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Efficacy and Safety of Erenumab for Nonopioid Medication Overuse Headache in Chronic Migraine
A Phase 4, Randomized, Placebo-Controlled Trial

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IMPORTANCE Patients with chronic migraine and medication overuse headaches (CM-MOH) represent a particularly burdened subpopulation. This trial provides first, to our knowledge, American Academy of Neurology class I evidence for a preventive therapy in CM-MOH.

OBJECTIVE To assess erenumab efficacy and safety in patients with nonopioid CM-MOH.

DESIGN, SETTINGS, AND PARTICIPANTS This randomized, double-blind, parallel-group, placebo-controlled trial took place at 67 centers in North America, Europe, and Australia from October 7, 2019, to November 2, 2022. This report reflects the primary analysis conducted in January 2023, using a database snapshot from December 1, 2022, which contains the complete dataset of the double-blind treatment period (DBTP). Participants included adults with CM-MOH who had 1 or more preventive treatment failure(s). There were 992 participants screened and 620 participants enrolled (584 in nonopioid cohort and 36 in opioid cohort)

INTERVENTIONS Erenumab, 70 mg, 140 mg, or placebo, once monthly for 24 weeks.

MAIN OUTCOMES AND MEASURES The primary end point was MOH remission at month 6. Secondary end points included change from baseline in mean monthly acute headache medication days (AHMD) at month 6 and sustained MOH remission throughout the DBTP. Safety end points were adverse events and changes in vital signs.

RESULTS The primary analysis population included 584 participants in the nonopioid-treated cohort with a mean age of 44 years and 482 participants were female (82.5%). Baseline demographics and disease characteristics were balanced across groups. At month 6, 134 participants in the erenumab, 140 mg group (69.1%) (odds ratio [OR], 2.01; 95% CI, 1.33-3.05; $P < .001$ vs placebo) and 117 in the erenumab, 70 mg group (60.3%) (OR, 1.37; 95% CI, 0.92-2.05; $P = .13$ vs placebo) achieved MOH remission vs 102 participants in the placebo group (52.6%). AHMD use was also reduced in the erenumab groups vs placebo. Least squares mean (standard error) change from baseline in average monthly AHMD was −9.4 (0.4) days in the erenumab, 140 mg group (difference from placebo, −2.7; 95% CI, −3.9 to −1.6; $P < .001$) and −7.8 (0.4) days in the erenumab, 70 mg group (difference from placebo, −1.2; 95% CI, −2.4 to −0.1; $P = .03$), vs −6.6 (0.4) days in the placebo group. MOH remission throughout the DBTP was sustained in 119 participants (61.3%,) 96 participants (49.5%), and 73 participants (37.6%) in the erenumab, 140 mg, 70 mg, and placebo groups, respectively. Adverse events were consistent with the known safety profile of erenumab. Treatment-emergent adverse events incidence in the combined erenumab group was 66.8% (259 participants; constipation 15.2% (59 participants) and COVID-19 13.9% (54 participants) were most common.

CONCLUSIONS AND RELEVANCE In this study, monthly, 140 mg, erenumab injections safely and effectively achieved MOH remission in patients with nonopioid CM-MOH within 6 months.

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Visual Abstract

Supplemental content

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Patients with migraine commonly overuse acute medications, including simple and combination analgesics, triptans, and opioids.[1-4] Medication overuse headache (MOH) is an International Classification of Headache Disorders (ICHD-3) recognized secondary headache disorder defined by sustained overuse of acute headache medication(s) with clinical observation of significant worsening of a preexisting headache or development of a new type of headache in association with the medication overuse.[5] According to the ICHD-3 criteria, MOH diagnosis is limited to patients with preexisting primary headache disorders who have developed a chronic headache pattern (ie, 15 or more headache days per month for more than 3 months) due to sustained medication overuse.

Prevalence estimates of MOH in an adult Western population have been reported to be 1% to 2%.[3] The most common presentation of MOH is in association with migraine. Chronic migraine (CM) associated with MOH (CM-MOH) has been linked to an increased risk of preventive treatment failure, stronger association with psychiatric comorbidities (eg, mood and/or substance-related disorders), increased migraine-related disability, higher levels of health care utilization, and overall decreased quality of life.[1-3] An analysis from The Medication Overuse Treatment Strategy trial including over 600 participants from 34 sites found that CM-MOH is associated with substantial negative consequences and that depression symptom severity had the strongest relationship with pain interference and headache impact.[6] In one observational study, patients with CM with high frequency medication use had significantly worse Headache Impact Test-6 (HIT-6) and Migraine Disability Assessment scores compared with patients with low-frequency medication use.[7] MOH is the most costly of the primary and secondary headache disorders. In the European Union (EU), the Eurolight project using survey data from 2008 to 2009 estimated that the total annual cost of MOH among adults aged 18 to 65 years amounted to €37 billion ($40.1 billion.)[8,9]

MOH management is predicated on a combination of educational, behavioral, and pharmacologic approaches with a historical emphasis on early withdrawal from the overused medication.[10] The emphasis on acute medication removal has been criticized for potentially stigmatizing patients, enhancing their suffering, and has been noted to be associated with high relapse rates over time.[3,11]

Erenumab-aooe, an anticalcitonin gene-related peptide (CGRP) receptor monoclonal antibody, was developed for the preventive treatment of migraine in adults and has demonstrated efficacy in reducing monthly migraine days.[12,13] A previous subgroup analysis of a pivotal CM trial revealed that participants who met thresholds for medication overuse at baseline experienced significant reduction of their monthly headache days (MHD) and were able to revert to a nonmedication overuse status more often than placebo-treated participants when treated with erenumab.[14] Subgroup analyses from large migraine studies with other CGRP pathway-targeting monoclonal antibodies further demonstrate that efficacy is maintained in participants with medication overuse.[15-18] A recent randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of eptinezumab to prevent migraine and headache in a primarily Asian patient population with the dual diagnosis of CM and MOH.[19] The primary efficacy end point was not met, as change from baseline in the number of mean monthly migraine days (MMDs) over weeks 1 to 12 was not statistically different between eptinezumab and placebo.

Based on the significant unmet medical need that MOH represents and limited knowledge of CGRP pathway inhibitor efficacy from randomized studies specifically in these patients, we sought to prospectively investigate the efficacy and safety of erenumab in a CM-MOH population. This study aimed a priori to examine the efficacy of a CGRP pathway inhibitor for MOH in CM. Key efficacy objectives of this study were to assess the ability of erenumab to induce and sustain MOH remission and reduce acute headache medication consumption. Evaluation of safety and tolerability was based on adverse events (AEs) and changes in vital signs. This analysis included the nonopioid-treated cohort only; patients with regular opioid use (ie, more than 4 days per month) were allowed to enroll in this study as a separate cohort, but will be analyzed separately and are not included in this article.

Key Points

Question Can erenumab induce remission of nonopioid medication overuse headache (MOH) in patients with chronic migraine?

Findings In this randomized clinical trial that included 584 participants in the main analysis cohort (nonopioid treated), 69.1% of participants in the erenumab, 140 mg group and 60.3% of the erenumab, 70 mg, group achieved MOH remission at month 6 compared with 52.6% of the placebo group. The statistical significance threshold was met for the erenumab, 140 mg, group vs placebo but not the 70 mg group; safety was consistent with prior studies.

Meaning In this study, monthly erenumab, 140 mg, was effective in inducing MOH remission in adults with chronic migraine and nonopioid MOH.

Methods

Study Design

This was a phase 4, randomized, double-blind, parallel-group, placebo-controlled study, evaluating the efficacy and safety of erenumab in adults (18 years or older) with CM with or without aura for at least 12 months who had a concomitant diagnosis of MOH per ICHD-3 criteria and had a history of at least 1 preventive treatment failure (NCT03971071). Compliance to study-specific guidelines was monitored through a comprehensive data monitoring plan that had been established prior to study start. Key compliance parameters were kept within prespecified quality threshold limits and no excess of protocol deviations had been observed in the trial. This trial also followed the 2018 International Headache Society guidelines for preventive trials in chronic migraine in adults. Participants in the nonopioid-treated cohort were randomized 1:1:1 to receive erenumab, 140 mg, erenumab, 70 mg, or placebo

subcutaneously once monthly for 24 weeks. No proactive acute medication withdrawal (detoxification) of overused medications was required or suggested as part of the study design. Participant education about the detrimental effects of MOH was provided following regional practices and investigator discretion. Eligible patients were stratified into nonopioid-treated cohort and opioid-treated cohort based on their opioid medication use profile at baseline (4 or less days per month vs more than 4 days per month). The study primary analysis was based on data from participants stratified into the nonopioid-treated cohort who were further stratified on the basis of their concomitant treatment with another preventive migraine medication during baseline. Per protocol, participants stratified to the opioid-treated cohort were part of an exploratory analysis and its results will be reported separately. The study protocol and all amendments, the informed consent form, and any accompanying materials provided to the participants were reviewed and approved by an institutional review board or independent ethics committee. All participants were required to sign and personally date the institutional review board/independent ethics committee–approved informed consent before any study-specific procedures were performed. The study design is summarized in eFigure 1 in Supplement 1 and key definitions used in this study are provided in eTable 1 in Supplement 1. Additional details are available in the study protocol and statistical analysis plan (eMethods in Supplement 1).

Participants

The study enrolled patients aged 18 or older and 65 years and younger with CM who had a history of 1 or more preventive treatment failure and were diagnosed with MOH. Further description of diagnosis and main criteria for eligibility is provided in the eMethods in Supplement 1 and full eligibility in the study protocol (Supplement 2).

End Points

The primary end point was absence of MOH at month 6 as defined by less than 10 mean monthly acute headache medication days (AHMD) over months 4, 5, and 6 or less than 14 days (in a 28-day study month) over months 4, 5, and 6 of the double blind treatment phase (DBTP) where AHMD included any electronic diary day in which an acute headache medication intake is reported. Per definition, a positive response was counted toward the primary end point if remission was achieved in either CM or excessive acute medication use. Safety end points included AEs and vital signs. Secondary end points included change from baseline in mean monthly AHMDs over months 4, 5, and 6 of the DBTP and sustained MOH remission during the DBTP, as defined by absence of MOH over months 1, 2, and 3 and over months 4, 5, and 6 of the DBTP. Patient-reported outcome secondary end points were evaluated separately by geographic region, change from baseline in mean monthly average physical impairment, and mean monthly average impact on everyday activities domain scores, as measured by the Migraine Physical Function Impact Diary (MPFID), over months 4, 5, and 6 of the DBTP was evaluated in the non-EU region and change from baseline in mean HIT-6 score over months 4, 5, and 6 of the DBTP was evaluated in the EU region. Change from baseline in MMDs was included as an exploratory end point. Primary and secondary end points are summarized in eTable 2 in Supplement 1.

Statistical Analysis

The sample size calculation was performed based on the primary end point (absence of MOH at month 6 [week 24]) for the nonopioid-treated cohort. Study sample size planning assumptions were based on findings from a subgroup analysis of participants for whom preventive migraine medication had failed, who overused acute headache medication, and who had at least 14 MHDs at baseline in the 12-week CM pivotal study or erenumab (Amgen study 20120295; 274 of 667 participants met MO criteria [41%]). In this subgroup analysis, 50 participants (33.1%), 46 participants (50.5%), and 66 participants (64.1%) in the placebo, erenumab 70 mg, and erenumab 140 mg treatment group, respectively, achieved absence of medication overuse at month 3.[20] Assuming a similar placebo and dose response pattern over months 4, 5, and 6, and considering a conservative dropout estimate of 20% during the 6-month DBTP, the planned sample size of 183 participants per group in the nonopioid-treated cohort would provide a nominal power of 85% for the 70 mg vs placebo comparison and more than 99% power for the 140 mg vs placebo comparison using a 2-sample χ^2 test with a 2-sided significance level of .05.

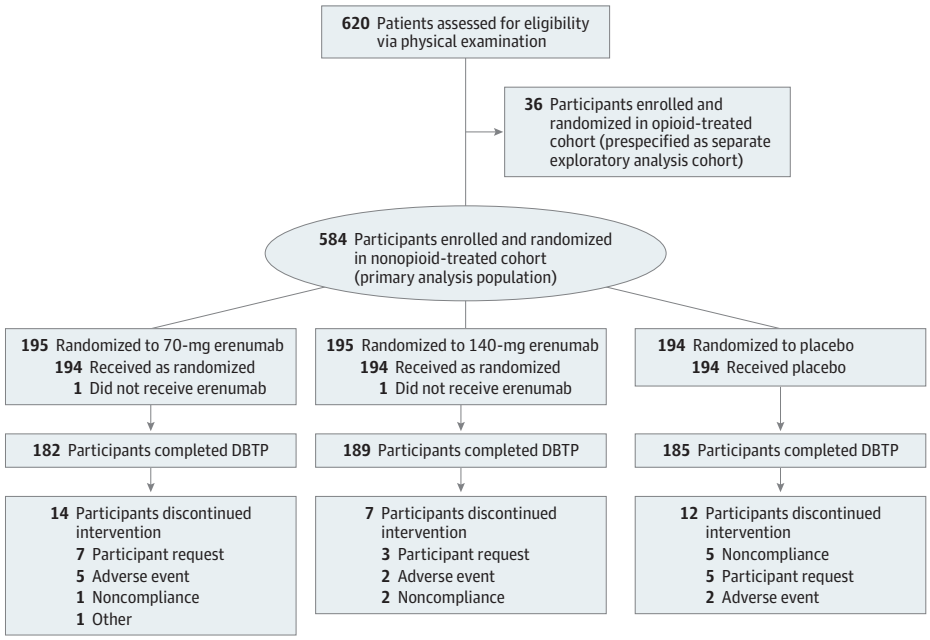
Each analysis set was defined separately for the nonopioid-treated cohort and the opioid-treated cohort. The full analysis set consisted of all participants who were randomized in the study. Efficacy analysis set for the binary efficacy end point during the DBTP was a subset of the full analysis set consisting of participants who received at least 1 dose of investigational product during the DBTP. The safety analysis set consisted of all randomized participants who received at least 1 dose of investigational product. Dichotomous end points were analyzed using the stratified Cochran-Mantel-Haenszel test with missing values imputed as nonresponse. Continuous end points were analyzed using a generalized linear mixed model including treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. Statistical significance was determined based on a prespecified hierarchical testing scheme controlling the multiplicity and was noted along with nominal *P* values (eFigure 2 in Supplement 1).

Results

Participant Disposition

The primary analysis study period was from October 7, 2019, to November 2, 2022. Participants were enrolled at 67 centers in North America, Europe, and Australia. The primary analysis population comprised 584 participants stratified in the nonopioid-treated cohort (**Figure 1**). Baseline demographics and disease characteristics were balanced across the treatment groups (**Table 1**). The mean age of participants was 44 years. There were 482 female participants (82.5%) and 102 male

Figure 1. CONSORT Diagram



DBTP indicates double-blind treatment period.

Table 1. Demographics and Key Clinical Characteristics at Baseline

Summary of baseline demographics and disease characteristics (nonopioid-treated cohort)	Placebo (n = 194)	Erenumab 70 mg/mo (n = 195)	Erenumab 140 mg/mo (n = 195)	Total (n = 584)
Age, mean, y (SD)	44.4 (12.6)	43.2 (11.8)	43.5 (12.0)	43.7 (12.1)
Sex, No. (%)				
Female	156 (80.4)	160 (82.1)	166 (85.1)	482 (82.5)
Male	38 (19.6)	35 (17.9)	29 (14.9)	102 (17.5)
Race,[a] No. (%)				
Black or African American	2 (1.0)	4 (2.1)	2 (1.0)	8 (1.4)
White	184 (94.8)	177 (90.8)	175 (89.7)	536 (91.8)
Other[b]	8 (4.1)	14 (7.2)	18 (9.2)	40 (6.8)
BMI,[c] mean (SD)	25.4 (5.3)	25.4 (5.4)	25.5 (4.9)	25.4 (5.2)
Monthly migraine days during baseline, mean (SD)	18.6 (4.6)	19.2 (4.6)	18.5 (4.6)	18.8 (4.6)
Monthly headache days during baseline, mean (SD)	20.8 (3.9)	20.8 (3.9)	20.7 (3.8)	20.8 (3.9)
Disease duration of chronic migraine, y, mean (SD)	11.8 (12.7)	11.4 (11.6)	12.4 (11.6)	11.9 (12.0)
Monthly acute headache medication use in days during baseline, mean (SD)	18.9 (4.4)	18.5 (4.0)	19.1 (4.2)	18.9 (4.2)
Prior migraine preventive medication at baseline, No. (%)	194 (100)	195 (100)	195 (100)	584 (100)
Number of prior migraine preventive treatment failures at baseline, No. (%)[d]				
1	69 (35.6)	57 (29.2)	62 (31.8)	188 (32.2)
2	62 (32.0)	54 (27.7)	65 (33.3)	181 (31.0)
≥2	125 (64.4)	137 (70.3)	133 (68.2)	395 (67.6)
≥3	63 (32.5)	83 (42.6)	68 (34.9)	214 (36.6)
Concomitant migraine preventive medication at baseline, No. (%)	55 (28.4)	50 (25.6)	53 (27.2)	158 (27.1)
Overuse of triptan during baseline, No. (%)	128 (66.0)	132 (67.7)	140 (71.8)	400 (68.5)
Overuse of simple analgesics/NSAIDs during baseline, No. (%)	19 (9.8)	18 (9.2)	12 (6.2)	49 (8.4)
Overuse of combination analgesics during baseline, No. (%)	12 (6.2)	17 (8.7)	16 (8.2)	45 (7.7)
Overuse of multiple drugs not individually overused during baseline, No. (%)	33 (17.0)	28 (14.4)	29 (14.9)	90 (15.4)

Abbreviations: BMI, body mass index; NSAIDS, nonsteroidal anti-inflammatory drugs.

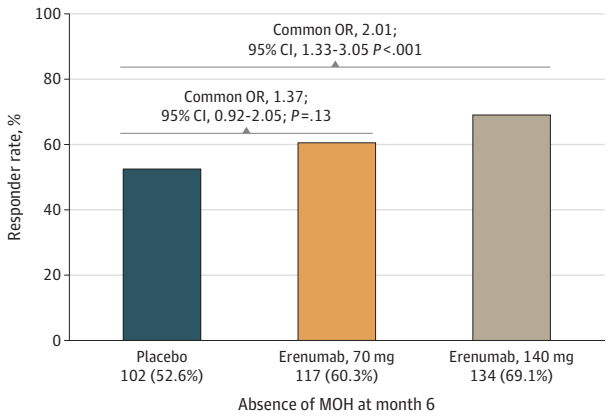
[a] Patients self-selected race and the electronic case report form allowed for selection of the following options: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, other.

[b] Other includes American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, and Other.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Medication reported by 1 participant was unknown and was not included in the number of treatment failures by category.

Figure 2. Absence of Medication Overuse Headache (MOH) at Month 6



Absence of MOH at month 6 was the primary end point of the study and was defined by mean monthly acute headache medication days (AHMD) less than 10 days over months 4, 5, and 6 or mean monthly headache days less than 14 days over months 4,5, and 6 of the double-blind treatment period where AHMD include any electronic diary day in which an acute headache medication intake is reported. Common odds ratio (OR) and *P* value are obtained from a Cochran-Mantel-Haenszel test, stratified by the stratification factor of concomitant oral migraine preventive treatment initiated before screening and taken during baseline (yes or no).

participants (17.5%). The number of participants with prior and concomitant migraine preventive medications are presented by medication category in eTable 3 in Supplement 1. At baseline, mean (SD) MHD were 20.8 (3.9) days and mean (SD) AHMD were 18.9 (4.2) days. The most commonly observed categories of medication overuse at baseline were 400 for triptan overuse (68.5%), 90 for overuse of multiple drugs not individually overused (15.4%), 49 for simple analgesics/nonsteroidal anti-inflammatory drugs overuse (8.4%), and 45 for combination analgesic overuse (7.7%) (Table 1).

Efficacy

Over months 4 through 6, 69.1% of participants in the erenumab, 140 mg group (odds ratio [OR], 2.01; 95% CI,1.33-3.05; *P* < .001 vs placebo) and 60.3% of the erenumab, 70 mg, group (OR, 1.37; 95% CI, 0.92, 2.05; *P*=0.13 vs placebo) achieved MOH remission compared with 52.6% of the placebo group (eTable 4 in Supplement 1; **Figure 2**). Reduction of AHMD and rates of sustained MOH remission were greater in the erenumab groups as compared with placebo. Starting from a baseline average monthly AHMD of 19.1 days in the erenumab, 140 mg, group, the least squares mean (LSM) estimate (SE) of change was -9.4 (0.4) days (difference from placebo, -2.7; 95% CI, -3.9 to -1.6; *P* < .001 [statistically significant]); baseline and change were 18.6 days and -7.8 (0.4) days (difference from placebo, -1.2; 95% CI, -2.4 to -0.1; *P* = .03), respectively, in the erenumab, 70 mg, group; baseline was 18.9 days in the placebo group with an LSM change (SE) of -6.6 (0.4) days (eTable 4 in Supplement 1; **Figure 3**A). MOH remission throughout the DBTP was sustained in 61.3% in the erenumab, 140 mg, group (OR, 2.63; 95% CI, 1.75-3.96; *P* < .001) and 49.5% in the erenumab, 70 mg, group (OR; 1.62; 95% CI, 1.08-2.43; *P* = .02), compared with 37.6% of participants in the placebo group (eTable 4 in Supplement 1; Figure 3B).

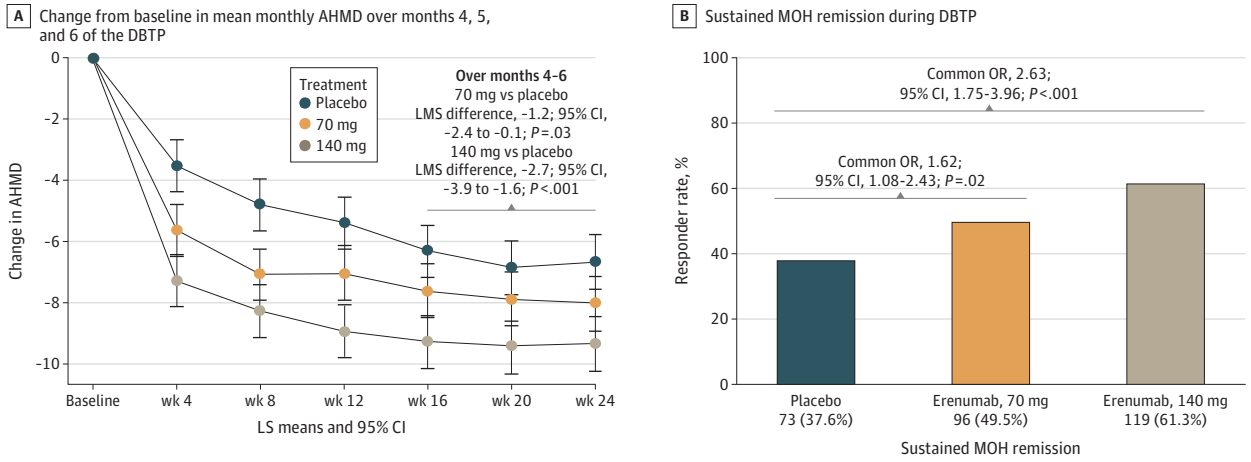
Changes from baseline in MPFID and HIT-6 during the DBTP were evaluated as secondary end points. The change from baseline in mean physical impairment average domain scores (SE) by MPFID was -10.6 (0.9) from a baseline of 27.6 for the 140-mg erenumab group (*P* = .08) and -11.8 (0.9) from a baseline of 31.3 for the 70-mg erenumab group (*P* = .01), compared with -8.5 (0.9) from a baseline of 27.6 in the placebo group; nominal *P* values are reported without multiplicity adjustment (eTable 5 in Supplement 1). The change from baseline in mean monthly average impact on everyday activities domain scores (SE) by MPFID was -13.3 (0.8) from a baseline of 29.9 for the 140-mg erenumab group (*P* = .04) and -13.5 (0.9) from a baseline of 33.1 for the erenumab, 70 mg,group (*P* = .03), compared with -10.9 (0.8) down from a baseline of 30.3 in the placebo group; nominal *P* values are reported without multiplicity adjustment (eTable 5 in Supplement 1). The LSM estimate (SE) of change from baseline in HIT-6 during DBTP was -8.8 (0.5) from a baseline of 64.2 for the erenumab, 140 mg, group (*P* < .001) and -6.2 (0.5) from a baseline of 64.8 for the erenumab, 70 mg, group (*P* = .09), compared with -5.0 (0.5) from a baseline of 64.2 in the placebo group; nominal *P* values are reported without multiplicity adjustment (eTable 6 in Supplement 1).

An ad hoc sensitivity analysis was performed with absence of MOH at month 6 being defined based on both mean monthly headache days less than 14 days and mean monthly acute headache medication days less than 10 days over months 4, 5, and 6 of the DBTP. According to this definition, 53.6% of participants in the erenumab, 140 mg, group (*P* < .001 vs placebo) and 45.9% of the erenumab, 70 mg, group (*P* = .06 vs placebo) achieved MOH remission compared with 36.6% of the placebo group (eTable 7 in Supplement 1). The study team also performed an ad hoc analysis of absence of medication overuse at month 6 based on AHMD medication days less than 10 days (eTable 8 in Supplement 1). Absence of medication overuse was achieved by 59.3% of participants in the erenumab, 140 mg, group (*P* < .001) and 49.0% of the erenumab, 70 mg, group (*P* = .08) compared with 40.2% of the placebo group.

Prespecified subgroup analyses were performed for absence of MOH at month 6 by concomitant migraine preventive treatment use and triptan overuse status at baseline. Results of these analyses are presented in the supplemental material (eTable 9 and 10 in Supplement 1).

MMD change over months 4 to 6 was evaluated as an exploratory end point in this study. LSM estimate of MMD change from baseline over months 4 to 6 (SE) was -9.0 (0.4) from a baseline of 18.6 days in the erenumab, 140 mg, group (*P* < .001) and -7.5 (0.4) from a baseline of 19.2 MMDs in the erenumab, 70 mg, group (*P* = .01), as compared with -6.0 (0.4) from a baseline of 18.6 MMDs in the placebo group; nominal *P* values are reported without multiplicity adjustment (eTable 11 in the Supplement). Achievement of 50% MMD reduction over months 4 to 6 showed a nominally significant improvement in the erenumab, 140 mg, group (109 [56.2%]) and 70 mg group (81 [41.8%]) relative to placebo (51 [26.3%]) (eTable 12 in Supplement 1).

Figure 3. Change From Baseline in Mean Monthly Acute Headache Medication Days (AHMD) and Sustained Medication Overuse Headache (MOH) Remission During the Double-Blind Treatment Period (DBTP)



A, Change from baseline in mean monthly AHMD over months 4, 5, and 6 of the DBTP. Adjusted analysis uses a generalized linear mixed model that includes treatment, visit, treatment-by-visit interaction, the stratification factor of concomitant oral migraine preventive treatment initiated before screening and taken during baseline (yes or no), and baseline value as covariates and assumes a first-order auto regression covariance structure. Adjusted analysis results were obtained using contrasts. Nominal *P* value is presented without multiplicity adjustment. B, Sustained MOH remission during DBTP, as defined by absence of MOH at months 3 and 6 of the DBTP, and the absence of MOH is achieved when mean monthly AHMD less than 10 days or mean MHD less than 14 days over the respective 3-month period. Common odds ratio (OR) and *P* value are obtained from a Cochran-Mantel-Haenszel test, stratified by the stratification factor of concomitant oral migraine preventive treatment initiated before screening and taken during baseline (yes or no). LMS indicates least squares mean; LS, least squares.

Safety

Overall participant incidence rates of AEs were consistent with the known safety profile of erenumab in migraine with most AEs being mild to moderate in severity (ie, Common Terminology Criteria for Adverse Events grade 1 or 2) (**Table 2**). Constipation, COVID-19 infection, injection site pain, nasopharyngitis, and insomnia were the most frequent AEs (incidence 3% or more in DBTP) (Table 2). Events of interest were monitored during the DBTP with constipation being the most common and elevated relative to placebo (eTable 13 in Supplement 1). Serious AEs were reported in 6 participants (1.5%) in the combined erenumab dose group and 8 (4.1%) in the placebo group (eTable 14 in Supplement 1). Serious AEs in the erenumab group included breast cancer, metastatic neuroendocrine carcinoma, presyncope, cholelithiasis, gastroenteritis, and migraine (all n = 1).

Discussion

Patients with CM-MOH are a highly burdened population in which high headache frequency is associated with substantial impact on functioning, pain interference, and quality of life.[21] Consensus treatment for MOH does not exist. Treatment approaches that have been proposed include patient education, mandatory full or partial removal or switching with minimum use of acute headache medication, and initiation of preventive therapies.[2,22,23] The abrupt cessation of acute headache medication is recognized for its effectiveness; however, it may entail the use of alternative acute pain medications, antinausea agents (such as antidopaminergic medications), or bridging therapy involving steroids.[24-27] This approach may also be associated with patient stigmatization, withdrawal symptoms, and unwarranted distress, while concurrently being correlated with a heightened relapse rate.[11,28] Use of effective preventive therapies with or without mandatory removal of the overused medication has been demonstrated to be an effective approach that appears to provide incremental benefit to patients with MOH over standalone acute medication removal.[11] Use of an effective background preventive therapy could help induce MOH remission for prolonged periods of time and ultimately reduce MOH recurrence rates. Monoclonal antibodies that target the CGRP pathway offer a distinct advantage in managing MOH in individuals with CM. Their enhanced safety and tolerability profile, coupled with evidence of superior efficacy over traditional nonspecific oral standard-of-care migraine prophylactic medications, underscore this asset.[29-31] This is further substantiated by the pivotal role of CGRP in the pathogenesis of MOH.[29,32,33]

The unique properties of monoclonal antibodies may be of particular relevance in the MOH population, as monoclonal antibodies could have reduced drug-drug interactions in patients who may be taking many medications to treat their headaches as well as comorbidities.

In our current study, we sought to confirm that preventive treatment with monthly injections of erenumab is a safe and effective approach to treating CM-MOH. The study findings demonstrate that erenumab treatment can yield and sustain high rates of MOH remission, reduce acute medication consumption and improve participants' functionality over a 6-month observation period. These results align with previously conducted post hoc analyses from several phase 2 and 3 studies and a prospective real-life cohort study showing that monoclonal antibodies targeting the CGRP pathway provide

Table 2. Summary of Treatment-Emergent Adverse Events in the Double-Blind Treatment Period (DBTP)

End point	No. (%)			
	Placebo (n = 194)	Erenumab, 70 mg/mo (n = 194)	Erenumab, 140 mg/mo (n = 194)	All erenumab (n = 388)
Treatment-emergent adverse events	126 (64.9)	127 (65.5)	132 (68.0)	259 (66.8)
CTCAE grade ≥2	92 (47.4)	85 (43.8)	100 (51.5)	185 (47.7)
CTCAE grade ≥3	16 (8.2)	14 (7.2)	15 (7.7)	29 (7.5)
CTCAE grade ≥4	1 (0.5)	0 (0.0)	1 (0.5)	1 (0.3)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	8 (4.1)	3 (1.5)	3 (1.5)	6 (1.5)
Leading to IP discontinuation[a]	3 (1.5)	4 (2.1)	4 (2.1)	8 (2.1)
Adverse events reported in ≥3% of participants (in any group) during DBTP				
Constipation	9 (4.6)	29 (14.9)	30 (15.5)	59 (15.2)
COVID-19	12 (6.2)	24 (12.4)	30 (15.5)	54 (13.9)
Injection site pain	6 (3.1)	10 (5.2)	10 (5.2)	20 (5.2)
Nasopharyngitis	3 (1.5)	11 (5.7)	9 (4.6)	20 (5.2)
Insomnia	3 (1.5)	7 (3.6)	11 (5.7)	18 (4.6)
Fatigue	3 (1.5)	9 (4.6)	9 (4.6)	18 (4.6)
Migraine	4 (2.1)	7 (3.6)	8 (4.1)	15 (3.9)
Injection site erythema	4 (2.1)	6 (3.1)	7 (3.6)	13 (3.4)
Back pain	9 (4.6)	6 (3.1)	6 (3.1)	12 (3.1)
Arthralgia	3 (1.5)	7 (3.6)	4 (2.1)	11 (2.8)
Nausea	3 (1.5)	6 (3.1)	4 (2.1)	10 (2.6)
Hypertension	3 (1.5)	3 (1.5)	6 (3.1)	9 (2.3)
Upper abdominal pain	2 (1.0)	7 (3.6)	2 (1.0)	9 (2.3)
Upper respiratory tract infection	6 (3.1)	3 (1.5)	5 (2.6)	8 (2.1)
Dizziness	6 (3.1)	4 (2.1)	1 (0.5)	5 (1.3)
Abdominal pain	6 (3.1)	1 (0.5)	3 (1.5)	4 (1.0)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; IP, investigational product.

[a] A total of 3 participants experienced adverse events during the DBTP, which led to IP discontinuation after completing the DBTP IP. One participant discontinued the IP during open-label treatment period after completing the IP during DBTP. Two participants experienced adverse events after completing the IP during the DBTP and did not continue with the open-label treatment period.

sustained efficacy in participants with and without acute medication overuse.[14-18,34] In SUNLIGHT, the randomized, double-blind, placebo-controlled phase 3 study of eptinezumab in patients with dual migraine-MOH diagnosis, end points numerically favored eptinezumab treatment when compared with placebo but the study did not meet its primary outcome of change from baseline in the number of MMDs over weeks 1 to 12.[19] Despite not reaching the prespecified outcome, this trial does not contradict the existing evidence on the efficacy of CGRP pathway inhibitors in treating MOH. There are several reasons that might help explain this apparent discrepancy. This was outlined by notable differences in MMD response across the European and Asian cohorts while patient-global impression of change scores remained consistent across these 2 geographies. In addition, differences in design, such as adoption of a smaller sample size, restriction of the dose-response exploration to the lowest dose of eptinezumab, and a shorter double-blind period duration, could also have influenced SUNLIGHT results. Of note, MOH remission rates and MMD responses could be significantly influenced by dose with the findings of our present study suggesting a clear dose-response association in favor of the 140-mg dose of erenumab. This observation is further substantiated by a previously reported analysis that indicated that erenumab, 140 mg, is likely to offer incremental benefit over 70 mg, specifically within the context of difficult-to-treat migraine subpopulations.[35]

The large placebo response observed in this study and other MOH trials is not an unique phenomenon to migraine MOH. It has been extensively documented in migraine prevention studies and noted to be on the rise over the last 30 years.[36] A recent meta-analysis has concluded that much of the benefit observed in contemporaneous migraine prevention studies is linked to contextual effects, such as placebo effect.[37] In the particular case of MOH trials, participant education and mandatory removal of the offending medication, as per regional medical practices, cannot be ruled out as having had an important contributory role to the impact of contextual effects in the overall study results. These nonpharmacologic treatment modalities of MOH have been reported to yield high rates of MOH remission in previously completed studies and have been integrated in different degrees to regional standard of care practices. As such, the adoption of background nonpharmacologic treatment methods is likely to have influenced the overall large remission rates observed within this trial but unlikely to have preferentially impacted a specific study arm due to their widespread use.[11,38-40] Additionally, it must be noted that patients stratified to the opioid cohort of our study were not included in the primary analysis, and thus, the findings reported herein cannot be extrapolated to this selected group of patients. The decision to not include opioid-related participants with MOH as part of the study primary analysis was based on the recognition that opioid medication overuse manage-

ment differs from other types of medication overuse often requiring cross-functional interventions and programmed medication tapering approaches aimed at reducing or alleviating withdrawal symptoms and addressing associated addictive disorders when present. Although medically warranted, these interventions were felt to be a potential source of bias to the study leading to the decision to evaluate the safety and efficacy of erenumab in this clinical context in an exploratory manner as a separate cohort.

This trial was also conducted throughout the COVID-19 pandemic with SARS-CoV-2 infection and/or disease being a commonly reported AE during study. The incidence of SARS-CoV-2 was imbalanced across treatment arms with erenumab-treated participants having between 2 to 2.5 times as many cases as placebo. Although treatment with anti-CGRP monoclonal antibodies has not been found to be associated with susceptibility to SARS-CoV-2 infection and/or disease, this finding is intriguing and raises questions on a potential contributory role for SARS-CoV-2 to study results.[41] Additional exploration of SARS-CoV-2 influence on study results is warranted but out of scope for this report.

Otherwise, overall participant incidence rates of AEs were consistent with the known safety profile of erenumab in migraine with adverse drug reactions, such as constipation and injection site reactions being more commonly reported in the active treatment arm as expected. No new treatment-emergent AEs were observed in this study.

Limitations

This study had some important limitations that need to be acknowledged. First, although MOH may occur in association to other primary headache disorders, this trial was not designed to evaluate the safety and efficacy of erenumab outside of the context of migraine and its findings and conclusions cannot be extrapolated to a broad MOH population. Second, although MOH management may involve a permutation of different pharmacologic and nonpharmacologic approaches, this study only sought to establish erenumab as an effective pharmacologic treatment option for patients with CM-MOH and no conclusion can be extracted from this study on the value of other therapeutic modalities for this patient population. Third, the 24-week DBTP used in this study, although being the maximally accepted duration of a placebo-controlled evaluation, may not allow for a complete evaluation of the long-term effects of pharmacologic treatment in this patient population. Fourth, this study had no formal recommendation for educating patients on medication overuse and was at investigator discretion, meaning participating centers may have advised patients differently, thus potentially influencing outcomes. On the other hand, this aspect of the trial may also be seen as a strength, as it represents a scenario closer to real life and avoids undue interference with the physician-patient relationship. In either case, double-blind randomization does provide some protection against bias. Fifth, this study was conducted in a number of countries where erenumab was available in clinical practice, which may have introduced a bias for selecting a less severe population that was willing to participate in the study. Six months of placebo in patients with CM-MOH represents a long period and the most severe patients may not be willing to undergo the trial for this reason. Of note, however, access to anti-CGRP therapy during trial participation varied considerably among participating countries with several facing considerable restrictions to drug access. Furthermore, contemporaneous epidemiology-based studies, such as the OVERCOME study,[42] continue to support low adoption rates of any type of pharmacologic preventive treatment, even among chronic migraine patients. This included a 28.9% self-reported adoption rate of preventive therapies among US chronic migraine respondents during a 2018 web survey in spite of commercial CGRP pathway inhibitors becoming commercially available in the US at that same year.[43] Sixth, the trial had an exclusion criterion for participants experiencing chronic daily headache that experienced no pain-free periods of any duration and at any moment, which may lead to a selection bias. However, based on baseline population characteristics, results of this CM-MOH erenumab trial resemble those of previously completed studies or subgroup analysis conducted with CM-MOH patients. Lastly, this study had limited ethnic representation with a predominantly White participant population, reflective of the higher contribution of European sites to study enrollment.

Conclusions

To our knowledge, this study is the first controlled trial to provide American Academy of Neurology class I evidence of beneficial effects of a migraine preventive treatment in patients with CM-MOH (nonopioid). In this study, erenumab was effective in achieving and sustaining high rates of MOH remission with the quantity and quality of AEs being consistent with the known safety profile of the medication.

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Dr Lanteri-Minet reported taking part in a study with Amgen during the conduct of the study and personal fees from Abbvie, Eli Lilly, Grunenthal, Lundbeck, Medtronic, Orion Pharma, Per Food, Orion Pharma, Pfizer, Reckitt Benckiser, Salvia Bio Electronics, Sanofi Aventis, Teva, and University of Professional Studies outside the submitted work. Dr Dolezil reported participating in clinical trials with Allergan/AbbVie, Amgen, and Novartis and personal fees from Lundbeck, Teva, Eli Lilly, and Organon outside the submitted work. Dr Gouveia reported being a principal investigator for an Amgen clinical trial during the conduct of the study, personal fees from AbbVie Pfizer, Teva, Organon, Lilly, Novartis, and grants from Novartis outside the submitted work. Dr Lucas reported personal fees from Abbvie, Amgen, Lilly, Lundbeck, Pfizer, Orion, Teva, and Reckitt during the conduct of the study. Dr Mikol reported personal fees and employment from Amgen during the conduct of the study and employment from NervGen outside the submitted work. Dr Chou reported prior employment and stock ownership from Amgen during the conduct of the study and current employment and stock ownership with Pfizer outside the submitted work. Dr Yang reported current employment and stock ownership with Amgen. Dr Paiva da Silva Lima reported being a fulltime employee and holding stocks/stock options of Amgen. No other disclosures were reported.

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