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# Efficacy and Safety of Erenumab in Adults With Medication Overuse Headache: Final Results From a Phase 4 Randomized Placebo-Controlled Study

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**Keywords:** calcitonin gene-related peptide | clinical trial | erenumab | headache disorders | migraine disorders | secondary

## ABSTRACT

**Background:** Erenumab-induced medication overuse headache (MOH) remission in participants with chronic migraine (CM) in a prospective, Phase 4, randomized, placebo-controlled trial with an open-label treatment period (OLTP). We present 1-year results from the combined double-blind treatment period (DBTP) and OLTP for the stratified nonopioid cohort.

**Methods:** Participants with CM-MOH were randomized 1:1:1 to subcutaneous 70 or 140 mg erenumab every 4 weeks (QM) or placebo for the initial 24 weeks (DBTP). Those successfully completing DBTP could continue the 28-week OLTP, maintaining the same erenumab dose received during DBTP or, if receiving placebo, randomly assigned 1:1 to erenumab 70 or 140 mg QM. OLTP endpoints were exploratory.

**Results:** Overall, 552 participants received erenumab (70 mg, $n = 274$; 140 mg, $n = 278$); 95.3% completed OLTP. One-year MOH relapse in participants who achieved MOH remission at DBTP Month 6 was 2.7% (3/111) and 2.4% (3/124) with erenumab 70 and 140 mg, respectively; absence of MOH at study end was observed in 69.0% (189/274) and 75.5% (210/278) of participants. Sustained MOH absence over 1 year was reported in 60.5% (107/177) and 68.8% (119/173) of participants, respectively. Sustained improvements in measures of headache days, medication days, and function were observed in both groups. No new safety concerns were identified (grade ≥ 3, 35 [6.3%]; serious, 17 [3.1%]; adverse events leading to treatment discontinuation, 5 [0.9%]).

**Conclusions:** Erenumab was effective in inducing and sustaining MOH remission and improving function over 1 year. Treatment compliance remained high, with safety events consistent with erenumab's known safety profile.

**Trial Registration:** NCT03971071

## 1 | Introduction

Medication overuse headache (MOH) is recognized by the International Classification of Headache Disorders, Third Edition (ICHD-3), as a secondary, chronic headache disorder defined by sustained overuse of acute headache medication(s) with significant worsening of a preexisting headache or development of a chronic headache pattern (i.e., ≥15 headache days/month for more than 3 months) [1]. The most common approach to MOH management is participant education combined with withdrawal from the overused medication, initiation or optimization of preventive therapy, and limited use of alternate medication or bridge therapy [2]. However, underutilization of preventive treatments [3] and high rates of relapse within 1 year of withdrawal (25%–41%) remain important challenges that limit effective long-term management of MOH [4, 5]. Underutilization of preventive therapies for MOH is, in part, due to inappropriate migraine management and devaluation of the condition by participants and physicians [3, 6]. High rates of relapse may be the result of psychosocial factors. In a qualitative study, participants with frequent relapse, defined as requiring ≥2 withdrawals for MOH within 3 years, tended to have a pessimistic attitude, poor coping strategies, and lacked awareness of their condition [7]. Although data with older nonspecific migraine-preventive drugs (e.g., topiramate) are questionable, migraine-specific preventive treatments are proving to be effective even in participants with associated MOH [8].

Monoclonal antibodies (mAbs) targeting the calcitonin gene related peptide (CGRP) pathway have shown promising results in reversing medication overuse status in participants with CM, with one study specifically evaluating CM-MOH [9–12]. Erenumab demonstrated superiority over placebo in a prospective randomized controlled trial (primary analysis of NCT03971071), inducing MOH remission in participants with CM-MOH [12]. In nonopioid-treated participants, treatment with monthly erenumab 140 mg (odds ratio [95% CI], 2.01 [1.33, 3.05]; $p < 0.001$), but not erenumab 70 mg (1.37 [0.92, 2.05]; $p = 0.13$), yielded statistically significantly higher rates of MOH remission over a 24-week double-blind treatment period (DBTP) compared with placebo while observing low rates of treatment discontinuation. Reduction in acute headache medication days (AHMD) and sustained MOH remission were also greater with erenumab 140 mg versus placebo ($p < 0.001$), with adverse events (AEs) remaining consistent with the known safety profile of erenumab in CM.

Given the long-term challenges of managing CM-MOH, including the well-reported tendency of MOH relapse and poor compliance with different MOH treatments, the erenumab CM-MOH trial was designed to include an open-label treatment period (OLTP) in which additional analyses of MOH relapse and remission rates were conducted alongside measurements of the residual number of headache medication days. Here, we present 1-year results from the combined DBTP and OLTP of the erenumab CM-MOH trial.

## 2 | Methods

### 2.1 | Study Design and Procedures

This global Phase 4, randomized, double-blind, parallel-group, placebo-controlled trial evaluated the efficacy and safety of erenumab in adults with CM and a concomitant diagnosis of MOH (per ICHD-3 criteria) who had a history of at least 1 preventive treatment failure. Key definitions are provided in Table S1. The study protocol and all amendments, the informed consent form, and any accompanying materials provided to participants were reviewed and approved by an institutional review board or independent ethics committee at each study center. This study was registered at ClinicalTrials.gov (NCT03971071) and was conducted in accordance with International Council for Harmonization Good Clinical Practice regulations and guidelines. All participants provided written informed consent before study participation.

Eligible participants were enrolled and randomized in a 1:1:1 ratio to receive either erenumab (70 mg or 140 mg) or matching placebo in a double-blind manner (Figure 1). Participants were stratified into nonopioid-treated and opioid-treated cohorts based on their opioid medication use profile at baseline (≤4 vs. >4 days per month). Erenumab (70 mg or 140 mg) or placebo was administered subcutaneously every 4 weeks (QM) for the first 24 weeks. Participants who successfully completed the 24-week DBTP of the study were offered an opportunity to continue in the 28-week OLTP. In the OLTP, participants who received erenumab during the DBTP continued to receive the same dose of erenumab, and those who received placebo were allocated 1:1 to receive erenumab 70 or 140 mg QM. Follow-up clinic visits were conducted at the start of OLTP (Week 24) and Weeks 28, 40, and 52; follow-up via telephone was conducted in Weeks 32, 36, 44, and 48. Adverse events were monitored throughout the OLTP, and physical examination and vital signs were assessed at Weeks 24, 40, and 52.

Results of the primary analysis (all randomized participants in the nonopioid-treated cohort who completed the Week 24 or early termination assessments for the DBTP) were previously reported [12]. Here, we provide the results of the final analysis for all nonopioid-treated participants who completed the Week 52 or end-of-study visit of the OLTP. Results from the opioid-treated cohort were analyzed separately as an exploratory cohort, and these data will be presented in a separate report.

### 2.2 | Participants

Eligibility and exclusion criteria were previously reported [12]. In brief, participants' eligibility was assessed during an initial 3-week screening period followed by a subsequent baseline period. Key inclusion criteria at screening were age ≥18 years; history of migraine without or with aura and MOH, according to the ICHD-3 classification, for ≥12 months at screening; history of CM for ≥6 months before screening; current diagnosis of MOH; and history of treatment failure with at least one preventive treatment. Key inclusion criteria at baseline were ≥14 headache days during a 28-day baseline period, ≥8 migraine days, and observation of a pattern of migraine medication intake consistent with medication overuse (defined in Table S1).

### 2.3 | Outcomes and Statistical Analysis

Endpoints in the OLTP were exploratory and are summarized in Table 1. Data regarding AEs were collected throughout the study.

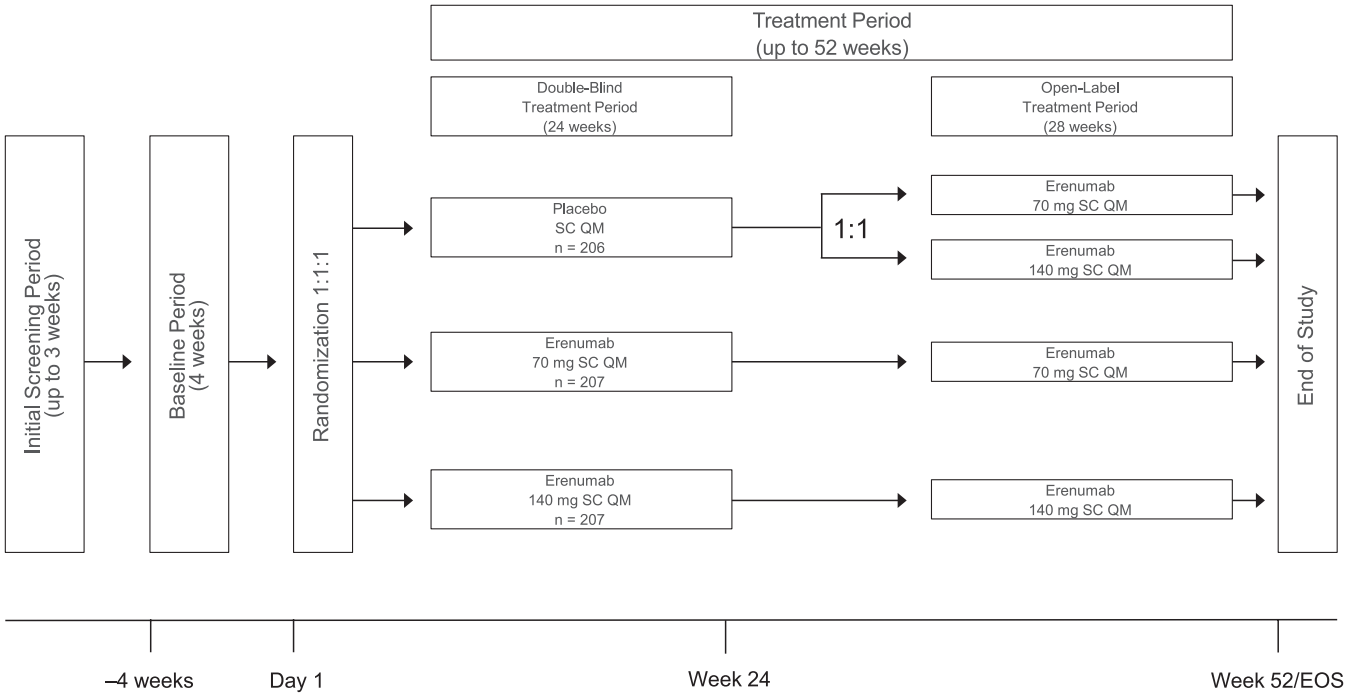


**FIGURE 1** | Study schema. Randomization was performed using interactive response technology. Randomization was stratified by concomitant treatment with an oral preventive (yes or no) in the nonopioid-treated cohort. During the DBTP, treatment assignment was blinded to all participants, site personnel, and sponsor. During the OLTP, all participants, personnel-in direct contact with sites, and investigators remained blinded to the initial dose level. Blinded individuals had no access to unblinded information until study completion. DBTP, double-blind treatment period; EOS, end of study; OLTP, open-label treatment period; QM, every 4 weeks; SC, subcutaneous.

Summary statistics were computed by treatment group and visit. For the OLTP, descriptive summaries for the efficacy endpoints were tabulated by visit based on observed data without imputation. No formal statistical hypothesis testing comparing treatment groups was performed in the efficacy or safety analyses. Exposure-adjusted participant incidence rates of all treatment-emergent AEs were tabulated by system organ class and preferred term.

## 3 | Results

### 3.1 | Participant Disposition

The study was conducted at 67 centers in North America, Europe, and Australia from October 7, 2019 (first participant enrolled) to June 13, 2023 (last participant completed the study), and included the span of the COVID-19 pandemic. Participant disposition is shown in Figure 2; 94.7% of participants ($n = 587$) continued in the OLTP (nonopioid-treated cohort, $n = 552$; opioid-treated cohort, $n = 35$). Of the 552 participants in the nonopioid-treated cohort who entered the OLTP, 274 received erenumab 70 mg and 278 received erenumab 140 mg. A total of 526 (95.3%) nonopioid-treated participants who entered the OLTP completed the trial for a total of 84.8% of participants who completed overall. Twenty-six participants (4.7%) discontinued erenumab during OLTP; reasons for discontinuation included participant request (19 [3.4%]), AEs (6 [1.1%]), and lost to follow-up (1 [0.2%]). Overall, 354 out of 369 (95.9%) participants in the nonopioid-treated cohort who were originally assigned to an erenumab treatment arm during DBTP continued the OLTP and successfully completed a full year of erenumab treatment.

Baseline demographics and disease characteristics were balanced across treatment groups (Table 2). In this trial, the mean (SD) age of participants was 43.6 (12.1) years (median [range], 44.0 [18–82] years); 82.6% were women, 91.7% were White, and 95.1% were not Hispanic/Latino. At baseline, overuse of acute headache medication treatment was reported for 544 (98.6%) participants.

### 3.2 | Efficacy

Relapse of MOH was uncommon, and most participants treated with erenumab showed sustained absence of MOH over the entire study period (Table 3). Sustained improvements in measures of headache quantity and medication days, as well as the effect of headache on physical impairment and everyday activities, were observed in both erenumab dosing groups, with additional numerical improvements seen at Month 13 relative to Month 6 (Table 3). Mean (SD) baseline monthly AHMD for the erenumab 70-mg group was 18.92 (4.09) and by Week 52 (Month 13) had been reduced by 10.49 (6.53) days/month. For the erenumab 140-mg group, mean (SD) baseline monthly AHMD was 18.77 (4.33) days/month, and by Week 52 (Month 13) had been reduced by 11.66 (5.71) days/month. For MMD, mean (SD) baseline values were 19.10 (4.69) for the erenumab 70-mg group and 18.53 (4.54) for the erenumab 140-mg group. By Week 52 (Month 13), mean (SD) MMD had been reduced by 10.01 (6.80) and 11.49 (6.27) days, respectively. Mean (SD) baseline MHD with at least moderate pain intensity was 19.57

**TABLE 1** | Summary of exploratory endpoints in the OLTP.

| Endpoints |
|---|
| MOH relapse at Year 1, defined as both mean monthly AHMD ≥ 10 days over Months 11–13 (Weeks 41–52) AND mean MHD ≥ 14 days over Months 11–13 (Weeks 41–52) in participant who achieved MOH remission at Month 6 of the DBTP. This endpoint was analyzed among participants who were treated with erenumab throughout the entire study |
| Absence of MOH at end of study as defined by mean monthly AHMD < 10 days over Months 11–13 (Weeks 41–52) OR mean MHD < 14 days over Months 11–13 (Weeks 41–52) |
| Sustained absence of MOH over 1 year as defined by absence of MOH over the DBTP (Months 1–3 [Weeks 1–12], OR Months 4–6 [Weeks 13–24]) AND OLTP (Months 11–13 [Weeks 41–52]) |
| Change from baseline in mean AHMD, MMD, and MHD of at least moderate pain intensity at assessment time points |
| Change from Week 24 (OLTP baseline) in mean AHMD, MMD, and MHD of at least moderate pain intensity at assessment time points during OLTP |
| Change from baseline in monthly average impact on everyday activities score as measured by the MPFID at assessment time points |
| Change from Week 24 (OLTP baseline) in monthly average impact on everyday activities score as measured by the MPFID at assessment time points during OLTP |
| Change from baseline in monthly average physical impairment score as measured by the MPFID at assessment time points |
| Change from Week 24 (OLTP baseline) in monthly average physical impairment score as measured by the MPFID at assessment time points during OLTP |
| Change from baseline in HIT-6 total score at Week 52 |
| Change from Week 24 (OLTP baseline) in HIT-6 total score at Week 52 |
| Change from baseline in MFIQ domain scores and overall impact on usual activities global item score at Week 52 |
| Change from Week 24 (OLTP baseline) in MFIQ domain scores and overall impact on usual activities global item score at Week 52 |
| Change from baseline in MIDAS total score, absenteeism score, and presenteeism score at Week 52 |
| Change from Week 24 (OLTP baseline) in MIDAS total score, absenteeism score, and presenteeism score at Week 52 |
| Change from baseline in monthly opioid/opioid-containing medication days at assessment time points during DBTP. Opioid-treated cohort only (findings to be published elsewhere). |
| Change from baseline in mean monthly opioid/opioid-containing medication days over Months 4–6 (Weeks 13–24) of the DBTP. Opioid-treated cohort only (findings to be published elsewhere). |
| Change from baseline in monthly opioid/opioid-containing medication days at assessment time points during OLTP. Opioid-treated cohort only (findings to be published elsewhere) |
| Safety (adverse events) |

Abbreviations: AHMD, acute headache medication day; DBTP, double-blind treatment period; HIT-6, 6-item Headache Impact Test; MFIQ, Migraine Functional Impact Questionnaire; MHD, monthly headache days; MIDAS, Migraine Disability Assessment; MMD, monthly migraine days; MOH, medication overuse headache; MPFID, Migraine Physical Function Impact Diary; OLTP, open-label treatment period.

(4.72) days for the erenumab 70-mg group, and by Week 52 (Month 13) had been reduced by 10.55 (7.03) days. In the erenumab 140-mg group, mean (SD) baseline MHD with at least moderate pain intensity was 19.23 (4.59) days, and by Week 52 (Month 13) had been reduced by 12.04 (6.55) days. For MPFID, mean (SD) baseline values for the erenumab 70-mg and 140-mg groups were 32.27 (15.49) and 30.14 (14.22), respectively, for monthly everyday activities, and 30.08 (16.50) and 27.62 (15.74), respectively, for monthly average physical impairment score. At 1 year, mean (SD) changes were −16.88 (16.16) and −17.39 (16.37), respectively, for monthly everyday activities score and −14.18 (17.23) and −14.61 (16.92) for monthly average physical impairment score. For the HIT-6 total score, mean (SD) baseline was 64.50 (5.02) for erenumab 70 mg and 64.26 (4.61) for erenumab 140 mg; mean (SD) changes at 1 year were −8.40 (9.29) and −9.10 (8.60), respectively (Table 4).

Erenumab produced sustained improvements in migraine-related disability and productivity metrics, also with additional numerical improvements seen at Month 13 relative to Month 6 (Table 4). The mean (SD) change from baseline at Week 52 (Month 13) in the erenumab 70- and 140-mg groups on MFIQ domain scores was −26.68 (29.63) and −29.45 (28.65), respectively, for overall impact on usual activities; −25.59 (26.70) and −26.82 (26.16) for impact on physical function; −23.83 (25.81) and −25.92 (24.89) for impact on usual activities; −25.30 (28.95)

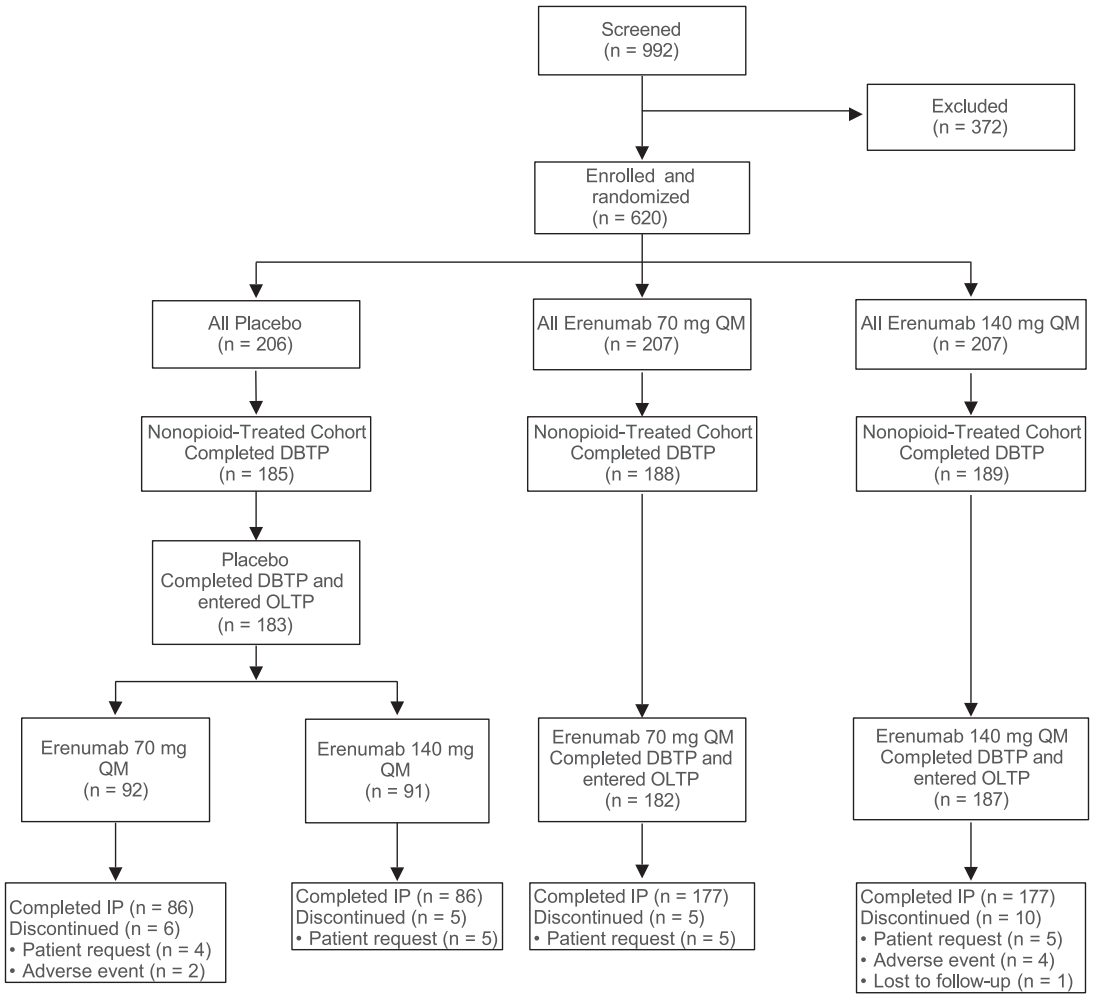


**FIGURE 2** | CONSORT diagram. DBTP, double-blind treatment period; IP, investigational product; OLTP, open-label treatment period; QM, every 4 weeks.

and −27.54 (26.79) for impact on social function; and −27.04 (29.40) and −29.19 (27.94) for impact on emotional function. The mean (SD) change from baseline at Month 13 in erenumab 70- and 140-mg groups was −40.4 (83.9) and −51.5 (70.7), respectively, for monthly MIDAS total score; −20.9 (49.3) and −24.3 (41.9) for MIDAS absenteeism score; and −19.5 (43.7) and −27.1 (37.3) for MIDAS presenteeism score.

### 3.3 | Safety

Of the 552 participants in the nonopioid-treated cohort, 515 (93.3%) received seven doses of erenumab during the OLTP. Median (range) duration of exposure to erenumab was 196 (1–224) days. Treatment-emergent AEs were reported in 340 (61.6%) participants, with an exposure-adjusted incidence rate per 100 participant-years of 200.9 (Table 5). Grade ≥3 AEs were reported in 35 (6.3%) participants, serious AEs in 17 (3.1%) participants, and AEs leading to discontinuation of erenumab in five participants (0.9%). AEs leading to discontinuation included upper abdominal pain, intestinal prolapse, drug hypersensitivity, migraine, and transient ischemic attack, occurring in one participant each. Treatment-related treatment-emergent drug hypersensitivity was reported in a participant who initially received placebo and was randomized to receive erenumab 70 mg in the OLTP, and a transient ischemic attack was reported in a participant who received erenumab 140 mg (this AE was considered serious). No fatal AEs were reported during the study.

Adverse events reported by ≥5% of participants were COVID-19 (12.0% [exposure-adjusted incidence rate per 100 participant-years, 23.9]), constipation (7.8% [15.6]), and nasopharyngitis (5.1% [9.8]; Table 6). Serious AEs included two cases (0.4% [0.7]) of COVID-19 pneumonia and one case (0.2% [0.3]) each of endometrial hyperplasia, hypertension, hypokalemia, migraine, ovarian cyst, periarthritis, sinusitis, transient ischemic attack, type 1 diabetes mellitus, uterine polyp, ventricular arrhythmia, appendicitis, breast cancer stage I, contusion, intestinal prolapse, sphincter of Oddi dysfunction, and vertigo. One case of grade ≥4 transient ischemic attack in the erenumab 140-mg group was deemed to be treatment related. The exposure-adjusted participant incidence rate of AEs of interest per 100 participant-years by preferred term was highest for COVID-19 (erenumab 70 mg, 20.1; erenumab 140 mg, 27.8) and constipation (erenumab 70 mg, 16.0; erenumab 140 mg, 15.2; Table S2).

**TABLE 2** | Demographics and key clinical characteristics at baseline for the nonopioid-treated cohort.

| | Erenumab 70 mg QM, OLTP | | | Erenumab 140 mg QM, OLTP | | | |
|---|---|---|---|---|---|---|---|
| | Placebo, DBTP ($n=92$) | 70 mg QM, DBTP ($n=182$) | All ($n=274$) | Placebo, DBTP ($n=91$) | 140 mg QM, DBTP ($n=187$) | All ($n=278$) | Total ($N=552$) |
| Age, mean (SD), y | 43.1 (11.9) | 43.2 (11.8) | 43.2 (11.8) | 45.9 (13.1) | 43.2 (11.9) | 44.1 (12.4) | 43.6 (12.1) |
| Female sex, *n* (%) | 75 (81.5) | 148 (81.3) | 223 (81.4) | 75 (82.4) | 158 (84.5) | 233 (83.8) | 456 (82.6) |
| BMI, mean (SD), kg/m$^2$ | 25.88 (5.66) | 25.40 (5.45) | 25.56 (5.52) | 25.00 (5.00) | 25.57 (4.92) | 25.38 (4.95) | 25.47 (5.23) |
| Monthly migraine days, mean (SD) | 18.82 (4.87) | 19.25 (4.60) | 19.10 (4.69) | 18.53 (4.35) | 18.52 (4.65) | 18.53 (4.54) | 18.81 (4.62) |
| Monthly headache days, mean (SD) | 21.33 (3.80) | 20.84 (3.93) | 21.00 (3.89) | 20.42 (3.96) | 20.72 (3.83) | 20.63 (3.87) | 20.81 (3.88) |
| Monthly headache days with at least moderate pain intensity, mean (SD) | 19.78 (4.64) | 19.46 (4.77) | 19.57 (4.72) | 19.06 (4.62) | 19.32 (4.59) | 19.23 (4.59) | 19.40 (4.65) |
| Acute headache medication use, mean (SD), days/month | 19.58 (4.23) | 18.58 (3.98) | 18.92 (4.09) | 18.25 (4.66) | 19.03 (4.15) | 18.77 (4.33) | 18.84 (4.21) |
| Overuse of acute headache medication, *n* (%) | 92 (100) | 182 (100) | 274 (100) | 87 (95.6) | 183 (97.9) | 270 (97.1) | 544 (98.6) |
| Overuse of triptans | 58 (63.0) | 127 (69.8) | 185 (67.5) | 64 (70.3) | 134 (71.7) | 198 (71.2) | 383 (69.4) |
| Overuse of combination therapies[a] | 15 (16.3) | 26 (14.3) | 41 (15.0) | 15 (16.5) | 29 (15.5) | 44 (15.8) | 85 (15.4) |
| Overuse of simple analgesics/ NSAIDs | 14 (15.2) | 14 (7.7) | 28 (10.2) | 5 (5.5) | 10 (5.3) | 15 (5.4) | 43 (7.8) |
| Overuse of combination analgesics | 6 (6.5) | 16 (8.8) | 22 (8.0) | 5 (5.5) | 15 (8.0) | 20 (7.2) | 42 (7.6) |

Abbreviations: BMI, body mass index; DBTP, double-blind treatment period; NSAIDs, non-steroidal anti-inflammatory drugs; OLTP, open-label treatment period; QM, every 4 weeks.
[a]Includes any combination of triptans, ergots, single analgesics, and combination analgesics that do not satisfy medication overuse criteria in any of the individual medication categories alone.

**TABLE 3** | Efficacy endpoints for the nonopioid-treated cohort.

| | Erenumab 70 mg QM, OLTP | | | Erenumab 140 mg QM, OLTP | | | |
|---|---|---|---|---|---|---|---|
| | Placebo, DBTP ($n=92$) | 70 mg QM, DBTP ($n=182$) | All ($n=274$) | Placebo, DBTP ($n=91$) | 140 mg QM, DBTP ($n=187$) | All ($n=278$) | Total ($N=552$) |
| Participants who achieved MOH remission at Month 6 of the DBTP[a] with MOH relapse at 1 year, *n* (%) | | 3/111 (2.7) | | | 3/124 (2.4) | | 6/235 (2.6) |
| Participants with absence of MOH at end of study, *n* (%) | 61 (66.3) | 128 (70.3) | 189 (69.0) | 70 (76.9) | 140 (74.9) | 210 (75.5) | 399 (72.3) |
| Participants with sustained absence of MOH, *n* (%) | | 107/177 (60.5) | | | 119/173 (68.8) | | 226/350 (64.6) |
| Change at Week 52 (Month 13), mean (SD) | | | | | | | |
| AHMD | | | | | | | |
| From baseline | −11.09 (6.37) | −10.21 (6.61) | −10.49 (6.53) | −11.11 (5.78) | −11.94 (5.67) | −11.66 (5.71) | −11.08 (6.16) |
| From Week 24 (OLTP baseline) | −3.36 (4.51) | −1.81 (4.96) | −2.31 (4.87) | −5.15 (5.22) | −2.45 (4.75) | −3.36 (5.06) | −2.83 (4.99) |
| MMD | | | | | | | |
| From baseline | −10.33 (6.82) | −9.87 (6.80) | −10.01 (6.80) | −11.48 (6.38) | −11.50 (6.38) | −11.49 (6.27) | −10.75 (6.57) |
| From Week 24 (OLTP baseline) | −3.49 (5.30) | −1.68 (4.87) | −2.26 (5.07) | −5.25 (5.43) | −2.36 (5.10) | −3.32 (5.38) | −2.79 (5.25) |
| MHD | | | | | | | |
| From baseline | −11.35 (7.03) | −10.17 (7.02) | −10.55 (7.03) | −12.23 (6.75) | −11.95 (6.46) | −12.04 (6.55) | −11.30 (6.83) |
| From Week 24 (OLTP baseline) | −3.24 (6.08) | −1.92 (5.36) | −2.34 (5.62) | −5.29 (5.86) | −2.35 (5.22) | −3.33 (5.61) | −2.84 (5.63) |

Abbreviations: AHMD, acute headache medication days; DBTP, double-blind treatment period; MHD, monthly headache days; MMD, monthly migraine day; MOH, medication overuse headache; OLTP, open-label treatment period; QM, every 4 weeks.

[a]Primary endpoint; composite that combined a requirement of mean monthly AHMD of < 10 days over Months 4, 5, and 6 or mean MHD of < 14 days over Months 4, 5, and 6.

**TABLE 4** | Mean (SD) change in disability and productivity endpoints at Week 52 (Month 13) for the nonopioid-treated cohort.

| | Erenumab 70 mg QM, OLTP | | | Erenumab 140 mg QM, OLTP | | | |
|---|---|---|---|---|---|---|---|
| | Placebo, DBTP ($n=92$) | 70 mg QM, DBTP ($n=182$) | All ($n=274$) | Placebo, DBTP ($n=91$) | 140 mg QM, DBTP ($n=187$) | All ($n=278$) | Total ($N=552$) |
| MPFID everyday activities score[a] | | | | | | | |
| From baseline | −16.71 (16.29) | −16.96 (16.14) | −16.88 (16.16) | −19.45 (16.39) | −16.35 (16.31) | −17.39 (16.37) | −17.14 (16.25) |
| From Week 24 (OLTP baseline) | −5.87 (10.83) | −1.24 (10.76) | −2.73 (10.97) | −6.97 (9.88) | −2.69 (9.52) | −4.13 (9.84) | −3.43 (10.43) |
| MPFID physical impairment score[a] | | | | | | | |
| From baseline | −13.09 (17.11) | −14.70 (17.31) | −14.18 (17.23) | −17.17 (16.52) | −13.32 (17.02) | −14.61 (16.92) | −14.40 (17.06) |
| From Week 24 (OLTP baseline) | −5.06 (11.46) | −1.03 (10.89) | −2.32 (11.21) | −7.17 (9.83) | −2.16 (8.85) | −3.84 (9.47) | −3.08 (10.39) |
| HIT-6 total score | | | | | | | |
| From baseline | −9.42 (9.64) | −7.91 (9.11) | −8.40 (9.29) | −8.92 (7.36) | −9.19 (9.15) | −9.10 (8.60) | −8.75 (8.95) |
| From Week 24 (OLTP baseline) | −4.07 (7.63) | −1.36 (5.91) | −2.25 (6.63) | −3.68 (6.95) | −0.12 (6.71) | −1.27 (6.98) | −1.77 (6.82) |
| MFIQ usual activities global item score[a] | | | | | | | |
| From baseline | −25.97 (32.30) | −27.02 (28.36) | −26.68 (29.63) | −32.67 (30.75) | −27.95 (27.58) | −29.45 (28.65) | −28.06 (29.15) |
| From Week 24 (OLTP baseline) | −14.81 (29.79) | −5.61 (25.95) | −8.64 (27.55) | −11.71 (27.40) | −3.03 (23.06) | −5.84 (24.83) | −7.24 (26.24) |
| Monthly MIDAS total score | | | | | | | |
| From baseline | −46.0 (72.0) | −37.8 (89.1) | −40.4 (83.9) | −62.2 (77.6) | −46.5 (67.0) | −51.5 (70.7) | −45.9 (77.7) |
| From Week 24 (OLTP baseline) | −22.3 (51.5) | −5.6 (67.1) | −11.1 (62.8) | −23.7 (74.0) | −5.4 (51.7) | −11.3 (60.3) | −11.2 (61.5) |

Abbreviations: DBTP, double-blind treatment period; HIT-6, headache impact test (6-item); MFIQ, Migraine Functional Impact Questionnaire; MIDAS, migraine disability assessment; MPFID, migraine physical function impact diary; OLTP, open-label treatment period; QM, every 4 weeks.
[a]Monthly average impact.

**TABLE 5** | Summary of exposure-adjusted participant incidence rates of treatment-emergent adverse events during the open-label treatment period for the nonopioid-treated cohort.

| | Erenumab 70 mg QM, OLTP | | | Erenumab 140 mg QM, OLTP | | | |
|---|---|---|---|---|---|---|---|
| **Treatment-emergent AEs, *n* (%)/*e* [*r*]** | **Placebo, DBTP (pt-y, 48.6) (*N* = 92)** | **70 mg QM, DBTP (pt-y, 97.8) (*N* = 182)** | **All (pt-y, 146.4) (*N* = 274)** | **Placebo, DBTP (pt-y, 48.3) (*N* = 91)** | **140 mg QM, DBTP (pt-y, 98.9) (*N* = 187)** | **All (pt-y, 147.2) (*N* = 278)** | **Total (pt-y, 293.6) (*N* = 552)** |
| All treatment-emergent AEs | 55 (59.8)/ 29.4 [186.9] | 113 (62.1)/ 56.2 [201.2] | 168 (61.3)/ 85.6 [196.3] | 53 (58.2)/ 29.4 [180.1] | 119 (63.6)/ 54.2 [219.6] | 172 (61.9)/ 83.6 [205.7] | 340 (61.6)/ 169.2 [200.9] |
| Grade ≥ 2 | 35 (38.0)/ 39.3 [89.0] | 74 (40.7)/ 71.6 [103.4] | 109 (39.8)/ 110.9 [98.3] | 36 (39.6)/ 37.6 [95.7] | 93 (49.7)/ 69.7 [133.5] | 129 (46.4)/ 107.3 [120.3] | 238 (43.1)/ 218.2 [109.1] |
| Grade ≥ 3 | 6 (6.5)/ 47.3 [12.7] | 7 (3.8)/ 95.2 [7.4] | 13 (4.7)/ 142.5 [9.1] | 4 (4.4)/ 46.9 [8.5] | 18 (9.6)/ 94.8 [19.0] | 22 (7.9)/ 141.7 [15.5] | 35 (6.3)/ 284.2 [12.3] |
| Grade ≥ 4 | 0 (0.0)/ 48.6 [0.0] | 0 (0.0)/ 97.8 [0.0] | 0 (0.0)/ 146.4 [0.0] | 0 (0.0)/ 48.3 [0.0] | 3 (1.6)/ 98.3 [3.1] | 3 (1.1)/ 146.6 [2.0] | 3 (0.5)/ 293.0 [1.0] |
| Fatal | 0 (0.0)/ 48.6 [0.0] | 0 (0.0)/ 97.8 [0.0] | 0 (0.0)/ 146.4 [0.0] | 0 (0.0)/ 48.3 [0.0] | 0 (0.0)/ 98.9 [0.0] | 0 (0.0)/ 147.2 [0.0] | 0 (0.0)/ 293.6 [0.0] |
| Serious | 3 (3.3)/ 48.2 [6.2] | 3 (1.6)/ 97.0 [3.1] | 6 (2.2)/ 145.2 [4.1] | 0 (0.0)/ 48.3 [0.0] | 11 (5.9)/ 96.3 [11.4] | 11 (4.0)/ 144.5 [7.6] | 17 (3.1)/ 289.7 [59] |
| Leading to discontinuation of investigational product | 2 (2.2)/ 48.4 [4.1] | 0 (0.0)/ 97.8 [0.0] | 2 (0.7)/ 146.2 [1.4] | 0 (0.0)/ 48.3 [0.0] | 3 (1.6)/ 98.3 [3.1] | 3 (1.1)/ 146.6 [2.0] | 5 (0.9)/ 292.7 [1.7] |

Abbreviations: AE, adverse event; DBTP, double-blind treatment period; *e*, sum across all participants, the total time at risk in OLTP in years (time at risk during OLTP is time from first dose of OLTP investigational product to onset of first event in OLTP or end of study); *n*, number of participants with observed data; *N*, number of participants in the analysis set; OLTP, open-label treatment period; pt-y, total participant-years of follow-up from first OLTP dose to end of study across all participants; QM, every 4 weeks; *r*, exposure-adjusted participant rate per 100 participant-years ($n/e \times 100$) %, $n/N \times 100$.

**TABLE 6** | Exposure-adjusted participant incidence rates of the most common treatment-emergent adverse events during the open-label treatment period for the nonopioid-treated cohort[a].

| | Erenumab 70 mg QM, OLTP | | | Erenumab 140 mg QM, OLTP | | | |
|---|---|---|---|---|---|---|---|
| **Treatment-emergent AEs, *n* (%)/*e* [*r*]** | **Placebo, DBTP (pt-y, 48.6) (*N* = 92)** | **70 mg QM, DBTP (pt-y, 97.8) (*N* = 182)** | **All (pt-y, 146.4) (*N* = 274)** | **Placebo, DBTP (pt-y, 48.3) (*N* = 91)** | **140 mg QM, DBTP (pt-y, 98.9) (*N* = 187)** | **All (pt-y, 147.2) (*N* = 278)** | **Total (pt-y, 293.6) (*N* = 552)** |
| COVID-19 | 7 (7.6)/ 47.0 [14.9] | 21 (11.5)/ 92.2 [22.8] | 28 (10.2)/ 139.2 [20.1] | 10 (11.0)/ 45.8 [21.9] | 28 (15.0)/ 90.7 [30.9] | 38 (13.7)/ 136.5 [27.8] | 66 (12.0)/ 275.6 [23.9] |
| Constipation | 13 (14.1)/ 43.0 [30.2] | 9 (4.9)/ 94.2 [9.6] | 22 (8.0)/ 137.2 [16.0] | 8 (8.8)/ 44.6 [17.9] | 13 (7.0)/ 93.1 [14.0] | 21 (7.6)/ 137.7 [15.2] | 43 (7.8)/ 274.9 [15.6] |
| Nasopharyngitis | 5 (5.4)/ 47.5 [10.5] | 10 (5.5)/ 95.5 [10.5] | 15 (5.5)/ 143.0 [10.5] | 1 (1.1)/ 48.1 [2.1] | 12 (6.4)/ 95.6 [12.6] | 13 (4.7)/ 143.7 [9.0] | 28 (5.1)/ 286.8 [9.8] |
| Injection site erythema | 5 (5.4)/ 46.7 [10.7] | 7 (3.8)/ 94.6 [7.4] | 12 (4.4)/ 141.3 [8.5] | 4 (4.4)/ 46.4 [8.6] | 5 (2.7)/ 96.9 [5.2] | 9 (3.2)/ 143.3 [6.3] | 21 (3.8)/ 284.7 [7.4] |
| Back pain | 2 (2.2)/ 48.2 [4.2] | 5 (2.7)/ 96.1 [5.2] | 7 (2.6)/ 144.3 [4.9] | 5 (5.5)/ 46.6 [10.7] | 5 (2.7)/ 97.4 [5.1] | 10 (3.6)/ 144.0 [6.9] | 17 (3.1)/ 288.3 [5.9] |
| URTI | 2 (2.2)/ 47.9 [4.2] | 2 (1.1)/ 97.0 [2.1] | 4 (1.5)/ 144.9 [2.8] | 5 (5.5)/ 46.9 [10.7] | 6 (3.2)/ 96.5 [6.2] | 11 (4.0)/ 143.4 [7.7] | 15 (2.7)/ 288.3 [5.2] |
| Injection site pain | 3 (3.3)/ 47.6 [6.3] | 4 (2.2)/ 96.6 [4.1] | 7 (2.6)/ 144.3 [4.9] | 1 (1.1)/ 48.0 [2.1] | 6 (3.2)/ 96.5 [6.2] | 7 (2.5)/ 144.5 [4.8] | 14 (2.5)/ 288.8 [4.8] |
| Influenza | 2 (2.2)/ 48.3 [4.1] | 5 (2.7)/ 96.3 [5.2] | 7 (2.6)/ 144.5 [4.8] | 1 (1.1)/ 48.0 [2.1] | 6 (3.2)/ 97.1 [6.2] | 7 (2.5)/ 145.1 [4.8] | 14 (2.5)/ 289.6 [4.8] |
| Migraine | 0 (0.0)/ 48.6 [0.0] | 5 (2.7)/ 95.7 [5.2] | 5 (1.8)/ 144.4 [3.5] | 1 (1.1)/ 48.0 [2.1] | 6 (3.2)/ 97.6 [6.2] | 7 (2.5)/ 145.5 [4.8] | 12 (2.2)/ 289.9 [4.1] |
| Injection site pruritus | 1 (1.1)/ 48.1 [2.1] | 1 (0.5)/ 97.3 [1.0] | 2 (0.7)/ 145.4 [1.4] | 0 (0.0)/ 48.3 [0.0] | 6 (3.2)/ 97.1 [6.2] | 6 (2.2)/ 145.3 [4.1] | 8 (1.4)/ 290.7 [2.8] |
| Urinary tract infection | 3 (3.3)/ 47.8 [6.3] | 3 (1.6)/ 96.9 [3.1] | 6 (2.2)/ 144.7 [4.1] | 1 (1.1)/ 47.8 [2.1] | 1 (0.5)/ 98.7 [1.0] | 2 (0.7)/ 146.6 [1.4] | 8 (1.4)/ 291.3 [2.7] |
| Fatigue | 0 (0.0)/ 48.6 [0.0] | 0 (0.0)/ 97.8 [0.0] | 0 (0.0)/ 146.4 [0.0] | 3 (3.3)/ 46.9 [6.4] | 2 (1.1)/ 98.2 [2.0] | 5 (1.8)/ 145.1 [3.4] | 5 (0.9)/ 291.5 [1.7] |
| Urticaria | 0 (0.0)/ 48.6 [0.0] | 0 (0.0)/ 97.8 [0.0] | 0 (0.0)/ 146.4 [0.0] | 3 (3.3)/ 47.9 [6.3] | 0 (0.0)/ 98.9 [0.0] | 3 (1.1)/ 146.8 [2.0] | 3 (0.5)/ 293.2 [1.0] |

Abbreviations: AE, adverse event; DBTP, double-blind treatment period; *e*, sum across all participants, the total time at risk in OLTP in years (time at risk during OLTP is time from first dose of OLTP investigational product to onset of first event in OLTP or end of study); *n*, number of participants with observed data; *N*, number of participants in the analysis set; OLTP, open-label treatment period; pt-y, total participant-years of follow-up from first OLTP dose to end of study across all participants; QM, every 4 weeks; *r*, exposure-adjusted participant rate per 100 participant-years ($n/e \times 100$) %, $n/N \times 100$; URTI, upper respiratory track infection.
[a]Treatment-emergent AE occurring in ≥ 3% of participants in any treatment group.

## 4 | Discussion

Study findings demonstrated that preventive treatment with erenumab in individuals with CM and MOH can yield and sustain MOH remission, reduce acute medication consumption, and improve function over a 1-year observation period while being well tolerated. Participants were not instructed on whether or how to initiate a wean from the medication causing MOH; rather, treatment with erenumab was the sole intervention.

MOH relapse at 1 year was uncommon, with only three participants in each dosage group relapsing (2.7% and 2.4% in the erenumab 70- and 140-mg groups, respectively). Most participants who completed the study achieved absence of MOH and showed sustained absence of MOH over the entire study period, with numeric increments in treatment response for the erenumab 140-mg group compared with the erenumab 70-mg group. Mean change from baseline at 1 year for all exploratory efficacy endpoints supports sustainability of treatment effects over time, with additional numeric improvements observed at 1 year compared with 6 months (end of DBTP) on all efficacy parameters. It is also important to note that, despite not having a required and structured approach to decrease acute medication intake, mean AHMD at Week 52 (Month 13) decreased by approximately 11 days from about 19 days at baseline. During the OLTP, erenumab treatment effect was consistent across participants who received either erenumab or placebo during their DBTP assignment. Moreover, our results are consistent with other long-term studies of erenumab [13, 14].

As expected, erenumab treatment of participants with CM-MOH was safe and well tolerated, with treatment discontinuation rates remaining low throughout the study. Exposure-adjusted participant incidence rate and the incidence of treatment-emergent and serious AEs per 100 participant-years were similar across treatment groups and were consistent with the overall safety profile of erenumab. Serious AEs were all single occurrences except COVID-19 pneumonia, which was reported in two participants; no fatal AEs were reported. The most frequent AEs of interest were COVID-19 and constipation. This trial was conducted throughout the COVID-19 pandemic, with SARS-CoV-2 infection and/or disease being a commonly reported AE during the study. Overall, no new safety concerns were identified from the final analysis, and the safety profile was consistent with those from previous studies of erenumab [13, 14].

The broader picture of long-term MOH treatment includes non-pharmacologic and pharmacologic approaches. Data available to evaluate the mid- to long-term effect of non-pharmacologic treatments for MOH, such as medication washout, show a wide range of remission rates and high relapse rates. In the large COMOESTAS study in 694 participants with MOH, the combination of wean and preventive treatment reduced headache by 58.5% and medication days/month by 70.0% [15]. However, only 70.9% of participants completed the study, and 6.5% of participants relapsed by the 6-month follow-up. Another study from the COMOESTAS group that evaluated participants with different types of primary headache disorders and MOH on a mandatory detoxification protocol with or without prophylactic association also observed similar challenges with participant attrition, with only 321 out of 376 (85.4%) participants being able to successfully complete detoxification protocols. Additionally, 64 participants were unable to complete the intended additional 6-month observation period, for an overall study non-completion rate of 31.7% [16]. Nonetheless, the study reported high remission rates, with 62.2% of the intent-to-treat population no longer meeting MOH criteria at Month 6% and 46.5% regressing from a chronic headache pattern to an episodic one. The reported relapse rate for the study was 8.9% among participants who completed the 6-month observation period.

In a systematic literature review of 27 studies investigating the therapeutic success of a medication pause or withdrawal for MOH, the completion rate varied from 39% to 93% [17]. Preventive medication was mostly given during participant discontinuation of acute medications or at discharge, and participants continued to use preventive medication at follow-up. From 2 to 6 months after medication discontinuation, remission rates ranged from 66% to 100% and relapse rates from 0% to 34%. Remission and relapse rates at 1 year were 57%–83% and 17%–43%, respectively; at 3 to 5 years, rates ranged from 58% to 66% and 34% to 45%. Overall, abrupt withdrawal of overused medications appears to more effectively reduce disability and improve quality of life than gradual withdrawal in participants with MOH. Although evidence for bridging therapies is low, adding preventive therapy to complete withdrawal may lead to better outcomes than discontinuation alone, and preventive therapy might be helpful in avoiding complete withdrawal [17]. In a 2020 study, participants with MOH were prospectively randomized to one of three different MOH strategies: withdrawal plus preventive treatment, preventive treatment without withdrawal, or withdrawal with optional preventive treatment given 2 months after withdrawal [18]. Although all three MOH strategies were effective, withdrawal therapy combined with preventive medication from the start of withdrawal was recommended as the preferred treatment for MOH management [18], which represented the standard prior to studying migraine-specific anti-CGRP therapies for MOH.

Four mAbs targeting CGRP (eptinezumab, fremanezumab, and galcanezumab) or its receptor (erenumab) have been approved for migraine prevention. Open-label extension studies have demonstrated the long-term efficacy and tolerability of erenumab (CM/episodic migraine [EM], up to 5 years) [13, 19, 20], eptinezumab (CM, 2 years) [21], fremanezumab (CM/EM, 1 year) [22], and galcanezumab (CM, 1 year) [23]. However, there are limited long-term data of mAbs targeting the CGRP pathway for CM-MOH. Most studies are limited to a three- to six-month follow-up, which is insufficient to properly assess persistence with treatment and long-term remission and relapse rates [24, 25]. One-year results from an open-label extension in 252 participants with CM-MOH receiving erenumab showed a reduction of 9.3 MMD compared with the parent study baseline; additionally, use of acute migraine-specific medication was reduced compared with the parent study baseline [13]. A post hoc analysis of up to 2 years' treatment with eptinezumab in 49 participants with CM-MOH showed a reduction in MHD and improvement in a number of participant-reported outcomes (MIDAS, HIT-6, Patient Global Impression of Change, and the 36-item Short-Form Survey) [26]. Long-term availability of relapse and remission rates from our study, as well as compliance rates, provide valuable clinical utility.

These data suggest that anti-CGRP pathway mAbs appear to have a better long-term outlook than non-pharmacologic therapy (i.e., medication pause/washout) when considering MOH relapse. The underlying mechanisms of action for CGRP pathway antagonism, therefore, are likely more fundamental to migraine pathophysiology than the variable neurotransmitter effects of the traditional, nonspecific migraine-preventive medications, which have modest and sometimes unpredictable effects in many migraine subtypes. Regarding the clinical basis for the effects observed in our study, it is possible that frequent recurrent migraine attacks may lead to neuroplastic brain changes and a greater effect on CGRP level effects, promoting further and more severe attacks. Medication overuse contributes to lowering the nociceptive threshold, expanding the receptive nociceptive field, and decreasing pain inhibitory control, thereby accelerating the chronification process [27]. An effective preventive therapy not only decreases the frequency of migraine attacks but also reduces migraine attack burden and intensity, requiring less acute medication to control attacks. The effect of anti-CGRP pathway mAbs is sustained, and the compliance rate is likely to be much better than with oral nonspecific preventives, with far fewer side effects and lower intake burden [28]. Therefore, it may be easier to maintain the efficacy of treatment and provide enough time to revert neuroplastic changes that promote central sensitization [29].

The clinical importance of reverting MOH with preventive treatment alone and in the absence of drug withdrawal should be highlighted, and evidence suggests the combination of limiting the overused medication combined with preventive treatment might not be the best strategy for participants [30]. This is especially salient in the primary care setting where the knowledge and limited time clinicians have for each participant means that drug withdrawal alone is neither practical nor in the participant's best interests, especially within the context of a high relapse rate and eventual use of preventive treatment. This issue is observed across the healthcare sector, including among headache specialists in highly specialized centers. Results from this study might translate into the development of practical recommendations for management of MOH in these participants by their primary care provider, where most receive their initial and sometimes only care.

Our study was strengthened by a relatively long follow-up period. Migraine is a long-term, sometimes lifelong, condition; however, migraine studies generally focus on short-term outcomes and limited follow-up periods. This is also the first prospective, placebo-controlled trial of an anti-CGRP pathway mAb in MOH with a 28-week OLTP that allowed assessment of long-term therapeutic benefit and rate of MOH relapse. A limitation of this study is that our trial was not designed to evaluate the safety and efficacy of erenumab outside of the context of migraine or in direct comparison with different modalities that have been postulated for CM-MOH. In addition, there was limited ethnic diversity in the trial.

Our study findings demonstrated that erenumab treatment achieved sustained MOH remission, reduced acute medication consumption, and improved function over a 12-month observation period. Erenumab treatment effect during the OLTP was consistent, regardless of whether participants received erenumab or placebo during the DBTP. Only three participants in each erenumab group (2.6% of participants overall) relapsed over the year study. AEs were consistent with the known safety profile of erenumab, and no new safety concerns were identified.

### Author Contributions

**Stewart J. Tepper** (co-lead): conceptualization, investigation, methodology, and writing – reviewing and editing. **David W. Dodick** (supporting): conceptualization, investigation, methodology, project administration, resources, and writing – reviewing and editing. **Michel Lanteri-Minet** (supporting): investigation and writing – reviewing and editing. **David Dolezil** (supporting): investigation, supervision, and writing – reviewing and editing. **Raquel Gil-Gouveia** (supporting): investigation, project administration, resources, supervision, and writing – reviewing and editing. **Christian Lucas** (supporting): investigation and writing – reviewing and editing. **Karolina Piasecka-Stryczynska** (supporting): investigation, supervision, and writing – reviewing and editing. **Gyöngyi Szabó** (supporting): investigation and writing – reviewing and editing. **Daniel D. Mikol** (supporting): conceptualization, investigation, methodology, supervision, and writing – reviewing and editing. **Mahan Chehrenama** (supporting): investigation, project administration, resources, and writing – reviewing and editing. **Denise E. Chou** (supporting): conceptualization, investigation, methodology, and writing – reviewing and editing. **Zilu Liu** (supporting): formal analysis (lead) and writing – reviewing and editing. **Gabriel Paiva da Silva Lima** (co-lead): conceptualization, formal analysis (supporting), funding acquisition, investigation, methodology, project administration, resources, supervision, writing – original draft preparation, and writing – reviewing and editing.


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### Conflicts of Interest

Stewart J. Tepper reports receiving research funding from AbbVie, Eon, Amgen, Annovis, Axsome, Cassava, Cognition, Eli Lilly, Inhibikase, Ipsen, Lundbeck, Merz, Neurolief, Pfizer, PrecisionMed, Revance, Scilex, Suven, and UCB; honoraria for consultant and/or advisory boards from AbbVie, Eon, Alphasights, Amgen, Aruene/eNeura, Atheneum, Axsome Therapeutics, Becker Pharmaceutical Consulting, Catch Therapeutics, ClearView Healthcare Partners, Click Therapeutics, CoolTech, CRG, Decision Resources, Defined Health, DRG, DocDelta, Dr. Reddy's, Eli Lilly, ExpertConnect, FCB Health, Fenix, Gilmartin Capital, GLG, Guidepoint Global, Health Advances, Health Science Communications, HMP Communications, Impel, Initiator Pharma, Interactive Forums, IQVIA, Keyquest, Ki Health Partners, Krog and Partners, Lundbeck, M3 Global Research, Magellan Health, Magnolia Innovation, Miravo Healthcare, MJH Holdings, Neurofront Therapeutics, Neurolief, Nocira, Novartis, P Value Communications, Pain Insights, Palion Medical, Perfood, Pfizer, Pulmatrix, Putnam Associates, Rehaler, SAI MedPartners, Satsuma, Scilex, Slingshot Insights, Spherix Global Insights, Strategy Inc., Synapse Medical Communication, System Analytic, Taylor and Francis, Tegus, Teva, Theranica, Third Bridge, Tonix, Trinity Partners, Unity HA, Vial, and XOC; salary from Dartmouth-Hitchcock Medical Center, Thomas Jefferson University, and Ki Health Partners; has participated in speakers bureaus for AbbVie, Dr. Reddy's, Eli Lilly, Lundbeck, Pfizer, Scilex, Teva, and Tonix; and CME honoraria from American Academy of Neurology, American Headache Society, Annenberg Center for Health Sciences, Catamount Medical Education, Diamond Education Foundation, Forefront Collaborative, Haymarket Medical Education, HMP Global, Medical Education Speakers Network, Medical Learning Institute Peerview, Migraine Association of Ireland, Miller Medical Education, National Association for Continuing Education, North American Center for CME, Ohio State University, Physicians' Education Resource, PlatformQ Education, Primed, Vindico Medical Education, and WebMD/Medscape. David W. Dodick reports consulting for AbbVie, Amgen, Allergan, Atria, AYYA Biosciences, Biohaven, CapiThera Ltd., Cerecin, Ceruvia Lifesciences LLC, CoolTech, Ctrl M, Escient, Genentech, GlaxoSmithKline, Halion, Impel, Lundbeck, Lilly, Nocira, Novartis, Perfood, Pfizer, Praxis, Revance, Satsuma, Theranica, and WL Gore; honoraria from the American Academy of Neurology, Headache Cooperative of the Pacific, Headache Cooperative of New England, Canadian Headache Society, MF Med Ed Research, Biopharm Communications, CEA Group Holding Company (Clinical Education Alliance LLC), Teva (speaking), Amgen Japan (speaking), Eli Lilly Canada (speaking), Lundbeck (speaking), Pfizer (speaking), Vector Psychometric Group, Clinical Care Solutions, CME Outfitters, Curry Rockefeller Group, DeepBench, Global Access Meetings, KLJ Associates, Academy for Continued Healthcare Learning, Majallin LLC, Medlogix Communications, Medica Communications LLC, MJH Lifesciences, Miller Medical Communications, WebMD Health/Medscape, Wolters Kluwer, Oxford University Press, and Cambridge University Press; nonprofit board membership in American Brain Foundation, American Migraine Foundation, Arizona Brain Injury Alliance, Atria Health Collaborative, Atria Academy of Science and Medicine, CSF Leak Foundation, Domestic Violence HOPE Foundation/Panfila, Global Patient Advocacy Coalition, ONE Neurology, and Precon Health Foundation; research support from the American Migraine Foundation, Department of Defense, Henry Jackson Foundation, National Institutes of Health, Patient Centered Outcomes Research

Institute (PCORI), and Sperling Foundation; stock options/shareholder/board of directors with Atria Health (stock/employee), Aural analytics (stock), Axon Therapeutics (stock/board), AYYA Biosciences (stock), Cephalgia Group (stock/board), Ctrl M (stock), EigenLyfe (stock/board), Epien (stock), ExSano (stock), Keimon Medical (stock), King-Devick Technologies (stock/board), Man and Science, Healint (stock), Matterhorn (shares), Nocira (stock), Ontologics (shares), Palion (stock), Precon Health (stock/board), ScotiaLyfe (board), Second Opinion/Mobile Health (stock), and Theranica (stock); Patent 17189376.1–1466: Title: Onabotulinum Toxin Dosage Regimen for chronic migraine Prophylaxis (non-royalty bearing); has a patent application submitted: Synaquell (Precon Health). Michel Lanteri-Minet reports taking part in a study with Amgen and receiving personal fees from AbbVie, Eli Lilly, Grunenthal, Ipsen, Lundbeck, Medtronic, Orion Pharma, Per Food, Pfizer, Reckitt Benckiser, Salvia bio Electronics, Sanofi Aventis, Teva, and USPA. David Dolezil reports being a consultant or advisory board member for Allergan/AbbVie, Amgen, Eli Lilly, Lundbeck, Novartis, Organon, and Teva; and honoraria from Allergan/AbbVie, Amgen, Eli Lilly, Lundbeck, Novartis, Organon, and Teva. Raquel Gil-Gouveia reports honoraria for consulting and/or advisory boards from Allergan/Abbvie, AstraZeneca, Almirall, Bial, Biogen, Bristol-Myers Squibb, CMBE, FLOAT, Lilly, Lundbeck, Merck, Novartis, Novo Nordisk, Organon, Pfizer, Roche, Sanofi, Tecnifar, and Teva; research funding from Fundação Ciência Tecnologia (Project 29,675, MigN2Treat, 02/SAICT/2017); Learning-Health, Luz Saúde (LiON, Luz Innovation on Neurosciences); Novartis-Sociedade Portuguesa de Cefaleias; Bolsa – Projecto Centro de Investigação Interdisciplinar em Saúde, and UCP. Christian Lucas reports receiving personal fees from Allergan-AbbVie, Homeperf, Lilly, Lundbeck, Novartis, Teva, Orion, Pfizer; Past President of the French Headache Society. Karolina Piasecka-Stryczynska and Gyöngyi Szabó have no disclosures to report. Daniel D. Mikol is an employee and shareholder of Nervgen Pharma Corporation and a shareholder of Amgen stock. Mahan Chehrenama is an employee of Manistee Therapeutics. Denise E. Chou is an employee of Pfizer Inc. and a shareholder of Amgen and Pfizer stock. Zilu Liu and Gabriel Paiva da Silva Lima are employees of Amgen Inc. and own Amgen stock.

### Data Availability Statement

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

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## Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Tables S1–S2.**