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Early Use of Erenumab vs Nonspecific Oral Migraine Preventives
The APPRAISE Randomized Clinical Trial

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IMPORTANCE Patients with migraine often cycle through multiple nonspecific preventive medications due to poor tolerability and/or inadequate efficacy leading to low adherence and increased disease burden.

OBJECTIVE To compare the efficacy, tolerability, patient adherence, and patient satisfaction between erenumab and nonspecific oral migraine preventive medications (OMPMs) in patients with episodic migraine (EM) who had previously failed 1 or 2 preventive treatments.

DESIGN, SETTING, AND PARTICIPANTS The 12-month prospective, interventional, global, multicenter, active-controlled, randomized clinical trial comparing sustained benefit of 2 treatment paradigms (erenumab qm vs oral prophylactics) in adult episodic migraine patients (APPRAISE) trial was a 12-month open-label, multicenter, active-controlled, phase 4 randomized clinical trial conducted from May 15, 2019, to October 1, 2021. This pragmatic trial was conducted at 84 centers across 17 countries. Overall, participants 18 years or older with a 12-month or longer history of migraine, and 4 or more but fewer than 15 monthly migraine days (MMDs) were included.

INTERVENTIONS Patients were randomized (2:1) to receive erenumab or OMPMs. Dose adjustment was permitted (label dependent).

MAIN OUTCOMES AND MEASURES The primary end point was the proportion of patients completing 1 year of the initially assigned treatment and achieving a reduction of 50% or greater from baseline in MMDs at month 12. Secondary end points included the cumulative mean change from baseline in MMDs during the treatment period and the proportion of responders according to the Patients' Global Impression of Change (PGIC) scale at month 12 for patients taking the initially assigned treatment.

RESULTS A total of 866 patients were screened, of whom 245 failed the screening and 621 completed the screening and baseline period. Of the 621 randomized patients (mean [SD] age, 41.3 [11.2] years; 545 female [87.8%]; 413 [66.5%] in the erenumab group; 208 [33.5%] in the OMPM group), 523 (84.2%) completed the treatment phase, and 98 (15.8%) discontinued the study. At month 12, significantly more patients assigned to erenumab vs OMPM achieved the primary end point (232 of 413 [56.2%] vs 35 of 208 [16.8%]; odds ratio [OR], 6.48; 95% CI, 4.28-9.82; P <.001). Compared with OMPMs, treatment with erenumab showed higher responder rate (314 of 413 [76.0%] vs 39 of 208 [18.8%]; OR, 13.75; 95% CI, 9.08-20.83; P <.001) on the PGIC scale (≥5 at month 12). Significant reduction in cumulative average MMDs was reported with erenumab treatment vs OMPM treatment (−4.32 vs −2.65; treatment difference [SE]: −1.67 [0.35] days; P < .001). Substantially fewer patients in the erenumab arm compared with the OMPM arm switched medication (9 of 413 [2.2%] vs 72 of 208 [34.6%]) and discontinued treatment due to adverse events (12 of 408 [2.9%] vs 48 of 206 [23.3%]). No new safety signals were identified.

CONCLUSIONS AND RELEVANCE Results of this randomized clinical trial demonstrated that earlier use of erenumab in patients with EM who failed 1 or 2 previous preventive treatments provided greater and sustained efficacy, safety, and adherence than continuous OMPM.

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Supplemental content

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Oral migraine preventive medications (OMPMs) including β-blockers, calcium channel blockers, antiepileptics, and antidepressants have long been used as a standard of care (SoC) for migraine prevention; however, OMPMs were not specifically developed for migraine, and most of them have insufficient or limited evidence of efficacy and safety.[1] Recently, monoclonal antibodies (mAbs) targeting calcitonin gene-related peptide (CGRP) pathway have been specifically developed for migraine and are now approved for the preventive treatment of migraine by the US Food and Drug Administration and European Medicines Agency, among many regulatory authorities worldwide, with the first approved treatment being the CGRP receptor inhibitor, erenumab.[2-10] However, nonspecific OMPMs remain the SoC in most countries, and only patients with prior preventive treatment failure are eligible for a CGRP-pathway targeting mAb, as recommended by the American Headache Society and European Headache Federation guidelines and determined by national reimbursement policies.[11-15]

Studies have shown that adherence to and persistence with OMPMs are low among patients with migraine, mainly due to poor tolerability and/or inadequate effectiveness.[1,16-20] Furthermore, as patients cycle through other classes of OMPMs after an initial treatment failure, discontinuation rates worsen, and disease burden, which is already substantial, increases.[21-28] These recurrent shortcomings emphasize the need for more effective, better tolerated, targeted treatments and their early implementation within the treatment paradigm.

The efficacy and safety of erenumab have been established in several placebo-controlled trials in episodic migraine (EM) and chronic migraine, in patients with 2 to 4 prior prophylactic treatment failures,[2,3,29-31] and continue to be corroborated in real-world studies.[32-36] The study, Head-to-Head Study of Erenumab Against Topiramate—Migraine Study to Assess Tolerability and Efficacy in a Patient-Centered Setting (HER-MES), was the first head-to-head study to demonstrate better tolerability and higher efficacy of erenumab vs topiramate (SoC).[37]

After erenumab established favorable clinical outcomes in patients with 2 to 4 prior prophylactic treatment failures,[31] broader evaluation of its extended long-term efficacy, tolerability, and adherence in comparison with OMPMs is essential, particularly given the potential consequences of delaying erenumab treatment as patients cycle through various OMPMs in line with national medical reimbursement policies.

In the 12-month prospective, interventional, global, multicenter, active-controlled, randomized clinical trial comparing sustained benefit of 2 treatment paradigms (erenumab qm vs oral prophylactics) in adult episodic migraine patients (APPRAISE) trial, we investigated whether initiating erenumab earlier in patients with 1 or 2 prior oral prophylactic treatment failures could provide long-term continued benefit compared with the commonly prescribed OMPMs. This pragmatic trial that emulated real-world clinical practice used a novel composite primary end point to evaluate the enduring advantages of the 2 treatment paradigms concerning their effectiveness, tolerability, and adherence.

Key Points

Question Does early initiation of erenumab in patients with episodic migraine who had failed 1 or 2 previous preventive treatments provide improved long-term outcomes and sustainability of improvement as compared with nonspecific oral migraine preventive medications (OMPMs)?

Findings The 12-month, interventional, global, multicenter, active-controlled, randomized clinical trial comparing sustained benefit of 2 treatment paradigms (erenumab qm vs oral prophylactics) in adult episodic migraine patients (APPRAISE), including 621 randomized patients, demonstrated that compared with nonspecific oral preventives, patients treated with erenumab were 6 times more likely to achieve 50% or greater reduction in monthly migraine days and 11 times more likely to complete the treatment on the first designated drug.

Meaning Results suggest that physicians should not prolong the treatment with nonspecific oral preventives because earlier initiation of erenumab provides a better long-term efficacy, tolerability, and adherence.

Methods

Study Design and Patients

The APPRAISE trial was a 12-month, prospective, interventional, global, multicenter, active-controlled, open-label, phase 4 randomized clinical trial comparing erenumab vs OMPMs in patients with EM who had failed 1 or 2 prior preventive treatments (tricyclic antidepressants [TCAs], valproate, divalproex, topiramate, flunarizine, β-blockers, and others). The study was conducted from May 15, 2019 (first patient enrolled), to October 1, 2021 (last patient completed last visit of the core phase). Patients were enrolled at 84 centers across 17 countries with written informed consent obtained before study initiation. The trial complied with International Conference on Harmonization E6 Good Clinical Practice Guidelines and was approved by the applicable independent ethics committees or institutional review boards for each participating center. The trial protocol is available in Supplement 1, and the statistical analysis plan is available in Supplement 2. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

The core phase included a screening period (up to 2 weeks), baseline period (4 weeks), and an open-label treatment period (52 weeks). If eligible, patients were randomized 2:1 to receive erenumab, either 70 mg or 140 mg (monthly subcutaneous dose determined by treating physician's judgment), or locally approved OMPMs (daily dose determined by treating physician's decision). Only monotherapy was allowed for migraine prevention, in either arm, and the decision to switch to a new treatment was at treating physician's and patient's discretion.

Clinical outcome assessments were collected by participants using an electronic diary (eDiary [Clario]). Study visits occurred at 4-week intervals after screening. Dose adjustments were evaluated in both arms at each visit, and the required changes were implemented. These decisions were based

on efficacy, tolerability, and/or treatment satisfaction and not on prespecified cutoffs for certain parameters. The last dose was given at week 48 for erenumab and at week 52 for OMPMs. Participants who discontinued treatment were monitored according to protocol.

The key eligibility criteria included (1) patients 18 years or older with (2) a documented history of migraine (with or without aura) for 12 months or longer before screening according to the *International Classification of Headache Disorders, Third Edition*,[38] (3) migraine symptoms for 4 or more days per month and fewer than 15 days per month on average across 3 months before screening, and (4) patients with 1 or 2 documented preventive treatment failures in the past 6 months due to lack of efficacy or poor tolerability. Patients were asked by the physicians and self-reported the following races: American Indian or Alaska Native, Asian, Black or African American, multiracial, White, or unknown. Patients also self-reported the following ethnicities: Hispanic or Latino, not Hispanic or Latino, not reported, or unknown. These data were captured to understand the ethnic diversity among included patients.

The key exclusion criteria included patients 50 years or older at migraine onset, history of cluster headache or hemiplegic migraine, failure of 2 or more approved migraine preventive therapies, use of CGRP-targeted mAbs within 3 months of baseline period, use of devices or invasive interventions within 2 months of baseline period, use of ergotamine or triptans (≥10 days per month), overuse of simple analgesics (≥15 days per month), or use of opioid- or butalbital-containing analgesics on 4 or more days per month within 2 months of baseline.

Randomization

Eligibility for randomization was assessed based on migraine frequency and eDiary compliance (≥80%) during the baseline period. Randomization was stratified by prior preventive treatment failure reported during the screening/baseline period: 1 treatment failure (TF1) vs 2 treatment failures (TF2). Stratification and a 30% cap of randomized patients to the TF2 strata were implemented using Interactive Response Technology (Cenduit, an IQVIA company) presenting so that only 30% of the preplanned patient number with TF2 strata were included. Unequal randomization favoring the erenumab arm was selected to facilitate recruitment, generate data on the impact of erenumab in patients with only TF1, and capture additional long-term efficacy and safety data for erenumab.

Outcomes

The novel composite primary end point was the proportion of patients completing 1 year of the randomized treatment while also achieving 50% or greater reduction from baseline in monthly migraine days (MMDs) at month 12.

The secondary end points included the proportion of patients completing the treatment period at month 12, the cumulative mean change from baseline in MMDs during the treatment period, and the proportion of responders as measured by the Patients' Global Impression of Change (PGIC) scale[39] at month 12, for patients on initially assigned treatment. The PGIC is a global assessment performed by the participant relating to the change in clinical status since the start of treatment. Subanalyses for patients who switched treatment were also performed.

Safety

Safety assessments consisted of collecting all adverse events (AEs) and serious AEs (SAEs) along with their severity and association with study drug during the core phase. Exposure-adjusted incidence rate (EAIR) per 100 patient-years of AEs was calculated as the number of AEs reported divided by total time at risk during the treatment period multiplied by 100.

Statistical Analysis

The full analysis set (FAS) comprised all randomized patients. Primary and secondary efficacy analyses used FAS.

A sample size of 394 patients in the erenumab arm and 197 in the OMPM arm was required to achieve 90% of power to reject the null hypothesis (ie, net benefit between treatment arms was the same) when the odds ratio (OR) was 2 and the success rate in the control arm was 0.18. Sample size calculations were done using PASS 11, version 11 (NCSS Statistical Software), and the Cochran-Mantel-Haenszel (CMH) test was used. SAS software, version 9.4-TS1M6 (SAS Institute) was used for all statistical analyses.

To evaluate the association between net benefit rate and treatment, a CMH test, stratified by the number of previous TFs, was used under a 2-sided significance level of .05. Estimated ORs and 95% CIs were reported. For the primary end point, nonresponder (participants who had missing data at week 52) imputation was used.

The cumulative average change from baseline in MMDs was analyzed using a linear mixed-effects repeated measures model, including treatment arm, baseline value, stratification factor(s), scheduled visit, and the interaction of treatment arm with scheduled visit. If applicable, an unstructured covariance structure was assumed. Least squares mean for each treatment arm and its associated 95% CIs and nominal 2-sided *P* values were tabulated by visit and treatment. Missing MMD data were not imputed.

Patients were considered responders if the PGIC score was 5 or greater at month 12 on initially assigned treatment. Patients with missing PGIC score data at week 52 of treatment and those who discontinued the initially assigned treatment before week 52 were imputed as nonresponders.

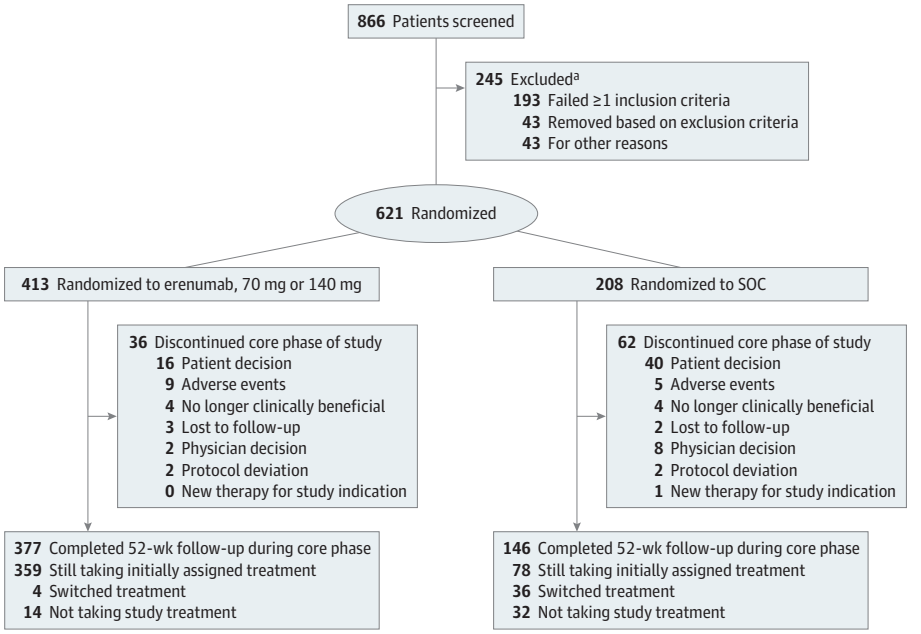
The safety analysis set included all patients who received 1 or more doses of any study treatment. Safety data were collected and coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 24.1. Missing safety data were not imputed. This study was not powered for safety data comparison.

Results

Patient Disposition and Baseline Characteristics

Of the 866 patients screened for eligibility, 245 failed the screening, and 621 (mean [SD] age, 41.3 [11.2] years; 545 female [87.8%]; 76 male [12.2%]) were randomized to receive erenumab (413 [66.5%]) or OMPMs (208 [33.5%]). Overall, 523

Figure 1. Flow Diagram of Patient Disposition (Full Analysis Set)



Patients were enrolled at 84 centers across 17 countries (Argentina, Austria, Belgium, Czech Republic, Finland, France, Germany, Greece, Israel, Italy, Netherlands, Poland, Portugal, Slovakia, Spain, UK, and US), and the full analysis set included all randomized patients (413 in the erenumab group and 208 in the oral migraine preventive medicines [OMPMs] group). The safety analysis set included all patients who received 1 or more doses of any study treatment (408 initially given erenumab; 206 given OMPMs [197 initially given nonspecific oral preventive treatment plus 9 who switched from the erenumab group]).

[a] Patients could have more than 1 reason for screen failure. Other reasons for exclusion at screening included the patient's or physician's decision, loss to follow-up, protocol deviation, or technical problems.

of 621 patients (84.2%) completed the 12-month treatment phase (erenumab, 377 of 413 [91.3%]; OMPMs, 146 of 208 [70.2%]), and 98 of 621 (15.8%) discontinued the study. The main reasons for the discontinuation included patient decision (erenumab, 16 of 413 [3.9%]; OMPMs, 40 of 208 [19.2%]), AE (erenumab, 9 of 413 [2.2%]; OMPMs, 5 of 208 [2.4%]), and physician decision (erenumab, 2 of 413 [0.5%]; OMPMs, 8 of 208 [3.8%]) (**Figure 1**).

In the OMPM arm, most patients were initially given β-blockers (65 of 208 [31.3%]), topiramate (46 of 208 [22.1%]), and tricyclic antidepressants (33 of 208 [15.9%]). The number of patients with cumulative number of switches was lower in erenumab arm vs SoC arm (≥1 switches: 7 vs 57 and ≥2 switches: 2 vs 12); 3 patients in the SoC arm had 3 or more switches.

Baseline demographic characteristics were balanced between the treatment arms. Patients self-reported with the following race categories: 1 American Indian or Alaska Native (0.2%), 2 Asian (0.3%), 3 Black or African American (0.5%), 2 multiracial (0.3%), 614 White (98.9%), and 3 unknown (0.5%). Patients self-reported the following ethnicity categories: 42 Hispanic or Latino (6.8%), 571 not Hispanic or Latino (91.9%), 7 not reported (1.1%), and 1 unknown (0.2%). Patients had a mean body mass index of 25.1 (calculated as weight in kilograms divided by height in meters squared). The mean (SD) MMDs were 9.5 (2.7) days and 9.1 (2.9) days for patients in the erenumab and OMPM arms, respectively (**Table 1**).

Primary and Key Secondary Efficacy Analyses

At month 12, significantly more patients assigned to erenumab (232 of 413 [56.2%]) achieved the primary end point vs patients receiving the initially assigned OMPMs (35 of 208 patients [16.8%]; OR, 6.48; 95% CI, 4.28-9.82; *P* <.001) (**Figure 2**A). Of those achieving the primary end point in the OMPM arm, 13 of 208 (6.3%) continued taking β-blockers, 12 of 208 (5.8%) continued taking topiramate, and 8 of 208 (3.9%) continued taking TCAs.

A significantly greater proportion of patients in the erenumab arm (359 of 413 [86.9%]) completed the study taking the initially assigned treatment vs those in the OMPM arm (78 of 208 [37.5%]; OR, 11.27; 95% CI, 7.53-16.87; *P* <.001). Overall, 81 of 621 patients (13.0%) switched from their initially assigned treatment (erenumab, 9 of 413 [2.2%]; OMPMs, 72 of 208 [34.6%]). Among patients who switched, 8 of 9 (88.9%; erenumab) and 31 of 72 (43.1%; OMPMs) reported a lack of efficacy, whereas 1 of 9 (11.1%; erenumab) and 36 of 72 (50.0%; OMPMs) reported a lack of tolerability as the primary reason. A greater proportion of patients who were assigned and continued taking treatment with erenumab at month 12 achieved a 50% or greater reduction in MMDs compared with those who switched treatment from week 12 through to week 52 (Figure 2B).

The mean change from baseline in cumulative average MMDs was significantly greater in the erenumab arm vs the OMPM arm, starting from month 1 and continuing through month 12 (**Figure 3**A). At month 12, the change from baseline in adjusted mean for MMDs was −4.32 days (erenumab) and −2.65 days (OMPMs) (mean, treatment difference [SE], −1.67 [0.35] days; *P* <.001). A significant mean (SE) treatment difference was also observed in patients who were assigned and remained on treatment with erenumab at month 12 vs those who switched treatment (−2.80 [0.43] days; *P* <.001) (Figure 3B**);** however, results were not consistent for OMPM for previous visits (−1.12 [0.56] days; *P* = .046) (Figure 3C).

The proportion of patients who completed 12 months taking the initially assigned treatment and were identified as responders on the PGIC scale (≥5 at month 12) was 76.0% (314

Table 1. Demographic and Clinical Characteristics of the 12-Month, Prospective, Interventional, Global, Multicenter, Active-Controlled, Randomized Clinical Trial Comparing Sustained Benefit of 2 Treatment Paradigms (Erenumab qm vs Oral Prophylactics) in Adult Episodic Migraine Patients (APPRAISE) Trial Population (Full Analysis Set)[a]

Characteristic	Erenumab (n = 413)	OMPMs (n = 208)	All patients (N = 621)
Age, y	41.1 (11.5)	41.5 (10.4)	41.3 (11.2)
Sex, No. (%)			
Male	50 (12.1)	26 (12.5)	76 (12.2)
Female	363 (87.9)	182 (87.5)	545 (87.8)
Race, No. (%)			
American Indian or Alaska Native	1 (0.2)	0	1 (0.2)
Asian	1 (0.2)	1 (0.5)	2 (0.3)
Black or African American	3 (0.7)	0	3 (0.5)
Multiracial	2 (0.5)	0	2 (0.3)
White	408 (98.8)	206 (99.0)	614 (98.9)
Unknown	2 (0.5)	1 (0.5)	3 (0.5)
Ethnicity, No. (%)			
Hispanic or Latino	25 (6.1)	17 (8.2)	42 (6.8)
Not Hispanic or Latino	381 (92.3)	190 (91.3)	571 (91.9)
Not reported	6 (1.5)	1 (0.5)	7 (1.1)
Unknown	1 (0.2)	0	1 (0.2)
BMI[b]	25.1 (5.4)	25.1 (5.2)	25.1 (5.3)
Monthly migraine days	9.5 (2.7)	9.1 (2.9)	9.4 (2.8)
Monthly headache days	10.3 (2.8)	10.0 (2.9)	10.19 (2.8)
Acute headache medication use, No. (%)			
Migraine specific	342 (82.8)	160 (76.9)	502 (80.8)
Nonmigraine specific	69 (16.7)	47 (22.6)	116 (18.7)
Monthly acute headache medication use, d	7.1 (2.7)	6.5 (2.9)	6.9 (2.8)
Monthly acute migraine-specific medication use, d	4.8 (3.4)	4.2 (3.3)	4.6 (3.4)
Prior prophylactic migraine treatment failures, No. (%)[c]			
1	291 (70.5)	146 (70.2)	437 (70.4)
2	122 (29.5)	62 (29.8)	184 (29.6)

Abbreviations: BMI, body mass index; OMPM, oral migraine preventive medication.

[a] Data presented are mean (SD) unless otherwise specified.

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

[c] Prior treatment failure reflects the randomization strata. It might be different from the actual value at baseline. Prior migraine prophylactic medication category includes (1) divalproex sodium and sodium valproate, (2) topiramate, (3) β-blockers, (4) lisinopril and candesartan, (5) serotonin-norepinephrine reuptake inhibitors, (6) flunarizine and verapamil, (7) tricyclic antidepressants, and (8) other locally approved migraine prophylactic medication.

of 413) in the erenumab arm vs 18.8% (39 of 208) in the OMPM arm (OR, 13.75; 95% CI, 9.08-20.83; *P* <.001) (Figure 3D). Of patients who switched treatment, 24.7% (20 of 81) were identified as responders at month 12.

Safety

The incidence of treatment-emergent AEs (TEAEs) was similar between the treatment arms (erenumab, 305 of 408 [74.8%]; OMPMs, 157 of 206 [76.2%]). However, after adjusting for exposure to treatment, the exposure-adjusted rate (per 100 patient-years [r]) was approximately 30.0% lower in patients treated with erenumab (r = 189.3) vs those treated with OMPMs (r = 267.2). The most common TEAEs are shown in **Table 2**.

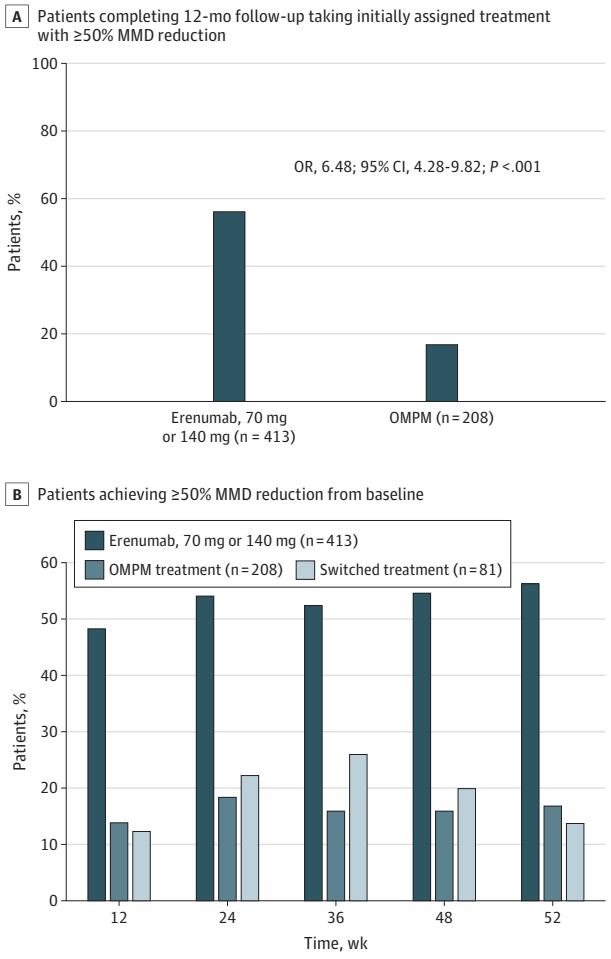
AEs were suspected to be related to study drug in 131 of 408 patients (32.1%) in the erenumab arm vs 116 of 206 patients (56.3%) in the OMPMs arm. The EAIR per 100 patient-years (r) for AEs suspected to be related to study drug was 46.2 in the erenumab arm vs 161.2 in the OMPM arm. The most common AEs suspected to be related to the erenumab treatment were constipation (50 of 408 [12.3%]) and injection site pain (19 of 408 [4.7%]), and those related to OMPMs were fatigue (29 of 206 [14.1%]) and weight increase (20 of 206 [9.7%]).

The incidence of SAEs was comparable between the treatment arms (erenumab, 15 of 408 [3.7%]; OMPMs, 8 of 206 [3.9%]). One patient in the erenumab arm reported an anaphylactic reaction of moderate severity, which was suspected to be treatment related. The EAIR for SAEs (per 100 patient-years) was low in both treatment arms (erenumab, r = 4.0; OMPMs, r = 5.5). No deaths occurred.

The incidence of AEs leading to treatment discontinuation was approximately 8 times lower in patients treated with erenumab (12 of 408 [2.9%] initially dosed with erenumab) vs OMPMs (48 of 206 patients [23.3%] in the OMPM arm group including 9 patients switched from erenumab arm). The most common AEs leading to erenumab discontinuation were abdominal pain, asthenia, and weight increase (0.5% each), and those leading to OMPMs discontinuation were fatigue (4.4%) and attention difficulties (2.9%). The incidence of AEs leading to dose adjustment was approximately 15 times lower in the erenumab arm (4 of 408 [1.0%]) vs the OMPM arm (32 of 206 [15.5%]).

Constipation occurred in 53 of 408 patients (13.0%) treated with erenumab vs 2 of 206 patients (1.0%) treated with OMPMs. Most events were mild (erenumab, 41 of 408 [10.0%]; OMPMs,

Figure 2. Patients With 50% or Greater Reduction in Monthly Migraine Days (MMDs)



A, Proportion of patients completing 12 months receiving the initially assigned treatment and achieving 50% or greater MMD reduction from baseline. Statistical analysis uses a Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factor (number of prior prophylactic migraine treatment failures = 1 vs 2) after missing data are imputed using multiple imputation assuming MAR. Odds ratio (OR) and corresponding 95% CI are based on imputed data. B, Proportion of completers on initially assigned treatment and switchers achieving 50% or greater MMD reduction from baseline at quarterly intervals (full analysis set).[a] OMPM indicates oral migraine preventive medicine.

[a] Completers were defined as patients who completed the study taking the initially assigned treatment (erenumab or nonspecific oral preventive therapy). In total, 9 patients in erenumab arm switched and were counted in switcher group.

2 of 206 [1.0%]) or moderate (erenumab only, 11 of 408 [2.7%]); however, 1 patient in the erenumab arm reported severe constipation, which resolved after treatment with a laxative (event not suspected to be study drug related). The incidence of hypertension (preferred term) was similar between treatment arms (erenumab, 14 of 408 [3.4%]; OMPMs, 6 of 206 [2.9%]). These events were not suspected to be study drug related.

No clinically meaningful trends in laboratory parameter abnormalities, vital signs, or ECGs were observed. No cases meeting Hy law criteria were observed.

Discussion

The APPRAISE trial was the first, to the authors' knowledge, pragmatic, multicenter, randomized clinical trial that directly compared 2 treatment paradigms (erenumab, an injectable anti-CGRP mAb, vs SoC oral therapy) in patients with EM who had failed 1 or 2 previous migraine preventive treatments. Access to CGRP-targeted mAbs is often limited to patients with 3 to 5 previous migraine preventive treatment failures[11-15] due to local reimbursement limitations, which can lead to chronification of migraine, and is associated with reduced quality of life and higher direct/indirect costs.[40-44] Using migraine-specific treatments at an earlier stage may provide greater benefit for patients as demonstrated by economic modeling.[45-47] Indeed, understanding how erenumab affects long-term outcome if prescribed earlier in the treatment paradigm is meaningful for both clinicians and patients.

The APPRAISE trial was also the first, to the authors' knowledge, clinical trial that reported a composite primary end point that combined widely accepted and clinically meaningful reduction of migraine frequency (≥50% MMD reduction) with sustained adherence to initially assigned treatment at 12 months, thus reflecting the 2 most common reasons for preventive treatment discontinuation: insufficient efficacy and/or tolerability.

In this study, a practical methodology was used, granting physicians the autonomy to determine the treatment trajectory after randomization, in both treatment arms and within local protocols, mirroring real-world clinical practice. Also, the 12-month study duration allowed for assessment of sustained long-term benefit between the 2 treatment arms.

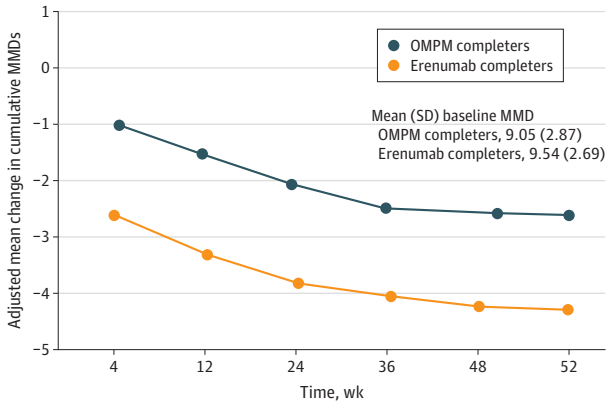
The study met all primary and secondary end points, demonstrating that in a scenario close to standard clinical practice, earlier use of erenumab improved tolerability and efficacy. Patients receiving erenumab were 6 times more likely to continue taking treatment at month 12 and to achieve 50% or greater reduction in MMDs compared with patients receiving the initially assigned OMPMs. Only a few patients (2.2%) in the erenumab arm switched from originally assigned medication vs 34.6% in the OMPM arm, signifying better adherence. Erenumab has the added benefit of not requiring dose titration and having a longer half-life, which enables monthly administration rather than the burden of taking medication daily, which may also have contributed to the better adherence observed in the erenumab arm. In fact, this was already seen in the HER-MES study.[37]

The change from baseline in MMDs incrementally improved in both treatment arms over 12 months; however, this effect was greater in the erenumab arm compared with the OMPM arm, at all time points starting at week 4. Because it typically takes time to establish the optimal dose for the OMPMs, one might have expected to see a larger difference between treatment arms in the first 3 months; however, the absolute difference between treatment arms remained stable over time.

The Migraine-Specific Quality of Life questionnaire and PGIC are the patient-reported outcomes that best correlated with response to CGRP-targeted mAbs from a patient's per-

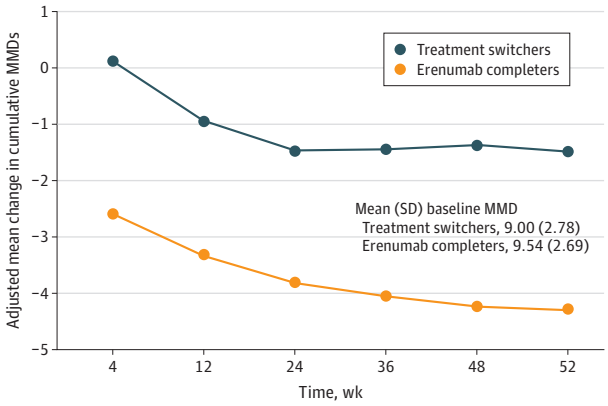
Figure 3. Change From Baseline in Cumulative Average Monthly Migraine Days (MMDs)

A Initially assigned erenumab completers vs initially assigned OMPM completers



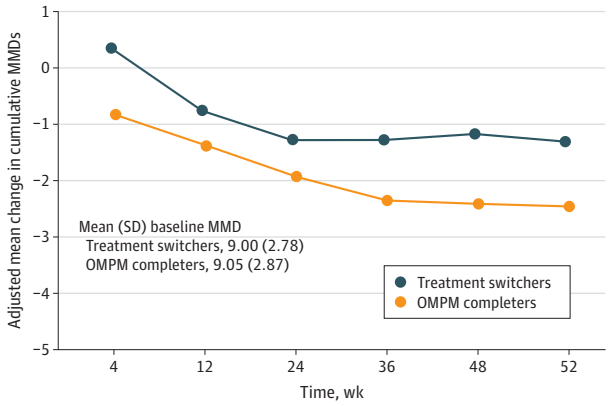
TD	−1.59	−1.78	−1.71	−1.55	−1.65	−1.67
(95% CI; SE)	(−2.26 to −0.92; 0.34)	(−2.45 to −1.10; 0.34)	(−2.38 to −1.03; 0.35)	(−2.23 to −0.87; 0.35)	(−2.33 to −0.96; 0.35)	(−2.36 to −0.99; 0.35)
P value	*P* <.001	*P* <.001	*P* <.001	*P* <.001	*P* <.001	*P* <.001

B Initially assigned erenumab completers vs treatment switchers



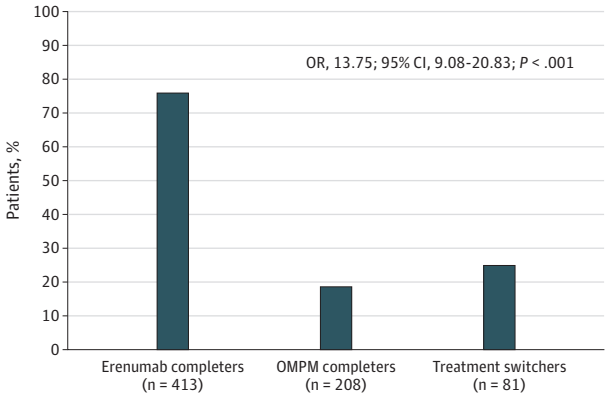
TD	−2.74	−2.36	−2.33	−2.58	−2.86	−2.80
(95% CI; SE)	(−3.54 to −1.94; 0.41)	(−3.17 to −1.56; 0.41)	(−3.14 to −1.51; 0.42)	(−3.41 to −1.76; 0.42)	(−3.70 to −2.20; 0.43)	(−3.64 to −1.95; 0.43)
P value	*P* <.001	*P* <.001	*P* <.001	*P* <.001	*P* <.001	*P* <.001

C Initially assigned OMPM completers vs treatment switchers



TD	−1.15	−0.59	−0.62	−1.04	−1.21	−1.12
(95% CI; SE)	(−2.18 to −0.12; 0.52)	(−1.63 to 0.46; 0.53)	(−1.69 to 0.44; 0.54)	(−2.12 to 0.04; 0.55)	(−2.32 to −0.11; 0.56)	(−2.23 to −0.02; 0.56)
P value	*P* = .03	*P* = .27	*P* = .25	*P* = .06	*P* = .03	*P* = .046

D PGIC responders at 12 mo



A, Patients receiving initially assigned treatment.[a,b] B, Completers vs switchers of erenumab by visit (full analysis set).[a,b] C, Completers vs switchers of oral migraine preventive medicine by visit (full analysis set).[a,b] D, Proportion of Patient Global Impression of Change (PGIC) responders at month 12[a,c] Statistical analysis utilized a Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factor (number of prior prophylactic migraine treatment failures = one vs two) after missing data were imputed as nonresponse. OMPM indicates oral migraine preventive medication; TD, treatment difference.

[a] Completers were defined as patients who completed the study taking the initially assigned treatment (erenumab or nonspecific oral preventive therapy).

[b] The linear mixed-effects model includes treatment groups, baseline value, stratification factor, scheduled visit, and the interaction of treatment group per scheduled visit; an unstructured covariate matrix was assumed.

[c] Patients were considered as PGIC responders if completed 12 months taking initially assigned treatment and the PGIC score was 5 or higher at month 12.

spective, reflecting several aspects other than migraine frequency.[48,49] In the APPRAISE trial, patients receiving erenumab were 13 times more likely to achieve a relevant clinical improvement at month 12, as assessed by PGIC, compared with patients receiving the initially assigned OMPMs. These findings correlate with the clinical response data and demonstrate that patients are more satisfied with erenumab treatment.

Tolerability was better in patients receiving erenumab vs the initially assigned OMPMs, with a lower exposure-adjusted incidence rate of AEs (r = 189.3 vs r = 267.2), lower exposure-adjusted AEs suspected to be related to study drug (r = 46.2 vs

Table 2. Exposure Adjusted Treatment-Emergent Adverse Events (AEs) by Preferred Term (≥3% in Either Treatment) (Safety Analysis Set)[a]

	No. (%)/e (r)		
Preferred term	Erenumab (n = 408)[b]	OMPMs (n = 206)[c]	All patients (N = 605)
Constipation	53 (13.0)/342.1 (15.5)	2 (1.0)/149.4 (1.3)	55 (9.1)/487.5 (11.3)
Nasopharyngitis	36 (8.8)/359.5 (10.0)	15 (7.3)/142.6 (10.5)	51 (8.4)/498.9 (10.2)
COVID-19	20 (4.9)/374.9 (5.3)	12 (5.8)/145.1 (8.3)	32 (5.3)/516.9 (6.2)
Influenza	20 (4.9)/370.1 (5.4)	3 (1.5)/149.1 (2.0)	23 (3.8)/516.1 (4.5)
Injection site pain	19 (4.7)/370.5 (5.1)	0	19 (3.1)/517.3 (3.7)
Back pain	19 (4.7)/373.8 (5.1)	9 (4.4)/144.0 (6.2)	28 (4.6)/514.7 (5.4)
Fatigue	18 (4.4)/367.8 (4.9)	33 (16.0)/134.4 (24.6)	51 (8.4)/499.0 (10.2)
Nausea	15 (3.7)/373.9 (4.0)	10 (4.9)/147.3 (6.8)	25 (4.1)/518.0 (4.8)
Insomnia	15 (3.7)/373.0 (4.0)	7 (3.4)/146.7 (4.8)	22 (3.6)/516.6 (4.3)
Cough	15 (3.7)/373.2 (4.0)	2 (1.0)/148.7 (1.3)	17 (2.8)/518.7 (3.3)
Hypertension	14 (3.4)/373.2 (3.8)	6 (2.9)/146.1 (4.1)	20 (3.3)/516.2 (3.9)
Oropharyngeal pain	14 (3.4)/375.6 (3.7)	2 (1.0)/148.8 (1.3)	16 (2.6)/521.3 (3.1)
Diarrhea	13 (3.2)/377.0 (3.4)	5 (2.4)/148.0 (3.4)	18 (3.0)/521.9 (3.4)
Upper respiratory tract infection	13 (3.2)/374.2 (3.5)	4 (1.9)/148.3 (2.7)	17 (2.8)/519.4 (3.3)
Arthralgia	13 (3.2)/375.6 (3.5)	7 (3.4)/146.7 (4.8)	20 (3.3)/519.2 (3.9)
Weight increased	12 (2.9)/375.1 (3.2)	22 (10.7)/136.8 (16.1)	34 (5.6)/508.2 (6.7)
Dizziness	7 (1.7)/377.9 (1.9)	18 (8.7)/140.4 (12.8)	25 (4.1)/515.2 (4.9)
Paresthesia	5 (1.2)/378.6 (1.3)	15 (7.3)/139.8 (10.7)	20 (3.3)/515.2 (3.9)
Somnolence	5 (1.2)/379.6 (1.3)	15 (7.3)/139.2 (10.8)	20 (3.3)/515.7 (3.9)
Dry mouth	2 (0.5)/381.0 (0.5)	9 (4.4)/144.9 (6.2)	11 (1.8)/522.7 (2.1)
Anxiety	7 (1.7)/378.2 (1.9)	9 (4.4)/145.7 (6.2)	16 (2.6)/520.8 (3.1)
Disturbance in attention	0	9 (4.4)/146.6 (6.1)	9 (1.5)/526.1 (1.7)
Vertigo	8 (2.0)/378.6 (2.1)	8 (3.9)/147.4 (5.4)	16 (2.6)/522.9 (3.1)
Asthenia	4 (1.0)/381.5 (1.0)	8 (3.9)/147.7 (5.4)	12 (2.0)/526.0 (2.3)
Hypotension	3 (0.7)/381.6 (0.8)	7 (3.4)/146.8 (4.8)	10 (1.7)/525.5 (1.9)
Dyspnea	2 (0.5)/381.9 (0.5)	7 (3.4)/149.2 (4.7)	9 (1.5)/528.0 (1.7)

Abbreviations: e, total time at risk during treatment period, summed across all the patients in that class; OMPM, oral migraine preventive medicines; r, exposure-adjusted patient rate per 100 patient years (n/e × 100).

[a] Exposure-adjusted treatment-emergent AEs are sorted by most frequent treatment-emergent AE in erenumab group than OMPMs group (more to less). A patient with multiple occurrences of an AE under 1 treatment is counted only once in this AE category for that treatment. Time at risk during the treatment period is the time from first dose of treatment to onset of first event in the treatment period or minutes (end of initially assigned treatment phase, last dose +27/1 days).

[b] Considered data while patients receiving erenumab.

[c] Includes 9 patients who switched from erenumab to nonspecific oral preventive treatment (n = 197, initially dosed with nonspecific oral preventive treatment).

r = 161.2), and a much lower discontinuation rate due to AEs (2.9% vs 23.3%). The incidence of constipation in the erenumab arm was low (13%), with events mostly mild or moderate. Although many patients in the OMPM arm were being treated with β-blockers, the incidence of hypertension was similar between the treatment arms. No new safety findings were identified.

Limitations

This study has some limitations. Only locally approved and marketed OMPMs at study onset were used as comparators, in accordance with the product label/package insert. As there are no clearly defined, evidence-based, or commonly accepted treatment algorithms for prescribing OMPMs, the choice of OMPMs was heterogeneous across geographies and highly dependent on both the individual experience of the treating physician and patient profiles. The open-label design of the study may have resulted in a placebo response in some patients; in addition, placebo effect could also occur with subcutaneous treatment and enhanced patient outcomes for satisfaction, as erenumab is administered in the clinic.[50-52] However, placebo effect peaks at 3 months, and this effect should have been leveled out, as the primary end point was measured at 12 months in this study.[53] In addition, because this study mimicked real-world practice, these potential placebo enhancements of efficacy would also be seen in real practice, implying that the efficacy results observed here were directly translatable to everyday treatment regardless of placebo effect.

Conclusions

The APPRAISE randomized clinical trial provided clinically meaningful evidence that early initiation of migraine prevention with erenumab was better tolerated, safer, and more efficacious than OMPMs and provided a sustained improvement in patient satisfaction. Earlier initiation of erenumab may ultimately lead to fewer patients discontinuing or switching medication in a real-world clinical practice. Moreover, these findings may help reduce health care resource utilization, decrease disability, and increase better quality of life. These findings lend further support to the recent guideline update issued by the European Headache Federation, in which CGRP-targeted mAbs are considered as a first-line treatment option for patients with migraine who require preventive treatment.

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Correction: This article was corrected on May 13, 2024, to fix author Cristina Lopez Lopez's surname, to properly align the graph curves in Figure 3A and C, and to add a footnote to Table 1.

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Author Contributions: Dr Patricia Pozo-Rosich had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Snellman, Arkuszewski, Ritter, Lopez Lopez, Maca, Ferraris, Gil-Gouveia.
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Supervision: Pozo-Rosich, Dolezil, Snellman, Arkuszewski, Lopez Lopez, Ferraris.

Conflict of Interest Disclosures: Dr Pozo-Rosich reported receiving grants from AbbVie, Novartis, and Teva and personal fees from AbbVie, Eli Lilly, Lundbeck, Novartis, Pfizer, and Teva outside the submitted work. Dr Dolezil reported participation in Allergan/AbbVie clinical trials and receiving personal fees from Amgen, Eli Lilly, Novartis, and Teva outside the submitted work. Dr Paemeleire reported being a part of the APPRAISE steering committee, with fees from Novartis paid directly to the home institution (the Ghent University Hospital); receiving speaker/advisory board fees from AbbVie, Novartis, Eli Lilly, Lundbeck Teva, Pfizer, and Man & Science outside the submitted work. Dr Stepien reported serving as a lecturer and advisory board expert for Allergan, Amgen, Bayer, Biogen, Eli Lilly, Novartis, Polpharma, and Teva. Dr Stude reported receiving personal fees from Novartis, Eli Lilly, Lundbeck, and Teva outside the submitted work. Dr Snellman reported being an employee of and owning stocks in Novartis. Dr Arkuszewski reported being an employee of and owning stocks in Novartis. Dr Stites reported receiving personal fees (stock compensation) from Novartis Pharmaceuticals and being employed by Novartis during the conduct of the study. Dr Ritter reported being an employee of and receiving stock options in Novartis during the conduct of the study. Dr Lopez Lopez reported receiving personal fees from and being a full-time employee of Johnson and Johnson outside the submitted work. Dr Maca reported being an employee of and owning stocks in Novartis. Dr Ferraris reported being an employee of and receiving stock options in Novartis AG during the conduct of the study. Dr Gil-Gouveia reported receiving personal fees from Hospital da Luz for participation as a local principal investigator in the APPRAISE clinical trial during the conduct of the study; personal fees from Novartis for consulting and participation in educational activities; grants from Novartis Portuguese Headache Society for headache research; personal fees from Teva, Lundbeck, Pfizer, AbbVie, and Eli Lilly for consulting and participation in educational activities, and being a member of the European Headache Federation Board and the Headache Panel of the European Neurology Academy, actively contributing to the development of therapeutic guidelines for headache disorders. No other disclosures were reported.

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Data Sharing Statement: See Supplement 3.

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