Received: 15 November 2020 | Accepted: 1 January 2021

DOI: 10.1111/ene.14715

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Long-term efficacy and safety of erenumab in migraine prevention: Results from a 5-year, open-label treatment phase of a randomized clinical trial

Messoud Ashina[1] | **Peter J. Goadsby**[2,3] | **Uwe Reuter**[4] | **Stephen Silberstein**[5] | **David W. Dodick**[6] | **Fei Xue**[7] | **Feng Zhang**[7] | **Gabriel Paiva da Silva Lima**[7] | **Sunfa Cheng**[7] | **Daniel D. Mikol**[7]

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

[2]NIHR/Wellcome Trust King's Clinical Research Facility, King's College London, London, UK

[3]Department of Neurology, University of California, Los Angeles, CA, USA

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

[5]Jefferson Headache Center, Thomas Jefferson University, Philadelphia, PA, USA

[6]Department of Neurology, Mayo Clinic, Scottsdale, AZ, USA

[7]Amgen Inc., Thousand Oaks, CA, USA

Correspondence
Messoud Ashina, Danish Headache Center, and Department of Neurology, Rigshospitalet Glostrup, Faculty of Health and Medical Sciences, University of Copenhagen, Valdemar Hansens Vej 5, DK-2600 Glostrup, Denmark.
Email: ashina@dadlnet.dk

Funding information
This study was funded by Amgen Inc. Erenumab is codeveloped in partnership between Amgen Inc. and Novartis. Role of the Funder/Sponsor: The funder was involved in the design and conduct of the study and the collection, management, analysis, and interpretation of the data. The funder was involved in the preparation, review, and approval of the manuscript. All authors had final responsibility for the decision to submit for publication.

Abstract

Background and purpose: Although erenumab has demonstrated significant reduction in migraine frequency and improved quality of life in studies lasting 3 to 12 months, little is known about long-term therapy.

Methods: This study was an open-label, 5-year treatment phase following a 12-week, double-blind, placebo-controlled trial in adults with episodic migraine. Patients initially received open-label erenumab 70 mg, which increased to 140 mg following a protocol amendment. Efficacy analyses included change from baseline in monthly migraine days (MMDs), monthly acute migraine-specific medication (AMSM) days, and health-related quality of life.

Results: Of 383 patients enrolled, 250 switched to 140 mg; 215 (56.1%) completed open-label treatment. Mean (standard error) change in MMDs from baseline of 8.7 (0.2) days was −5.3 (0.3) days; an average reduction of 62.3% at year 5. Among patients using AMSM at baseline (6.3 [2.8] treatment days), mean change in monthly AMSM days was −4.4 (0.3) days at the end of 5 years. Patient-reported outcomes indicated stable improvements in disability, headache impact, and migraine-specific quality of life. Exposure-adjusted patient incidence rates of adverse events (AEs) were 123.0/100 patient-years; AEs were

Abbreviations: AEs, adverse events; AMSM, acute migraine-specific medication; CGRP, calcitonin gene-related peptide; DBTP, double-blind treatment phase; EF, emotional function; EM, episodic migraine; HIT-6, Headache Impact Test; MID, minimally important difference; MIDAS, Migraine Disability Assessment; MMDs, monthly migraine days; MSQ, Migraine-Specific Quality-of-Life Questionnaire; OLTP, open-label treatment phase; RFP, role function–preventive; RFR, role function–restrictive; SAEs, serious adverse events; SE, standard error.

Trial Registration: ClinicalTrials.gov NCT01952574

most frequently nasopharyngitis, upper respiratory tract infection, and influenza. Serious AEs (SAEs) reported by 49 patients (3.8/100 patient-years) were mostly single occurrence. Two fatal adverse events were reported. There were no increases in incidence of AEs, SAEs, or AEs leading to treatment discontinuation over 5 years of exposure.

Conclusions: Treatment with erenumab was associated with reductions in migraine frequency and improvements in health-related quality of life that were maintained for at least 5 years. No new safety signals were observed.

KEYWORDS
CGRP receptor, efficacy, headache, headache frequency, monoclonal antibody

INTRODUCTION

Clinical benefits of monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) receptor pathway have been demonstrated in multiple 12- to 24-week double-blind trials with significant reductions in migraine frequency and improved health-related quality of life [1]. Because migraines are often a lifelong disorder, patients may require treatment for many years. Thus, migraine preventive treatments require favorable long-term benefit–risk profiles.

Erenumab (erenumab-aooe in the United States) is a human anti-CGRP receptor monoclonal antibody developed for migraine prevention [2–7] Across the clinical development program, erenumab has been evaluated in over 3,800 patients, representing approximately 3,600 patient-years of exposure [2–6,8] Here, we present extended efficacy and safety data after a 5-year open-label treatment phase (OLTP) following completion of a 12-week double-blind treatment phase (DBTP). Efficacy and safety results from the DBTP, a preplanned, 1-year, open-label interim analysis, and a safety analysis through year 3 of the OLTP have been previously published [5,9,10] This study provides important evidence for sustained efficacy and safety of erenumab treatment over 5 years.

METHODS

Study design

This multicenter, open-label, 256-week (5-year) treatment phase was a continuation of a 12-week double-blind, placebo-controlled study conducted at headache and clinical research centers in North America and Europe (Figure 1). Patients not transitioning directly to commercial erenumab completed an 8- or 12-week safety follow-up depending on completed dose in the OLTP. In the DBTP, patients with episodic migraine (EM) received placebo or erenumab (7 mg, 21 mg, or 70 mg) subcutaneously every 4 weeks [5] In the OLTP, patients received open-label erenumab every 4 weeks, initially 70 mg, increasing to 140 mg following a protocol amendment. Efficacy data were to be collected via a daily electronic diary (eDiary) for the first 52 weeks of the OLTP; a later protocol amendment reinstituted eDiary collection for 4-week periods every 24 weeks (weeks 189–192, 213–216, 237–240, and 261–264) and at weeks 265 to 268 to assess long-term efficacy over OLTP years 4 to 5. Most patients had passed the week 189 to 192 data collection; thus, no efficacy data were collected or reported for that time point. This was a preplanned analysis following OLTP completion of data from all patients who entered the OLTP. Efficacy data were assessed for erenumab 70 mg up to OLTP year 1 and for erenumab 140 mg during years 4 to 5.

Patients

Men and women aged 18 to 60 years who successfully completed the DBTP [5] were eligible for this OLTP study. Eligibility criteria for enrollment in the parent study have been previously reported [5] In brief, key inclusion criteria for the DBTP included history of migraine (4–14 migraine days per month and <15 headache [migraine and nonmigraine] days per month) based on the International Classification of Headache Disorders Second Edition [11] for ≥12 months prior to screening. Treatment continuation in the OLTP had to be considered appropriate by the investigator.

Study outcomes

Efficacy endpoints included change in monthly migraine days (MMDs), change in monthly acute migraine-specific medication (AMSM) days in patients with baseline AMSM use, and change in health-related quality of life as measured by patient-reported outcomes. The Headache Impact Test (HIT-6) is a global measure assessing the previous month's headache severity and change in a patient's clinical status over a short period of time [12,13] The within-person minimally important difference (MID) for the HIT-6 is ≥5 points reduction [14] Migraine-Specific Quality-of-Life Questionnaire (MSQ) measures three dimensions: role function–restrictive (RFR), role function–preventive (RFP), and emotional function (EF), with higher scores indicating better quality of life [15,16] For within-group analyses, the MID is 5.0 for MSQ-RFR, 5.0–7.9 for MSQ-RFP, and 8.0–10.6 for MSQ-EF [17]. Migraine Disability Assessment (MIDAS) is a five-item self-administered questionnaire summing the number of productive days lost in the workplace and home over the past 3 months [18] The total score is

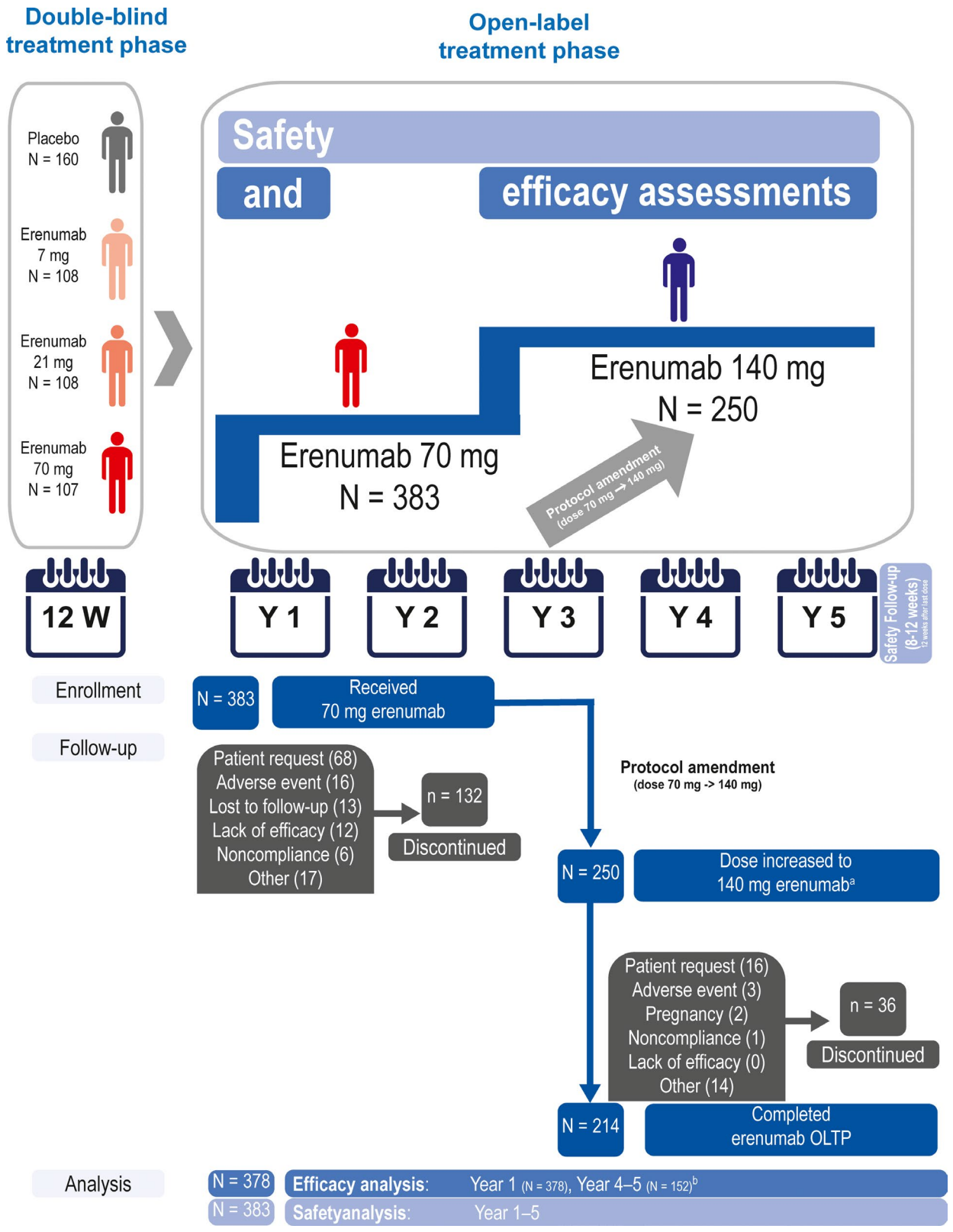

FIGURE 1 Study design and patient flow. Patients were treated with placebo, erenumab 7 mg, erenumab 21 mg, or erenumab 70 mg every 4 weeks during the 12-week double-blind treatment phase. All patient who entered the 5-year open-label treatment phase initially received erenumab 70 mg every 4 weeks. [a]The dosage was increased to 140 mg following a protocol amendment. [b]An additional protocol amendment reinstituted electronic diary data collection for efficacy assessments during years 4 to 5. For year 1, N = number of patients who entered the open-label treatment phase and had efficacy data available. For years 4 to 5, N = number of patients who received 140 mg erenumab during the open-label treatment phase and had efficacy data available. OLTP, open-label treatment phase.

the sum of absenteeism (missed days from paid work, housework, and nonwork activities due to headache) and presenteeism (days at paid work or housework where productivity was reduced by at least one-half) subdomain scores. Although no MID has been established for MIDAS, preliminary analyses based on an anchor of 25% change in monthly headache days estimated that a MIDAS total score decrease of 5 days per 3 months represents meaningful within-person change [19] HIT-6 data were collected every 4 weeks through week 64 and then every 12 weeks through week 268. MSQ data were collected every 4 weeks through week 64 and then at weeks 216, 240, 264, and 268. MIDAS data were collected every 12 weeks up to week 64 and then at weeks 216, 240, 264, and 268. Baseline for all efficacy measures was DBTP baseline.

Safety and tolerability were assessed by monitoring adverse events (AEs), vital signs including blood pressure/heart rate, and development of anti-erenumab antibodies. AEs were coded according to the Medical Dictionary for Regulatory Activities version 22.1 [20] Severity was graded using Common Terminology Criteria for Adverse Events version 4.03 [21] Dose level was classified based on the dose at which the AE occurred. Immunogenicity of erenumab was evaluated using an electrochemiluminescence-based bridging immunoassay for detection of binding anti-erenumab antibodies. For patients whose sera tested positive in the immunoassay, an in vitro biological assay was performed to detect neutralizing anti-erenumab antibodies.

Statistical considerations

All patients who received at least one dose of erenumab in the OLTP were included in the analysis. Descriptive summaries were provided. Data were reported as observed, without imputation for missing data. MMDs and monthly AMSM days were prorated to 28-day equivalents to handle missing daily diary data.

Adverse events were summarized as exposure-adjusted patient incidence rates (total number of patients reporting that event in a given follow-up time period divided by total patient-years of exposure in that period). Total patient-years of exposure was defined as the sum of the duration of exposure from first erenumab dose to the earliest of end-of-study date or first report of event across all patients during the OLTP. For context, exposure-adjusted patient incidence rates during the OLTP were compared with exposure-adjusted patient incidence rates obtained from pooled data from four double-blind treatment studies [2,3,5,6] Immunogenicity of erenumab was assessed for the entire study following first exposure to 70 mg or 140 mg erenumab in either the DBTP or OLTP.

Standard protocol approvals, registrations, and patient consents

Trial registered with ClinicalTrials.gov (NCT01952574). All procedures were approved by institutional review boards at all participating sites. Patients provided written informed consent.

RESULTS

Patients

The OLTP enrolled 383 patients (Figure 1). Demographics and disease characteristics at parent study baseline of these patients are presented in Table 1. After a median (Q1, Q3) of 104.0 (68.0, 116.0)

TABLE 1 Demographics and clinical characteristics at parent study baseline for patients who entered the open-label treatment phase[a]

	All patients (*N* = 383)
Age, years, mean (SD)	41.3 (10.9)
Sex, female, *n* (%)	303 (79)
Race, white, *n* (%)	354 (92)
Age at migraine onset, years, mean (SD)	20.9 (11.3)
Duration of disease, years, mean (SD)	20.9 (11.9)
History of migraine with aura, *n* (%)	137 (36)
Monthly migraine days, mean (SD)	8.7 (2.7)
Monthly headache days, mean (SD)	9.8 (2.7)
Acute migraine-specific medication users, *n* (%)	260 (68)
Acute monthly migraine-specific medication days,[b] mean (SD)	6.3 (2.8)
Prior prophylactic medication history, *n* (%)	
Naïve	214 (56)
Prior use	169 (44)
≥1 Treatment failure[c]	138 (36)
HIT-6, median score (Q1, Q3)	61.0 (56.0, 64.0)
MSQ, median score (Q1, Q3)	
MSQ-RFR	60.0 (48.6, 71.4)
MSQ-RFP	75.0 (65.0, 90.0)
MSQ-EF	73.3 (60.0, 86.7)
MIDAS, median score (Q1, Q3)	
Total score	22.0 (11.0, 38.0)
Absenteeism[d]	10.0 (5.0, 19.0)
Presenteeism[e]	10.0 (5.0, 19.0)

Abbreviations: EF, emotional function; HIT-6, Headache Impact Test-6; MIDAS, Migraine Disability Assessment; MSQ, Migraine-Specific Quality-of-Life Questionnaire; Q1, first quartile; Q3, third quartile; RFP, role function-preventive; RFR, role function-restrictive; SD, standard deviation.

[a]Baseline was prior to the parent study's double-blind phase.

[b]Acute migraine-specific medications were triptans and ergotamine derivatives. Data represent mean of migraine-specific medication users during the baseline period.

[c]Treatment failure included discontinuation due to lack of efficacy and/or side effects.

[d]Absenteeism indicates missed days, attributable to a headache, from paid work, housework, and nonwork activities.

[e]Presenteeism indicates days at paid work or housework in which productivity was reduced by at least half.

weeks exposure to 70 mg in the OLTP, the dosage in 250 patients remaining in the study was increased to 140 mg, with a median (Q1, Q3) of 140.7 (128.3, 151.7) weeks of exposure. Erenumab treatment was discontinued by 132 patients before the dose increase and by 36 patients while receiving 140 mg after the dose increase. Very few discontinuations were due to AEs or lack of efficacy; most were driven by patient request. Further details on the reasons for patient requests were not captured, such that additional information cannot be provided for these patients.

Efficacy outcomes

Migraine frequency and acute migraine-specific medication use

The significant reduction in MMDs and AMSM use days observed in the 70-mg group during the DBTP was sustained throughout the OLTP (Figure 2).

Mean (standard error [SE]) MMDs among patients enrolled in the OLTP was 8.7 (0.2) days at baseline (prior to double-blind treatment in the parent study). After switching from placebo or lower erenumab dosages (7 mg, 21 mg) to 70 mg at parent study week 12, MMDs reductions similar to those with 70 mg erenumab were observed at week 16, the first efficacy assessment time point of the OLTP (Figure 2a). MMDs reductions were maintained throughout the 5-year OLTP with a mean (SE) change from baseline in MMDs to the last 4-week period of the 5-year OLTP of −5.3 (0.3) days (Figure 2a), reflecting an average MMDs reduction from baseline of 62.3%. The proportion of patients with ≥50%/≥75%/100% reduction in MMDs were maintained throughout the 5-year OLTP with response rates of 71.0%/47.1%/35.5%, respectively, over the last 4-week period (Figure 2a and Figure S1).

Among patients using AMSM at baseline, mean (SE) baseline usage was 6.2 (0.2) treatment days. The reduction in AMSM use with 70 mg erenumab, or after switching from lower dosages or placebo, was maintained throughout the 5-year OLTP (Figure 2b). Mean (SE) change from baseline was −4.4 (0.3) days over the last 4-week period at week 268.

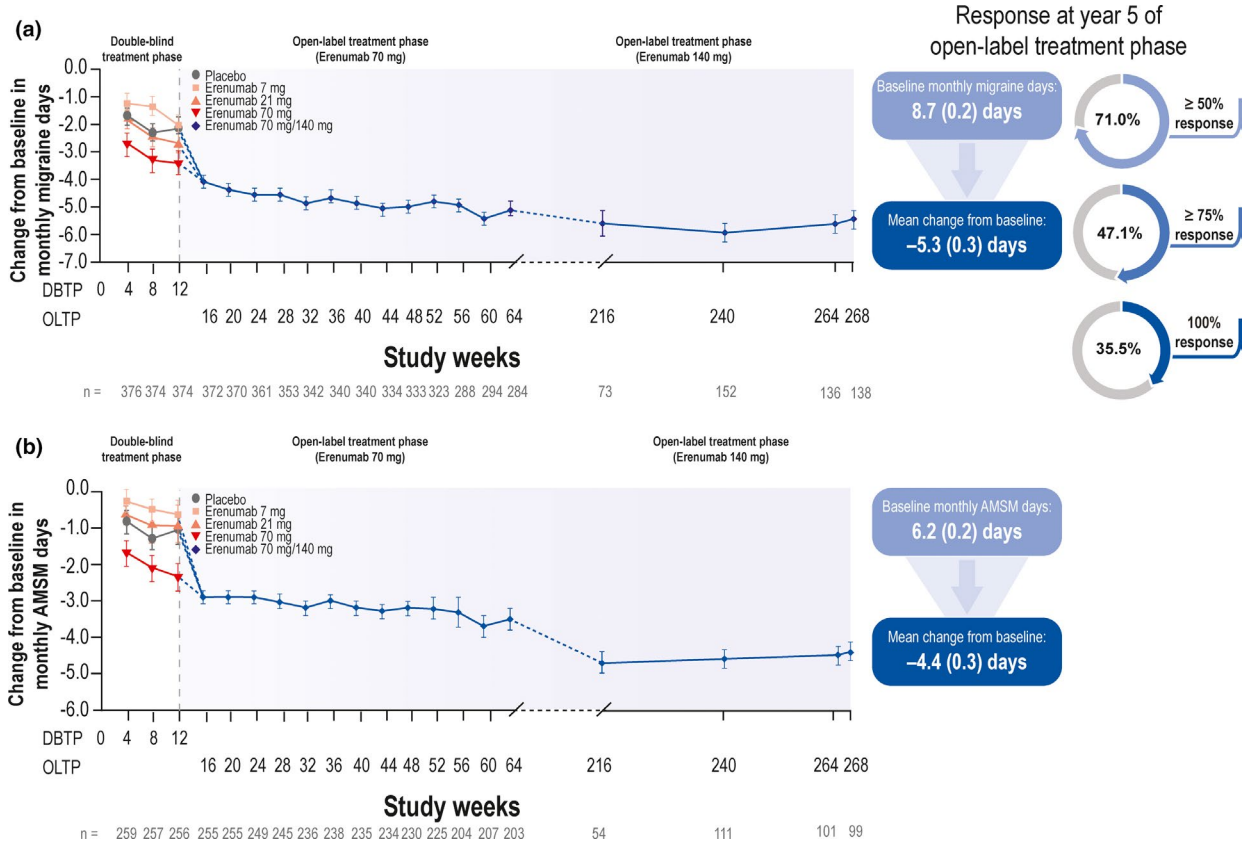

FIGURE 2 Efficacy over time. (a) Change from baseline in monthly migraine days. The mean change from baseline in MMDs is shown for patients enrolled in the parent double-blind study receiving placebo, erenumab 7 mg, erenumab 21 mg, erenumab 70 mg, and for patients receiving erenumab 70/140 mg in the open-label treatment phase. Error bars represent SE. Proportions of patients who achieved ≥50%, ≥75%, and 100% reduction from baseline in MMDs (≥50%, ≥75%, and 100% responses) over weeks 253 to 256 are shown. (b) Change from baseline in monthly AMSM days in patients with baseline monthly acute migraine-specific medication use. The mean change from baseline in monthly AMSM days is shown for patients in the parent double-blind study receiving placebo, erenumab 7 mg, erenumab 21 mg, and erenumab 70 mg, and for patients receiving erenumab 70/140 mg in the open-label treatment phase. Error bars represent SE. AMSM, acute migraine-specific medication; DBTP, double-blind treatment phase; MMDs, monthly migraine days; OLTP, open-label treatment phase; SE, standard error.

Patient-reported outcomes

At baseline, the mean (SE) HIT-6 total score was 60.2 (0.3), and at week 268 it improved to 49.4 (0.6) (Figure 3). Clinically relevant improvements in HIT-6 scores were maintained throughout the study, with 66% of patients achieving ≥5-point reduction (the within-person MID) in HIT-6 score at week 64 and 73% at week 268 (Figure 3). MSQ-RFR, MSQ-RFP, and MSQ-EF scores improved from baseline and were maintained through week 268 (Figure S2). Similarly, the MIDAS total score, presenteeism, and absenteeism improved from baseline and were maintained through week 268 (Figure S3). Reduction from baseline in MIDAS total score was >5 days, indicative of a clinically meaningful improvement [19]

Safety

Median (Q1, Q3) erenumab exposure among patients receiving ≥1 dose of open-label erenumab 70 mg or 140 mg (n = 383) was 255 (68, 256) weeks, for a total exposure of 1305.7 patient-years. Exposure-adjusted patient incidence rate of AEs was 123.0/100 patient-years (Table 2). The most frequent AEs were nasopharyngitis, upper respiratory tract infection, and influenza. Exposure-adjusted patient incidence rates in the OLTP were not increased compared with placebo or erenumab rates from the pooled double-blind placebo-controlled analysis. Eighteen patients (4.7%; 1.3/100 patients-years) reported AEs leading to treatment discontinuation (Table 3). None of the AEs leading to treatment discontinuation occurred in more than one patient except for rash and depression (each reported in two patients). Serious adverse events (SAEs) were reported by 49 patients (12.8%), with an exposure-adjusted incidence rate of 3.8/100 patient-years (Table S1). Exposure-adjusted patient incidence rates of SAEs in the OLTP were not increased compared with the placebo (6.3/100 patient-years) or erenumab rates (5.9/100 patient-years) from the DBTP pooled analysis. Generally, SAEs were isolated events without a clear treatment-related pattern. One SAE (ligament rupture) was reported by three patients, seven SAEs (osteoarthritis, uterine leiomyoma, adjustment disorder, syncope, appendicitis, deep vein thrombosis, and breast cancer) were reported by two patients. All other SAEs were single occurrence. Two deaths were reported, both assessed as unrelated to erenumab by the investigator. The fatal AE of arteriosclerosis (70 mg), reported as arteriosclerosis and hypertensive heart disease, was confounded by pre-existing cardiovascular risk factors and was previously reported [9] as a 54-year-old male with a history of migraine without aura, hypertension, and left anterior hemiblock with a family history of hypertension and heart attack (father died at the age of 39 years). He had received erenumab treatment for approximately 18 months at the time of death. This case was confounded by the presence of a combination of alcohol and cardiac stimulants (including an illicit one) in the setting of severe coronary arteriosclerosis found at autopsy. The other fatality (140 mg) was a 48-year-old male who died unattended with unclear cause of death after 5 years and 1 month of treatment with erenumab. The patient had a medical history of systemic lupus erythematosus. No additional information was provided, and an autopsy was not performed.

There were no new safety signals, increased incidence rates of AEs or SAEs, or AEs leading to treatment discontinuation over 5 years of exposure compared with that observed in the pooled DBTP data. There were no meaningful changes in mean systolic/diastolic blood pressure or heart rate through the end of study after safety follow-up. Mean systolic blood pressure was 118 mm Hg at baseline and 121 mm Hg at safety follow-up, and mean diastolic blood pressure was 75 mm Hg at baseline and 78 mm Hg at safety follow-up. Similar changes were seen in categorical assessment of blood pressure change from baseline.

Immunogenicity

The incidence of binding anti-erenumab antibodies was low, with only a small subset of patients having neutralizing antibodies (Table S2). The incidence of development of binding anti-erenumab antibodies during the entire study after the first erenumab dose of 70 mg or 140 mg was 9.8% (39 of 400; three of whom had in vitro

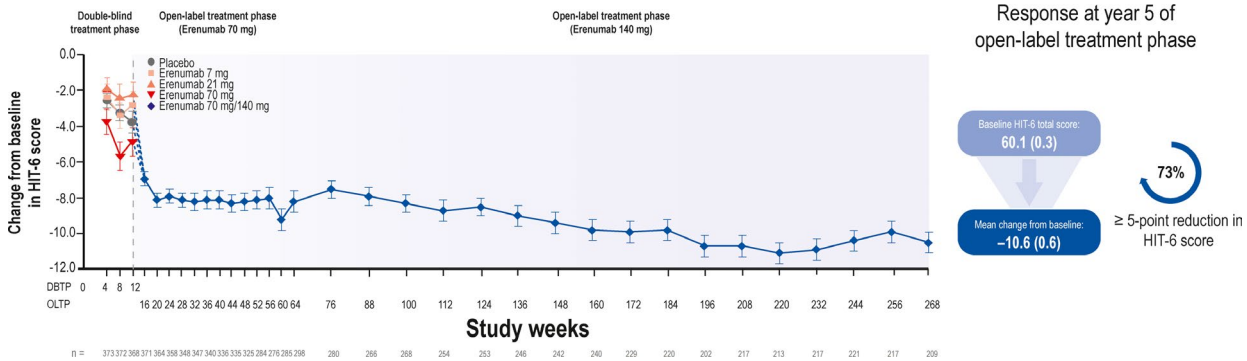

FIGURE 3 Change in headache impact over time. The mean change from baseline in HIT-6 total score is shown for patients on placebo, erenumab 7 mg, erenumab 21 mg, and erenumab 70 mg during the double-blind parent study and for all patients on erenumab 70/140 mg during the OLTP. Error bars represent SE. The proportions of patients who achieved ≥5-point reduction in HIT-6 score over weeks 253 to 256 is shown. DBTP, double-blind treatment phase; HIT-6, Headache Impact Test; OLTP, open-label treatment phase; SE, standard error.

TABLE 2 Exposure-adjusted patient incidence rates of adverse event (per 100 patient-years)

	Double-blind treatment phase pooled data from four studies				Open-label treatment phase of current study		
		Erenumab			Erenumab		
	Placebo, *N* = 1043, *n* [*r*]	70 mg, *N* = 893, *n* [*r*]	140 mg, *N* = 507, *n* [*r*]	Total, *N* = 1,400, *n* [*r*]	70 mg, *N* = 383, *n* [*r*]	140 mg, *N*= 250, *n* [*r*]	Total, *N* = 383 *n* [*r*]
All AEs	551 [280.2]	460 [261.2]	267 [230.5]	727 [249.0]	323 [142.0]	216 [109.9]	340 [123.0]
Grade ≥2	321 [126.5]	252 [108.7]	153 [100.4]	405 [105.4]	249 [68.7]	180 [57.7]	286 [59.3]
Grade ≥3	40 [12.8]	36 [12.9]	22 [11.7]	58 [12.4]	55 [8.8]	40 [6.4]	83 [7.1]
Serious AEs	20 [6.3]	18 [6.4]	10 [5.2]	28 [5.9]	30 [4.5]	25 [3.8]	49 [3.8]
AEs leading to discontinuation of investigational product	13 [4.1]	15 [5.3]	12 [6.3]	27 [5.7]	16 [2.3]	2 [0.3]	18 [1.3]
Fatal AEs	0 [0.0]	0 [0.0]	0 [0.0]	0 [0.0]	1 [0.1]	1 [0.1]	2 [0.1]
Nasopharyngitis[b]	77 [25.4]	61 [22.5]	42 [23.2]	103 [22.8]	82 [14.2]	59 [10.1]	111 [10.6]
Upper respiratory tract infection	40 [12.7]	46 [16.6]	21 [11.1]	67 [14.4]	52 [8.3]	53 [8.8]	78 [6.7]
Influenza	20 [6.3]	20 [7.1]	11 [5.8]	31 [6.6]	36 [5.5]	31 [4.8]	56 [4.6]

Abbreviations: AEs, adverse events; *n*, number of patients reporting at least 1 occurrence of event; *r*, exposure-adjusted subject incidence rate per 100 subject-years.

[a]Events with ≥5 patients per 100 patient-years in either erenumab 70 mg/140 mg group during the open-label treatment phase.

[b]Nasopharyngitis was coded as viral upper respiratory tract infection in Medical Dictionary for Regulatory Activities version 20.0 used for double-blind treatment phase pooled analysis.

neutralizing activity). Most anti-erenumab antibodies responses were transient; 76.9% (30/39) of patients who developed binding antibodies and 66.7% (2/3) of patients who developed neutralizing antibodies reverted to negative status by end of study, and the third patient withdrew from the study so subsequent neutralizing antibody status could not be determined. Among those with anti-erenumab antibody responses, most (35/39) occurred during the first year with the majority (23/39) during the first 6 months of treatment; three were observed during the second year, and the last case was observed in year 4 (Table S2). There was no evidence of an association between anti-erenumab antibodies and safety events.

DISCUSSION

Erenumab treatment resulted in long-term durable, clinical improvements including reduction in MMDs and AMSM use, and stable improvements in disability, headache impact, and migraine-specific quality of life. Reductions in MMDs were sustained throughout the OLTP, such that at the end of the 5-year OLTP patients experienced a 5.3-day (62.6% overall) reduction in MMDs compared to parent study baseline. Among patients originally receiving placebo or lower erenumab dosages (7 mg, 21 mg), reductions in MMDs were evident 4 weeks (the first OLTP assessment time point) after patients switched to 70 mg erenumab.

By decreasing migraine frequency, by even a few days, effective preventive treatment can reduce economic and social impacts of migraine resulting from impairments in normal day-to-day tasks or productive work with significant indirect costs (e.g., absenteeism and presenteeism). Furthermore, capturing the impact of migraine beyond simple counts of migraine days better represents the patient perspective. Erenumab led to sustained, significant improvements consistent across multiple measures of disability, headache impact, and migraine-specific quality of life, with treatment effects exceeding established clinically meaningful differences.

With longer-term exposure for more than 5 years, there was neither an increase over time in incidence rates of AEs nor an occurrence of new AEs. Safety and tolerability profiles during the OLTP (total exposure 1306.0 patient-years) were similar to those observed for erenumab 70 mg (total exposure 267.5 patient-years) and placebo (298.5 patient-years) in the pooled double-blind placebo-controlled analysis. Data from the current analysis suggest no new safety signals with erenumab therapy for more than 5 years in this patient population beyond the safety profile described in the existing product label. Exposure-adjusted patient incidence rates of AEs, SAEs, and AEs leading to treatment discontinuation were not increased with longer-term treatment, and there were no new events or apparent dose-dependency of observed events. Patient incidence rates during OLTP for AEs, SAEs, and AEs leading to treatment discontinuation were not increased compared with placebo across four pooled erenumab studies [22], where the safety and tolerability profile of erenumab was largely comparable to placebo, confirming previous data.

The trend and extent of blood pressure increase (2–3 mm Hg) over 5 years was similar to age-related blood pressure increases reported in the Framingham Heart Study [23,24] Increased blood pressure with age has been mostly associated with structural changes in arteries, especially with large artery stiffness [25]

TABLE 3 Adverse events during the open-label treatment phase leading to treatment discontinuation

	Erenumab		
	70 mg, *N* = 383, *n* [*r*]	**140 mg, *N* = 250, *n* [*r*]**	**Total, *N* = 383, *n* [*r*]**
All adverse events leading to treatment discontinuation	16 [2.3]	2 [0.3]	18 [1.3]
Rash	2 [0.3]	0 [0.0]	2 [0.1]
Depression	2 [0.3]	0 [0.0]	2 [0.1]
Asthma	1 [0.1]	0 [0.0]	1 [<0.1]
Pancreatic cyst	1 [0.1]	0 [0.0]	1 [<0.1]
Febrile convulsion	1 [0.1]	0 [0.0]	1 [<0.1]
Renin increased	0 [0.0]	1 [0.1]	1 [<0.1]
Breast cancer	1 [0.1]	0 [0.0]	1 [<0.1]
Suicide attempt	0 [0.0]	1 [0.1]	1 [<0.1]
Dyspnea exertional	1 [0.1]	0 [0.0]	1 [<0.1]
Edema peripheral	1 [0.1]	0 [0.0]	1 [<0.1]
Headache	1 [0.1]	0 [0.0]	1 [<0.1]
Primary biliary cholangitis	1 [0.1]	0 [0.0]	1 [<0.1]
Invasive lobular breast carcinoma	1 [0.1]	0 [0.0]	1 [<0.1]
Syncope	1 [0.1]	0 [0.0]	1 [<0.1]
Myocardial ischemia	1 [0.1]	0 [0.0]	1 [<0.1]
Influenza-like illness	1 [0.1]	0 [0.0]	1 [<0.1]
Lung adenocarcinoma stage III	1 [0.1]	0 [0.0]	1 [<0.1]

Abbreviations:: *n*, number of patients reporting at least one occurrence of event; *r*, exposure-adjusted incidence rate per 100 patient-years (*n*/e × 100).

Hypertension rates in this study were lower than those observed in placebo patients in the pooled, double-blind, placebo-controlled analysis (1.9 vs. 3.8/100 patient-years) [22] In the pooled, double-blind, placebo-controlled analysis, constipation was observed at higher rates than placebo [22] However, in the current analysis, constipation did not increase after the parent study, and overall rates were lower than those reported in the pooled, double-blind placebo-controlled analysis (1.8 vs. 7.0/100 patient-years). Furthermore, no patient discontinued due to constipation, indicating that resolution and/or conservative treatments successfully managed the constipation and allowed continued erenumab treatment, consistent with the observation that when constipation occurs, it is most often early after erenumab initiation and tends to dissipate over time [22]

Clinical consequences of immune responses to therapeutic protein products range from no effect to SAEs and/or interference with patient safety and therapy efficacy, making it important to assess new protein therapeutics for potential immunogenicity. Anti-erenumab antibodies incidence remained low, with very few neutralizing antibodies, and did not increase with longer exposure to erenumab. The majority of anti-erenumab antibodies developed within the first 6 months of treatment and were transient in nature.

Retention rates in long-term clinical trials provide an indication of long-term efficacy and tolerability of therapies and thus are of particular importance in chronic conditions. Patient retention rates at year 3 (62%) and completion rates of the 5-year OLTP (56% of all patients and 86% of those whose dosage was increased to 140 mg) highlight the favorable long-term tolerability profile of erenumab and patient satisfaction with treatment. The 5-year completion rates were impacted by patients who opted to discontinue treatment when the protocol amendment mandated a switch to a higher 140 mg dosage. Discontinuation rates due to AEs were low (5% over 5 years), in contrast to oral migraine preventives associated with high discontinuation rates [26-28] In comparison, in a much shorter 8-month OLTP of pivotal topiramate trials, 29% of participants entering the OLTP withdrew, with 42% of those withdrawing due to an AE [26]

Erenumab appeared effective and well tolerated for at least 5 years in patients with EM. This study is somewhat limited by the observed nature of the data, restricted to patients remaining in the study. Although these results suggest long-term positive clinical effects, the lack of a long-term placebo control group makes it difficult to interpret possible relatedness of an AE by distinguishing spontaneously occurring AEs from AEs due to erenumab. This can be mitigated somewhat by comparisons with DBTP exposure-adjusted patient incidence rates to provide some contextualization.

This analysis represents the longest-term efficacy and safety data of a CGRP pathway antibody to date. Overall, retention rates, efficacy, patient-reported outcomes, and safety results support the use of erenumab as a preventive treatment for patients with EM.

Ongoing comparative clinical studies and postmarketing surveillance will provide further information on the benefit–risk profile in real-world settings.

ACKNOWLEDGMENTS

The authors thank all patients, their families, and the investigators who participated in this trial. Medical writing and editorial assistance for this article was provided by Jon Nilsen, PhD (Amgen Inc.).

CONFLICT OF INTEREST

Messoud Ashina has received personal fees from Alder BioPharmaceuticals, Allergan, Amgen, Eli Lilly, Lundbeck, Novartis, and Teva Pharmaceuticals. He is currently a principal investigator on clinical trials for Allergan, Amgen, Eli Lilly, Lundbeck, and Novartis. Messoud Ashina has no ownership interest and does not own stocks of any pharmaceutical company. He also serves as an Associate Editor of *Cephalalgia*, Associate Editor of *Headache*, and Associate Editor of the *Journal of Headache and Pain*. Messoud Ashina reports research grants from Lundbeck Foundation, Novo Nordisk Foundation, and Novartis. Peter J. Goadsby reports consulting fees, speaking/teaching fees, and/or research grants from Alder BioPharmaceuticals, Allergan, Amgen, Autonomic Technologies, Celgene, Clexio, electroCore, Eli Lilly, eNeura, Epalex, Impel, Mundipharma, Journal Watch, Massachusetts Medical Society, *Medico-Legal Journal*, Novartis, Oxford University Press, Pfizer, Teva Pharmaceuticals, Trigemina, Inc., UpToDate, WL Gore, and Wolters Kluwer. Uwe Reuter reports consulting fees, speaking/teaching fees, and/or research grants from Allergan, Amgen, Autonomic Technologies, CoLucid, electroCore, Novartis, Pharm Allergan, Eli Lilly, and Teva Pharmaceuticals. Stephen Silberstein reports consultant and/or advisory panel member for and/or honoraria from Alder, Allergan, Amgen, Avanir, Dr. Reddy's, eNeura, electroCore Medical, Medscape, Medtronic, Mitsubishi Tanabe Pharma America, NINDS, Supernus, Trigemina, and Teva Pharmaceuticals. David W. Dodick reports the following conflicts within the past 12 months: Consulting: Aeon, Amgen, Clexio, Cerecin, Allergan, Alder, Biohaven, Linpharma, Promius, Eli Lilly, eNeura, Novartis, Impel, Theranica, WL Gore, Nocira, Xoc, Zosano, Upjohn (Division of Pfizer), Pieris, Revance, and Equinox. Honoraria: CME Outfitters, Curry Rockefeller Group, DeepBench, Global Access Meetings, KLJ Associates, Majallin LLC, MedLogix Communications, Miller Medical Communications, Southern Headache Society (MAHEC), WebMD Health/Medscape, Wolters Kluwer, Oxford University Press, and Cambridge University Press. Research Support: Department of Defense, National Institutes of Health, Henry Jackson Foundation, Sperling Foundation, American Migraine Foundation, and Patient-Centered Outcomes Research Institute (PCORI). Stock Options/Shareholder/Patents/Board of Directors: Aural Analytics (options), ExSano (options), Palion (options), Healint (options), Theranica (options), Second Opinion/Mobile Health (options), Epien (options/board), Nocira (options), Ontologics (options/board), King-Devick Technologies (options/board), Precon Health (options/board). Patent 17189376.1–1466:vTitle: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis. Fei Xue, Feng Zhang, Gabriel Paiva da Silva Lima, Sunfa Cheng, and Daniel D Mikol are employees of and stockholders in Amgen Inc.

AUTHOR CONTRIBUTIONS

Messoud Ashina: Investigation (equal); Resources (equal); writing–review and editing (equal). **Peter J. Goadsby:** Investigation (equal); resources (equal); writing–review and editing (equal). **Uwe Reuter:** Investigation (equal); resources (equal); writing–review and editing (equal). **Stephen Silberstein:** Investigation (equal); resources (equal); writing–review and editing (equal). **David W. Dodick:** Investigation (equal); resources (equal); writing–review and editing (equal). **Fei Xue:** Data curation (equal); validation (equal); writing–review and editing (equal). **Feng Zhang:** Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); validation (equal); writing–review and editing (equal). **Gabriel Paiva da Silva Lima:** Data curation (equal); validation (equal); writing-review and editing (equal). **Sunfa Cheng:** Conceptualization (equal); formal analysis (equal); methodology (equal); validation (equal); writing–review and editing (equal). **Daniel D Mikol:** Conceptualization (equal); methodology (equal); writing–review and editing (equal).

DATA AVAILABILITY STATEMENT

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

ORCID

Peter J. Goadsby https://orcid.org/0000-0003-3260-5904

REFERENCES

1. Dodick DW. CGRP ligand and receptor monoclonal antibodies for migraine prevention: evidence review and clinical implications. *Cephalalgia*. 2019;39(3):445-458.
2. Dodick DW, Ashina M, Brandes JL, et al. ARISE: a phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia*. 2018;38(6):1026-1037.
3. Goadsby PJ, Reuter U, Hallstrom Y, et al. A controlled trial of erenumab for episodic migraine. *N Engl J Med*. 2017;377(22):2123-2132.
4. 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(10161):2280-2287.
5. Sun H, Dodick DW, Silberstein S, et al. Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurol*. 2016;15(4):382-390.
6. 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(6):425-434.
7. Lipton RB, Tepper SJ, Reuter U, et al. Erenumab in chronic migraine: Patient-reported outcomes in a randomized double-blind study. *Neurology*. 2019;92(19):e2250-e2260.

8. Sakai F, Takeshima T, Tatsuoka Y, et al. A randomized phase 2 study of erenumab for the prevention of episodic migraine in Japanese adults. *Headache*. 2019;59(10):1731-1742.
9. Ashina M, Dodick D, Goadsby PJ, et al. Erenumab (AMG 334) in episodic migraine: interim analysis of an ongoing open-label study. *Neurology*. 2017;89(12):1237-1243.
10. Ashina M, Goadsby PJ, Reuter U, et al. Long-term safety and tolerability of erenumab: three-plus year results from a five-year open-label extension study in episodic migraine. *Cephalalgia*. 2019;39(11):1455-1464.
11. Headache Classification Subcommittee of The International Headache Society. The international classification of headache disorders (second edition). *Cephalalgia*. 2004;24(Suppl 1):1-151.
12. Dowson AJ. Assessing the impact of migraine. *Curr Med Res Opin*. 2001;17(4):298-309.
13. Kosinski M, Bayliss MS, Bjorner JB, et al. A six-item short-form survey for measuring headache impact: the HIT-6. *Qual Life Res*. 2003;12(8):963-974.
14. Yang M, Rendas-Baum R, Varon SF, Kosinski M. Validation of the headache impact test (HIT-6™) across episodic and chronic migraine. *Cephalalgia*. 2011;31(3):357-367.
15. Jhingran P, Davis SM, LaVange LM, Miller DW, Helms RWMSQ. Migraine-specific quality-of-life questionnaire. further investigation of the factor structure. *Pharmacoeconomics*. 1998;13(6):707-717.
16. Jhingran P, Osterhaus JT, Miller DW, Lee JT, Kirchdoerfer L. Development and validation of the migraine-specific quality of life questionnaire. *Headache*. 1998;38(4):295-302.
17. Cole JC, Lin P, Rupnow MFT. Minimal important differences in the migraine-specific quality of life questionnaire (MSQ) version. *Cephalalgia*. 2009;29(11):1180-1187.
18. Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the migraine disability assessment (MIDAS) questionnaire to assess headache-related disability. *Neurology*. 2001;56(6 Suppl 1):S20-28.
19. Lipton R, Desai P, Sapra S, Buse D, Fanning K, Reed M. *How much change in headache-related disability is clinically meaningful? Estimating minimally important difference (MID) or change in MIDAS using data from the AMPP Study [abstract]*. Boston, MA: American Headache Society Annual Meeting; 2017.
20. Maintenance and Support Services Organization (MSSO). Medical Dictionary for Regulatory Activities (MedDRA®) Introductory Guide MedDRA Version 22.1. A registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). Vol MSSO-DI-6003-221. 2019.
21. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03 ed. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. 2010. Accessed July 24, 2020.
22. Ashina M, Kudrow D, Reuter U, et al. Long-term tolerability and nonvascular safety of erenumab, a novel calcitonin gene-related peptide receptor antagonist for prevention of migraine: A pooled analysis of four placebo-controlled trials with long-term extensions. *Cephalalgia*. 2019;39(14):1798-1808.
23. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart Disease? The Framingham heart study. *Circulation*. 1999;100(4):354-360.
24. Franklin SS, Larson MG, Khan SA, et al. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham heart study. *Circulation*. 2001;103(9):1245-1249.
25. Pinto E. Blood pressure and ageing. *Postgrad Med J*. 2007;83(976):109-114.
26. Rapoport A, Mauskop A, Diener H-C, Schwalen S, Pfeil J. Long-term migraine prevention with topiramate: open-label extension of pivotal trials. *Headache*. 2006;46(7):1151-1160.
27. Blumenfeld AM, Bloudek LM, Becker WJ, et al. Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second international burden of migraine study (IBMS-II). *Headache*. 2013;53(4):644-655.
28. Silberstein SD, Neto W, Schmitt J, Jacobs D, MIGR-001 Study Group. Topiramate in migraine prevention: results of a large controlled trial. *Arch Neurol*. 2004;61(4):490-495.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Ashina M, Goadsby PJ, Reuter U, et al. Long-term efficacy and safety of erenumab in migraine prevention: Results from a 5-year, open-label treatment phase of a randomized clinical trial. *Eur J Neurol*. 2021;00:1–10. https://doi.org/10.1111/ene.14715