and ≥3 TF medication categories]). Notably, AE incidence rates increased with increasing number of patients in whom prior preventive treatments had failed. While the reasons for this are unclear, this may be attributable to increased reporting rates in patients who have tried and in whom prior preventive treatments had failed, or to differences in concomitant medications or comorbidities. The safety profile of erenumab in the OLTP was consistent with previous studies of erenumab, with no new safety concerns.

In conclusion, long-term treatment with erenumab showed sustained efficacy in patients with CM in whom prior preventive treatments had failed, with the 140 mg dose showing numerically greater benefit than 70 mg in the completer subset of the TF subgroup. Consistent with the DBTP, the magnitude of absolute treatment effect during the long-term OLTP was numerically less in patients with increasing numbers of preventive treatments that had failed. The long-term treatment with erenumab was well tolerated, with no increase in AEs compared with the DBTP, no new safety signals, and no dose dependency of AEs across TF subgroups. This study supports the use of erenumab in CM including patients with multiple prior preventive treatment failures and adds to the growing body of evidence for erenumab in this setting, of patients with CM.

ACKNOWLEDGMENTS

This study was fully funded by Amgen Inc., Thousand Oaks, CA. Erenumab is co-developed in partnership with Amgen and Novartis.

CONFLICTS OF INTEREST

Messoud Ashina is a consultant or scientific advisor for AbbVie, Allergan, Amgen, Eli Lilly, Lundbeck, Novartis, and Teva; currently primary investigator for AbbVie, Amgen and Lundbeck; research grants from Lundbeck Foundation, Novo Nordisk Foundation, and Novartis. Stewart J. Tepper was an employee of the Cleveland Clinic during this study. Grants for research (no personal compensation): Allergan, Amgen, ElectroCore, Eli Lilly, Neurolief, Novartis, Satsuma, Teva, Zosano. Consultant and/or Advisory Boards (honoraria): Aeon, Align Strategies, Allergan/Abbvie, Alphasights, Amgen, Aperture Venture Partners, Aralez Pharmaceuticals Canada, Axsome Therapeutics, Becker Pharmaceutical Consulting, BioDelivery Sciences International, Biohaven, ClearView Healthcare Partners, CoolTech, CRG, Currax, Decision Resources, DeepBench, DRG, Eli Lilly, Equinox, ExpertConnect, GLG, Guidepoint Global, Healthcare Consultancy Group, Health Science Communications, HMP Communications, Impel, Lundbeck, M3 Global Research, Magellan Rx Management, Medicxi, Navigant Consulting, Neurolief, Nordic BioTech, Novartis, Pulmatrix, Reckner Healthcare, Relevale, SAI MedPartners, Satsuma, Slingshot Insights, Spherix Global Insights, Sudler and Hennessey, Synapse Medical Communications, System Analytic, Teva, Theranica, Thought Leader Select, Trinity Partners, XOC, Zosano Salary: Dartmouth-Hitchcock Medical Center, American Headache Society, Thomas Jefferson University. CME honoraria: American Academy of Neurology, American Headache Society, Cleveland Clinic Foundation, Diamond Headache Clinic, Elsevier, Forefront Collaborative, Hamilton General Hospital, Ontario, Canada, Headache Cooperative of New England, Henry Ford Hospital, Detroit, Inova, Medical Learning Institute Peerview, Medical Education Speakers Network, Miller Medical Communications, North American Center for CME, Physicians Education Resource, Rockpointe, ScientiaCME, WebMD/Medscape. Jan Lewis Brandes has received research grants or support from Allergan, Amgen, Biohaven, CoLucid, Teva, and Zotrip; is a consultant for Amgen, Eli Lilly, Promius, and Supernus; served on an advisory board for Teva; and a speakers bureau for Amgen, Teva, Depomed, Promius, Avanir, and Supernus. Uwe Reuter has received consulting fees, speaking/teaching fees or research grants from Abbvie, Allergan, Amgen, Autonomic Technologies, ElectroCore, Eli Lilly, Lundbeck, Medscape, Novartis, StreamMedUp, and Teva Pharmaceuticals. Guy P. Boudreau has nothing to disclose. Mark

Weatherall has received honoraria and fees for lecturing from Allergan, Novartis, Teva pharmaceuticals, Eli Lilly, and Sapphire Medical Clinics. Andreas R. Gantenbein has received honoraria for consulting or lecturing from Allergan, Almirall, Curatis, Eli Lilly, Mepha, Novartis, Pfizer, Roche, and Teva Pharmaceuticals. David Doležil has received consulting fees and speaking and/or teaching fees from Allergan, Amgen, Biogen Idec, Novartis, Bayer, Eli Lilly, and Teva. Jan Klatt was an employee of Novartis at the time of the study and manuscript preparation. Andrea Wang and Sunfa Cheng are employees and stockholders of Amgen. Daniel D. Mikol was an employee of Amgen at the time of the study and manuscript preparation and is a current employee of NervGen Pharma. Ananda Krishna Karanam is an employee of Novartis.

AUTHOR CONTRIBUTIONS

Study concept and design: Messoud Ashina, Stewart J. Tepper, Jan Lewis Brandes, Uwe Reuter, Guy P. Boudreau, Andreas R. Gantenbein, Daniel D. Mikol. *Acquisition of data*: Messoud Ashina, Stewart J. Tepper, Jan Lewis Brandes, Uwe Reuter, David Doležil. *Analysis and interpretation of data*: Messoud Ashina, Stewart J. Tepper, Jan Lewis Brandes, Uwe Reuter, David Doležil, Mark Weatherall, Andreas R. Gantenbein, Jan Klatt, Andrea Wang, Ananda Krishna Karanam, Sunfa Cheng, Daniel D. Mikol. *Drafting of the manuscript*: Messoud Ashina, Jan Lewis Brandes, David Doležil, Ananda Krishna Karanam, Sunfa Cheng, Daniel D. Mikol. *Revising it for intellectual content*: Messoud Ashina, Stewart J. Tepper, Jan Lewis Brandes, Uwe Reuter, Guy P. Boudreau, David Doležil, Mark Weatherall, Andreas R. Gantenbein, Jan Klatt, Andrea Wang, Ananda Krishna Karanam, Sunfa Cheng. *Statistical analysis*: Andrea Wang. *Final approval of the completed manuscript*: Messoud Ashina, Stewart J. Tepper, Jan Lewis Brandes, Uwe Reuter, Guy P. Boudreau, Mark Weatherall, Andreas R. Gantenbein, David Doležil, Jan Klatt, Andrea Wang, Ananda Krishna Karanam, Sunfa Cheng, Daniel D. Mikol.

CLINICAL TRIALS REGISTRATION NUMBERS

Parent study: NCT02066415; Open-label treatment phase: NCT02174861.

DATA AVAILABILITY STATEMENT

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

ORCID

Messoud Ashina https://orcid.org/0000-0003-0951-5804

REFERENCES

1. Cho SJ, Song TJ, Chu MK. Treatment update of chronic migraine. *Curr Pain Headache Rep*. 2017;21:26.
2. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59:1-18.
3. Hepp Z, Dodick DW, Varon SF, et al. Persistence and switching patterns of oral migraine prophylactic medications among patients with chronic migraine: a retrospective claims analysis. *Cephalalgia*. 2017;37:470-485.
4. Hepp Z, Dodick DW, Varon SF, Gillard P, Hansen RN, Devine EB. Adherence to oral migraine-preventive medications among patients with chronic migraine. *Cephalalgia*. 2015;35:478-488.
5. Shi L, Lehto SG, Zhu DXD, et al. Pharmacologic characterization of AMG 334, a potent and selective human monoclonal antibody against the calcitonin gene-related peptide receptor. *J Pharmacol Exp Ther*. 2016;356:223-231.
6. AimovigTM United States prescribing information. Accessed March 23, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761077s000lbl.pdf
7. Aimovig™ Summary of product characteristics. Accessed March 23, 2022. https://www.ema.europa.eu/documents/product-information/aimovig-epar-product-information_en.pdf
8. Novartis marks a new era for migraine patients with the EU approval of Aimovig®, a first-of-its-kind treatment specifically designed for migraine prevention. Press release, July 30, 2018. Accessed March 23, 2022. https://www.novartis.com/news/media-releases/novartis-marks-new-era-migraine-patients-eu-approval-aimovigr-first-its-kind-treatment-specifically-designed-migraine-prevention
9. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol*. 2017;16:425-434.
10. Goadsby PJ, Reuter U, Hallström Y, et al. A controlled trial of erenumab for episodic migraine. *N Engl J Med*. 2017;377:2123-2132.
11. Tepper SJ, Ashina M, Reuter U, et al. Long-term safety and efficacy of erenumab in patients with chronic migraine: results from a 52-week, open-label extension study. *Cephalalgia*. 2020;40(6):543-553.
12. Ashina M, Tepper S, Brandes JL, et al. Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: a subgroup analysis of a randomized, double-blind, placebo-controlled study. *Cephalalgia*. 2018;38:1611-1621.
13. Lipton RB, Tepper SJ, Silberstein SD, et al. Reversion from chronic migraine to episodic migraine following treatment with erenumab: results of a post-hoc analysis of a randomized, 12-week, double-blind study and a 52-week, open-label extension. *Cephalalgia*. 2021;41:6-16.
14. Reuter U, Goadsby PJ, Lanteri-Minet M, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. *Lancet*. 2018;392:2280-2287.
15. Reuter U, Gaodsby PJ, Lanteri-Minet M, et al. Long-term efficacy and safety of erenumab: results from 64 weeks of the LIBERTY study. [IHC-OR-006]. *Cephalalgia*. 2019;39(1 Suppl);10-11.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Ashina M, Tepper SJ, Brandes JL, et al. Long-term efficacy and safety of erenumab in patients with chronic migraine in whom prior preventive treatments had failed: A subgroup analysis. *Headache*. 2022;62:624–633. doi:10.1111/head.14313