Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study

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Summary

Background A substantial proportion of patients with migraine does not respond to, or cannot tolerate, oral preventive treatments. Erenumab is a novel CGRP-receptor antibody with preventive efficacy in migraine. We assessed its efficacy and tolerability in patients with episodic migraine in whom previous treatment with two-to-four migraine preventives had been unsuccessful.

Methods LIBERTY was a 12-week, double-blind, placebo-controlled randomised study at 59 sites in 16 countries. Eligible patients were aged 18–65 years and had a history of episodic migraine with or without aura for at least 12 months, had migraine for an average of 4–14 days per month during the 3 months before screening, and had been treated unsuccessfully (in terms of either efficacy or tolerability, or both) with between two and four preventive treatments. Eligible participants were randomly assigned (1:1) to receive either erenumab 140 mg (via two 70 mg injections) or placebo every 4 weeks subcutaneously for 12 weeks. Randomisation was by interactive response technology and was stratified by monthly frequency of migraine headache (4–7 vs 8–14 migraine days per month) during the baseline phase. Cenduit generated the randomisation list and assigned participants to groups. Participants, investigators, people doing various assessments, and the study sponsor were masked to treatment assignment. The primary endpoint was the proportion of patients achieving a 50% or greater reduction in the mean number of monthly migraine days during weeks 9–12. Efficacy was measured in the full analysis set, which included all randomly assigned patients who started their assigned treatment and completed at least one post-baseline monthly migraine day measurement. Safety and tolerability were assessed by recording adverse events and by physical examination, assessment of vital signs, clinical laboratory assessments, and electrocardiography. Safety was assessed in all randomly assigned patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT03096834. The trial is closed to new participants, but the open-label extension phase is ongoing.

Findings Between March 20, 2017, and Oct 27, 2017, 246 participants were randomly assigned, 121 to the erenumab group and 125 to the placebo group. 95 of 246 (39%) participants had previously unsuccessfully tried two preventive drugs, 93 (38%) had tried three, and 56 (23%) had tried four. At week 12, 36 (30%) patients in the erenumab had a 50% or greater reduction from baseline in the mean number of monthly migraine days, compared with 17 (14%) in the placebo group (odds ratio 2·7 [95% CI 1·4–5·2]; p=0·002). The tolerability and safety profiles of erenumab and placebo were similar. The most frequent treatment-emergent adverse event was injection site pain, which occurred in seven (6%) participants in both groups.

Interpretation Compared with placebo, erenumab was efficacious in patients with episodic migraine who previously did not respond to or tolerate between two and four previously unsuccessful preventive treatments. Erenumab might be an option for patients with difficult-to-treat migraine who have high unmet needs and few treatment options.

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Introduction

Migraine is a neurological disease that is typically characterised by recurrent attacks of severe, unilateral, pulsating headaches associated with nausea, vomiting, photophobia, and phonophobia. As of 2016, migraine is the second leading cause of disability worldwide. Episodic migraine is defined as migraine that manifests on fewer than 15 days per month, whereas patients with chronic disease have headache on 15 or more days per month—at least 8 of which have to fulfil migraine criteria or have been successfully treated with migraine-specific medication—for at least 3 months. Pharmacological management of migraine includes acute and preventive treatment of attacks. Commonly used preventive treatments for episodic migraine include β blockers (mainly propranolol and metoprolol),...
Articles

Research in context

Evidence before this study
We searched PubMed with the terms “episodic migraine”, “CGRP OR calcitonin gene-related peptide”, and “antibody OR antibodies” to identify articles published in English between Jan 1, 2010, and June 18, 2018. We identified 38 articles. Published work suggests that CGRP is involved in the pathophysiology of migraine. Biologics targeting CGRP (eg, erenumab, galcanezumab, fremanezumab, eptinezumab) showed efficacy compared with placebo in phase 2 and 3 trials of episodic migraine. However, efficacy and safety data have not yet been published for patients with episodic migraine in whom multiple previous preventive treatments were unsuccessful. Oral preventive therapies for episodic migraine are associated with low adherence because of poor efficacy or tolerability, or both. Thus, management of patients who have unsuccessfully tried multiple treatments becomes a challenge for physicians. Erenumab is a fully human monoclonal antibody that inhibits the canonical CGRP receptor. It has been approved in the USA by the Food and Drug Administration and in Australia for the preventive treatment of migraine in adults. In phase 2 and 3 studies in chronic and episodic migraine, erenumab was associated with significant reductions in monthly migraine days and use of acute migraine medications compared with placebo. The effects on monthly migraine days were sustained for up to 15 months in an open-label extension study in episodic migraine (4–14 headache days per month).

Added value of this study
In this 12-week, randomised, double-blind, placebo-controlled trial in patients with episodic migraine in whom multiple previous preventive treatments were unsuccessful, the proportion of patients with a 50% or greater reduction in the mean monthly number of migraine days from baseline was significantly higher in the erenumab 140 mg group than in the placebo group. In line with previously reported evidence, the tolerability and safety profiles of erenumab were similar to those of placebo, and no patients developed binding or neutralising antibodies during the double-blind treatment phase. These results suggest that erenumab is a potential treatment for difficult-to-treat episodic migraine in patients who have previously unsuccessfully tried multiple preventive medications.

Implications of all the available evidence
Erenumab 140 mg is a well tolerated and potentially effective preventive treatment for patients with episodic migraine, even in those in whom multiple other migraine preventives had either low efficacy or low tolerability.

antiepileptics (mainly topiramate and valproate), and antidepressants (eg, amitriptyline).1 None of these therapies were specifically developed for migraine,3–5 and their mode of action in the disease is not clearly defined.1,3 Efficacy and tolerability are considered to be poor by up to 50% of patients resulting in early discontinuation of treatment.4–6 As a result, many patients’ conditions cannot be managed with available preventives, and patients experience high disability and severely impaired quality of life.1

CGRP is a neuropeptide that has an important role in migraine pathophysiology7,8 and is a target for migraine preventive therapies.10,11 Erenumab is a fully human monoclonal antibody that inhibits the canonical CGRP receptor.8 At 4-weekly doses of 70 mg and 140 mg, erenumab efficaciously reduced monthly days with migraine and migraine-specific medications in episodic12,13 and chronic14 migraine. A subset of the participants in these studies had previously unsuccessfully tried other preventive treatments.7 In this study, we aimed to compare the efficacy and tolerability of erenumab with placebo in a well defined group of patients with episodic migraine who had previously not responded adequately to two-to-four preventive treatments, or who could not tolerate these treatments.

Methods

Study design and participants

LIBERTY was a 12-week, randomised, double-blind, placebo-controlled, phase 3b study done at 59 sites in 16 countries across Europe and Australia. A summary of patient enrolment by country is in the appendix. Eligible patients were aged 18–65 years and had a history of episodic migraine with or without aura18 for at least 12 months. They also fulfilled the criteria for migraine in the third edition of the international classification of headache disorders, and had to have had migraine symptoms for an average of 4–14 days per month (ie, every 28 days) during the 3 months before screening and during the baseline period, but for no more than 14 days per month headache (irrespective of whether these symptoms were associated with migraine).

Eligible participants also had to have previously been treated unsuccessfully (in terms of either efficacy or tolerability, or both) with between two and four of the preventive treatments propranolol or metoprolol, topiramate, flunarizine, valproate, amitriptyline, venlafaxine, lisinopril, candesartan, or other locally approved preventives (cinnarizine in Czech Republic, indoramin and oxerutin in France, nadolol in Spain, and pizotifen in Austria, Czech Republic, France, the Netherlands, Sweden, and the UK); to have been treated unsuccessfully with, or deemed unsuitable for, at least one of propranolol, metoprolol, topiramate, or flunarizine; or to have been treated unsuccessfully with, or deemed unsuitable for, valproate. Efficacy failure was defined as no meaningful reduction in frequency of migraine headaches after administration of drugs for at least 2–3 months as recommended by the European Headache Federation treatment guidelines19 at generally accepted
therapeutic doses within the 5 years before screening. Tolerability failure was defined as documented discontinuation due to adverse events at any previous time. For the purposes of this study, being deemed unsuitable for treatment was defined as a patient being considered to be ineligible for a treatment for medical reasons such as contraindications or precautions included in local labels, national guidelines, or other locally binding documents, or other medically relevant reasons as confirmed by the treating physician. Treatment failure and unsuitability were assessed on the basis of the patient’s medical history and medical judgment.

Patients were excluded from the study if they were older than 50 years at migraine onset; were pregnant or nursing; had a history of cluster headache, hemiplegic migraine headache, seizure, or psychiatric disorder; had active chronic pain syndrome, hepatic disease, or malignancy of any organ; used a preventive migraine medication within five times the drug’s half-life before baseline or a device or procedure within the month before the baseline phase (or during the baseline phase); or received botulinum toxin A treatment in the head or neck region within the 4 months before the start of the baseline phase or during the baseline phase. Patients with pre-existing myocardial infarction, stroke, transient ischaemic attack, or unstable angina, or who had undergone coronary artery bypass surgery or other revascularisation procedures within the 12 months before screening, were also excluded, as were patients with medication overuse for any indication in the month before the baseline phase or during the baseline phase. A complete list of inclusion and exclusion criteria is in the appendix.

The final study protocol, the informed consent form, and accompanying materials provided to study patients were reviewed and approved by an independent ethics committee or relevant institutional review board at all participating sites. This study was done in accordance with International Council for Harmonisation Good Clinical Practice regulations and guidelines. All participants provided written informed consent before participation.

Randomisation and masking
Participants were enrolled by investigators and randomly assigned (1:1) to either placebo or erenumab via interactive response technology. The randomisation list was generated by Cenduit, a vendor providing interactive voice response services. Cenduit also allocated participants to groups. Randomisation was stratified by monthly frequency of migraine headache (4–7 vs 8–14 migraine days per month) during the baseline phase. Study treatment was administered by study staff members masked to treatment assignment. Both erenumab and placebo were delivered via individually packaged prefilled syringes that were identical in appearance. Participants, investigators, people doing various assessments, and the study sponsor were masked to treatment assignment.

Procedures
The study included a screening phase (0–2 weeks), baseline phase (4 weeks), double-blind treatment phase (12 weeks), open-label treatment phase (156 weeks), and a follow-up phase (12 weeks). In this publication, we report data from the double-blind treatment phase only. The open-label phase is ongoing. During screening, all participants underwent a thorough medical examination and eligibility assessments. They also received training on how to use an electronic diary (eDiary) for daily reporting. During the baseline phase, participants completed their eDiary daily by recording any headache or migraine symptoms experienced and any rescue medications used. Compliance with completion of eDiary was measured. Eligibility for randomisation was based on migraine frequency and eDiary compliance of at least 80% during the baseline phase.

Participants who were randomly assigned received treatment on day 1 and then every 4 weeks for the 12-week double-blind treatment phase. Patients in the erenumab group received two subcutaneous injections of erenumab 70 mg/1 mL (total dose 140 mg); those in the placebo group received a matching dose of placebo. Participants recorded efficacy information every day in their eDiary. To improve compliance, participants were recommended to record information in the eDiary at the same time every day. Patients were allowed to retroactively complete their eDiary up to 1 day late, but entries more than 2 days old were not allowed and data were considered to be missing. Participant-reported outcome questionnaires (ie, Migraine Physical Function Impact Diary, Headache-Impact Test, Work Productivity and Activity Impairment, Beck Depression Inventory, and EQ-5D-5L) were completed using the eDiary as per the assessment schedule (appendix), either daily or during scheduled visits to the clinic. During the scheduled clinic visits (4 weeks before randomisation, randomisation visit, and weeks 4, 8, and 12), the questionnaires that were to be completed in clinic were done before other assessments, such as measurement of blood pressure, electrocardiography, and withdrawal of blood samples. At the follow-up visits at weeks 4, 8, and 12, patients were assessed for efficacy, safety, and tolerability, and eDiary compliance was reviewed.

Outcomes
The primary endpoint was the proportion of patients who achieved at least a 50% reduction from their individual baseline in the number of monthly migraine days during the third month of the double-blind treatment phase (ie, weeks 9–12). A migraine day was defined as any calendar day on which the patient had onset, continuation, or recurrence of a qualified migraine as recorded in the eDiary. A qualified migraine was defined as a migraine with or without aura lasting at least
30 min and manifesting with at least two headache features or at least one associated non-headache feature, or both (appendix). Any calendar day on which acute migraine-specific medication was used was also counted as a migraine day.

Secondary efficacy endpoints were change from baseline in monthly migraine days, change from baseline in monthly acute migraine-specific medication days (including triptans or ergotamine derivatives), the proportion of patients with a 75% or greater or 100% reduction from baseline in monthly migraine days, and change from baseline in scores on the everyday activities and physical activity subdomains of the Migraine Physical Function Impact Diary. All secondary efficacy endpoints were assessed for weeks 9–12 of the double-blind treatment phase. The primary and secondary efficacy endpoints were also analysed at weeks 0–4 and weeks 5–8 as exploratory endpoints to assess the overall timecourse of efficacy.

Safety, tolerability, and immunogenicity were also assessed by recording observed or reported adverse events and by physical examination, measurement of vital signs, clinical laboratory assessments, and electrocardiography (ECG).

Statistical analysis
On the basis of previous experience with erenumab in patients with episodic migraine, we estimated that, with a two-sided α of 0·05 and 90% power, and assuming an absolute 20% point improvement on the response rate for the 50% reduction in monthly migraine days, with an 18% response rate in the placebo group (equivalent to an odds ratio [OR] of 2·8), approximately 220 patients (110 per treatment group) would be needed for this study. No formal interim analyses were planned during the double-blind treatment phase. No multiplicity adjustment was applied.

The randomised analysis set included all randomly assigned patients (ie, intention-to-treat population) and was the basis for summaries of patient disposition, demographics, and baseline disease characteristics. The full analysis set, which was used for efficacy analyses, included all randomly assigned patients who started their study medication, completed at least one post-baseline monthly migraine day measurement in the double-blind treatment phase, and were analysed on the basis of the preplanned randomised treatment. The safety analysis set included all randomly assigned patients who received at least one dose of study drug. Analyses were based on actual treatment received.

Demographic variables and other baseline characteristics were summarised with descriptive statistics. We used the Cochran-Mantel-Haenszel test to measure the association between 50% responder rate and treatment group; analysis was stratified by migraine frequency, with a one-sided significance level of 0·025 (0·05 two-sided). ORs, 95% CIs, and two-sided p values are reported. Patients with missing data for monthly migraine days at month 3 of the double-blind treatment phase were imputed as non-responders. The continuous change from baseline efficacy endpoints (least-square means) was analysed with a linear mixed-effects model, including treatment group, baseline value, stratification factors, study visit, and the interaction of treatment group with study visit, without any imputation for missing data. The dichotomous secondary efficacy endpoints derived from corresponding continuous endpoints were analysed with the stratified Cochran-Mantel-Haenszel test after imputation of missing data as non-response. Estimates (treatment difference or OR) of erenumab compared with placebo with associated 95% CI and p values are reported.

In previous studies of erenumab for prevention of episodic migraine, patients in whom more than two drug classes were not effective were excluded. Thus, we also did a post-hoc analysis of the primary and secondary efficacy endpoints at week 12 on the basis of treatment failure of previous preventive medication (two treatment failures vs more than two treatment failures). For continuous variables, \( p_{\text{treatment}} \) was defined from the modified primary model with additional terms of subgroup and subgroup-by-treatment-group interaction as two additional effects. For the subgroup of dichotomous variables, \( p_{\text{treatment}} \) was calculated via logistic regression that included treatment group, stratification factor, subgroup factor, and treatment-by-subgroup-factor interaction as fixed effects, with the baseline value as covariate. The adjusted mean changes from baseline, SEs, and 95% CIs for each subgroup and the nominal p value for subgroup-by-treatment interactions were calculated.

For safety analyses, the Medical Dictionary for Regulatory Activities (version 20.1) was used to code all adverse events. Adverse events were tabulated as participant incidence and exposure-adjusted participant incidence. Summary statistics were provided for...
laboratory data, ECG, vital signs, and immunogenicity assessments. We used SAS (version 9.4) for all statistical analyses. This trial is registered with ClinicalTrials.gov, number NCT 03096834.

Role of the funding source
Employees of the study funder had roles in trial design; data collection, analysis, and interpretation, and writing of the report. All authors had full access to all study data and had final responsibility for the decision to submit for publication.

Results
Between March 20, 2017 (first patient first visit), and Oct 27, 2017 (last patient last visit of the double-blind treatment phase), 333 patients were screened for eligibility, and 246 were randomly assigned: 121 to the erenumab group and 125 to the placebo group (figure 1). Three participants (two in the erenumab group and one in the placebo group) were excluded from the full analysis set and safety analysis for protocol deviations—specifically, they did not receive study drug. Six patients discontinued the double-blind treatment phase (figure 1). No patient in either group discontinued treatment because of an adverse event.

The treatment groups were generally well balanced in terms of baseline demographic and disease characteristics (table 1). At baseline, the mean monthly number of migraine days was 9·2 (SD 2·6) in the erenumab group and 9·3 (2·7) in the placebo group (table 1). The most common unsuccessfully used preventive drugs were topiramate (used by 209 patients [85%] overall), amitriptyline (112 [46%]), and propranolol (111 [45%]). For most treatments, the main cause of treatment failure was lack of efficacy, except for topiramate, for which the main reason was low tolerability (appendix).

At 12 weeks, 36 (30%) of 119 patients in the erenumab group had a 50% or greater reduction in the monthly number of migraine days, compared with 17 (14%) of 124 in the placebo group (OR 2·7 [95% CI 1·4–5·2]; p=0·002; figure 2; table 2). A significantly greater proportion of patients in the erenumab group than in the placebo group also had a 50% or greater reduction in the monthly number of migraine days during weeks 0–4 and weeks 5–8 (figure 2; table 2).

At 12 weeks, 14 (12%) of patients in the erenumab group and five (4%) in the placebo group had a 75% or greater reduction in the monthly number of migraine days (OR 3·2 [95% CI 1·1–9·0]; p=0·025; table 2). ORs could not be calculated for the proportion of patients who had a 100% reduction in the monthly number of migraine days because there were no events in the placebo group (table 2). Significant improvements in all secondary endpoints—including monthly days with migraine and monthly migraine-specific medication days—for weeks 9–12 were also noted in the erenumab group compared with the placebo group (table 3). Differences in efficacy between the erenumab and placebo groups were apparent for all secondary outcomes at week 4 (table 3).

Results for subgroup analyses based on the number of previously unsuccessful treatments are shown in the
appendix. Results for the primary endpoint in subgroups of patients who discontinued β blockers, topiramate, or amitriptyline because of poor efficacy or tolerability were similar to those in the overall study population (appendix).

All patients in both treatment groups received at least two treatments, and most (>98%) received all three treatments (ie, six injections in total; data not shown). Overall, erenumab was well tolerated. The proportions of patients reporting at least one adverse event and serious adverse events were similar between treatment groups (table 4). Most adverse events observed were mild or moderate in severity (table 4), and no deaths occurred during the double-blind treatment phase. The most frequent treatment-emergent adverse events were nasopharyngitis, injection site pain, and back pain (table 4).

Two treatment-emergent serious adverse events were reported in the erenumab group: one case of migraine and one traumatic orbital fracture. Neither was thought to be related to the study drug.

![Figure 2: Proportion of patients with a 50% or greater reduction in monthly migraine days in the erenumab and placebo groups](image-url)

OR=odds ratio.

<table>
<thead>
<tr>
<th>Weeks 1–4</th>
<th>Erenumab group (n=119)</th>
<th>Placebo group (n=124)</th>
<th>OR (95% CI); p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50% responder rate</td>
<td>27 (23%)</td>
<td>6 (5%)</td>
<td>5·9 (2·3–14·9); p&lt;0·001</td>
</tr>
<tr>
<td>≥75% responder rate</td>
<td>11 (9%)</td>
<td>0</td>
<td>.*</td>
</tr>
<tr>
<td>100% responder rate</td>
<td>4 (3%)</td>
<td>0</td>
<td>.*</td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise indicated. Responder rates were reported as recorded in the week of assessment. For statistical analysis, we used the Cochran-Mantel-Haenszel test, adjusted for stratification (ie, 4–7 vs 8–14 monthly migraine days at baseline), in which missing data were imputed as non-responders. OR=odds ratio.

*Because there were no responders in the placebo group, the OR could not be calculated.

Table 2: Responder rates in the full analysis set

<table>
<thead>
<tr>
<th>Weeks 1–4</th>
<th>Erenumab adjusted mean change (SE)</th>
<th>Placebo adjusted mean change (SE)</th>
<th>Mean difference (95%CI); p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monthly migraine days</td>
<td>-1.8 (0.4)</td>
<td>0.1 (0.3)</td>
<td>-1.8 (-2.7 to -0.9); &lt;0.001</td>
</tr>
<tr>
<td>MSMDs</td>
<td>-1.1 (0.2)</td>
<td>0.3 (0.2)</td>
<td>-1.4 (-2.0 to -0.8); &lt;0.001</td>
</tr>
<tr>
<td>MPFID</td>
<td>-2.4 (0.6)</td>
<td>1.3 (0.6)</td>
<td>-3.7 (-5.3 to -2.1); &lt;0.001</td>
</tr>
<tr>
<td>Everyday activities</td>
<td>-3.5 (0.6)</td>
<td>0.5 (0.6)</td>
<td>-3.9 (-5.6 to -2.3); &lt;0.001</td>
</tr>
</tbody>
</table>

n=119 in the erenumab group and 124 in the placebo group. A linear mixed effects model includes treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit. Unstructured covariance matrix assumed. MSMDs=monthly acute migraine-specific medication days. MPFID=Migraine Physical Function Impact Diary. *n=118. †n=120.

Table 3: Change from baseline in monthly migraine days, MSMDs, and MPFID items in the full analysis set
reported in the placebo group. No clinically meaningful differences were noted between the erenumab and placebo groups with regards to results of hepatic-function testing, creatinine concentrations, total neutrophil counts, vital signs, or ECG findings (data not shown). None of the 119 patients who received erenumab and provided testing samples developed binding or neutralising antibodies during the double-blind treatment phase (data not shown).

Discussion
LIBERTY is, to our knowledge, the first study to show that a CGRP-directed therapy could have preventive efficacy in patients with episodic migraine in whom multiple previous preventive treatments have been unsuccessful. At 12 weeks, significantly more patients in the erenumab group than in the placebo group had a 50% or greater reduction from baseline in the mean number of monthly migraine days. As in previous large placebo-controlled trials, in migraine prevention, adverse events reported in the erenumab group were similar to those reported in the placebo group. Erenumab was also significantly more efficacious than placebo for all secondary endpoints, including improvements in migraine frequency, medication use, and functional outcomes. Our results suggest that erenumab might be a new treatment option for patients with difficult-to-treat migraine in whom traditional oral migraine preventive treatments were unsuccessful, not tolerated, or contraindicated.

Whereas a low frequency of binding antibodies has been reported in previous trials with longer double-blind treatment periods (3.2% of patients given erenumab 140 mg in one study, and 2% in another study, developed binding antibodies; no patients in either study developed neutralising antibodies), no patients in the erenumab group developed binding or neutralising antibodies in this study, which provides further evidence that erenumab is a fully human antibody with low immunogenic potential. However, longer-term follow-up is needed, because anti-drug antibodies could develop later.

Our trial population comprised patients with episodic migraine in whom two-to-four previous treatments were unsuccessful, who are typically excluded in pivotal trials to avoid refractory patients and negative study outcomes. Although our results therefore cannot be directly compared with those of pivotal trials, they extend the findings from analyses of subgroups of patients with previous treatment failure in earlier migraine trials with erenumab. In the chronic migraine pivotal study of 667 patients, 453 (68%) patients had previously unsuccessfully tried at least one preventive drug, 327 (49%) had tried at least two, and 232 (35%) had tried at least three. Erenumab 70 mg and 140 mg were consistently more efficacious in terms of reduction in the mean number of migraine days than placebo in patients in whom previous treatments were unsuccessful, with greater clinical benefit noted for the erenumab 140 mg dose than for the 70 mg dose. Although not significant, numerically higher differences from placebo in terms of monthly migraine days and monthly acute migraine-specific medication days were noted with erenumab in participants who had previously unsuccessfully tried one or more or two or more preventive medications than in those in whom no previous treatments had failed. This finding was particularly true for erenumab 140 mg (although statistical comparison with the 70 mg dose was not done), which is why we chose the 140 mg dose for our study. Similar findings were reported in the STRIVE study, in which the representation of patients in whom previous treatment was unsuccessful was lower than that in the other pivotal study: 369 (39%) had unsuccessfully tried at least one previous preventive treatment and 161 (17%) had tried at least two. Although the difference was not significant, erenumab was associated with numerically better results than placebo in the treatment failure subgroups compared with the respective full populations in terms of monthly migraine days and 50% or greater responder rates, differences that were mainly driven by lower placebo responses in the patients in whom previous treatments had been unsuccessful.

Our results are further supported by a post-hoc analysis of a trial of galcanezumab, which showed efficacy in episodic and chronic migraine in patients in whom previous preventives were unsuccessful. Taken altogether, the CGRP mechanism seems to work even in difficult-to-treat patients in whom previous preventive treatments did not work or were not tolerated.

The absolute responses in our study appear to be lower numerically than those in populations in whom fewer treatments have been unsuccessful. This finding is partly related to placebo behaviour in this population of patients who have taken several treatments unsuccessfully. Placebo

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<table>
<thead>
<tr>
<th>At least one adverse event</th>
<th>Erenumab group (n=119)</th>
<th>Placebo group (n=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>65 (55%)</td>
<td>67 (54%)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Any adverse event leading to treatment discontinuation</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>7 (6%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>5 (4%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5 (4%)</td>
<td>12 (10%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (3%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (3%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>3 (3%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Neck pain</td>
<td>3 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>3 (3%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Treatment-emergent adverse events recorded in at least 2% of patients in the erenumab group are included in the table. Data are n (%). If patients got the same adverse event more than once, it was counted only once. *Patients with more than one adverse event were counted only once.

Table 4: Treatment-emergent adverse events in the safety population
response is complex in indications such as migraine and has historically shown some degree of variability, which frequently depends on methodological and unblinding issues. In previous trials of erenumab, placebo response was higher in treatment-naive patients than in patients in whom previous treatments had been unsuccessful. In line with findings in the subgroups of patients who had unsuccessfully taken previous preventive drugs, placebo response was lower in our trial than overall placebo response in previous trials of erenumab. This low response could possibly reflect lower expectations in patients who have unsuccessfully tried previous treatments. The overall temporal pattern of the placebo response in our study follows that in the STRIVE study, in which placebo response gradually built up during the first 3 months, and then reached a plateau afterwards.

A limitation of our study is that 12 weeks is not long enough to establish long-term adherence to treatment. This shortcoming will be addressed in the open-label extension of our trial. Ascertainment of previous treatment failure was done retrospectively on the basis of documented medical history, without other corroborating evidence. Although patients with comorbidities such as anxiety and depression were allowed in the study, patients with other major comorbidities were excluded, which limits the generalisability of our findings. Furthermore, the secondary endpoints were not controlled for multiplicity and the subgroup analysis based on treatment failure categories should be interpreted with caution because of the small sample size.

So far, few data are available to guide evidence-based treatment decisions in patients in whom previous treatments have been unsuccessful. Our study provides the first direct, controlled trial evidence for a novel CGRP-directed therapy, which will allow practitioners to consider the place of these novel therapies in evidence-based treatment algorithms.

Contributors
UR, PJG, and JK designed the study. The chief investigators were UR, PJG, ML-M, and MDF. SW was responsible for statistical analyses. PH-Z participated in patient data collection. All authors interpreted data, agreed on the content of the manuscript, reviewed drafts, and approved the final version.

Declaration of interests
UR has received consulting fees, speaking fees, teaching fees, or research grants from Allergan, Amgen, Autonomic Technologies, CoLucid, ElectroCore, Eli Lilly, Medscape, Novartis, StreamMedUp, and Teva. PJG has received grants and personal fees from Amgen and Eli Lilly, company and personal fees from Alder Biopharmaceuticals, Allergan, Autonomic Technologies, Dr Reddy’s Laboratories, Electrocore, eNeura, Novartis, Scion, Teva, and Trigemina, and personal fees from MedicoLegal work, Journal Watch, Up-to-Date, Oxford University Press, Massachusetts Medical Society, and Wolters Kluwer. He holds a patent related to magnetic stimulation for headache, which is assigned to eNeura without fee. ML-M has received honoraria for advisory boards, speaker panels, or investigation studies from Allergan, Amgen, Astellas, AT&I, Bristol-Myers Squibb, Boehringer Ingelheim, Boston Scientific, CoLucid, Convergence, GlassSmithKline, Grünenthal, Lilly, Medtronic, Menarini, MSD, Novartis, Pfizer, Reckitt Benckiser, Saint-Jude, Sanofi-Aventis, Teva, UCB, and Zambon. MDF has received grants, consultancy fees, or trial support from Medtronic, Electrocore, Amgen, Lilly, Teva, and Novartis, and independent support of the European Community, NWO, the US National Institutes of Health, and the Dutch Heart Foundation. SW, PH-Z, and JK are employees of, and hold stock in, Novartis.

Data sharing
Institutions wishing to analyse data from the study can apply via www.clinicalstudydatarequest.com.

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