Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial

Stewart Tepper, Messoud Ashina, Uwe Reuter, Jan L Brandes, David Doležil, Stephen Silberstein, Paul Winner, Dean Leonardi, Daniel Mikol, Robert Lenz

Summary
Background The calcitonin gene-related peptide (CGRP) pathway is important in migraine pathophysiology. We assessed the efficacy and safety of erenumab, a fully human monoclonal antibody against the CGRP receptor, in patients with chronic migraine.

Methods This was a phase 2, randomised, double-blind, placebo-controlled, multicentre study of erenumab for adults aged 18–65 years with chronic migraine, enrolled from 69 headache and clinical research centres in North America and Europe. Chronic migraine was defined as 15 or more headache days per month, of which eight or more were migraine days. Patients were randomly assigned (3:2:2) to subcutaneous placebo, erenumab 70 mg, or erenumab 140 mg, given every 4 weeks for 12 weeks. Randomisation was centrally executed using an interactive voice or web response system. Patients, study investigators, and study sponsor personnel were masked to treatment assignment. The primary endpoint was the change in monthly migraine days from baseline to the last 4 weeks of double-blind treatment (weeks 9–12). Safety endpoints were adverse events, clinical laboratory values, vital signs, and anti-erenumab antibodies. The efficacy analysis set included patients who received at least one dose of investigational product and completed at least one post-baseline monthly measurement. The safety analysis set included patients who received at least one dose of investigational product. The study is registered with ClinicalTrials.gov, number NCT02066415.

Findings From April 3, 2014, to Dec 4, 2015, 667 patients were randomly assigned to receive placebo (n=286), erenumab 70 mg (n=191), or erenumab 140 mg (n=190). Erenumab 70 mg and 140 mg reduced monthly migraine days versus placebo (both doses −6·6 days vs placebo −4·2 days; difference −2·5, 95% CI −3·5 to −1·4, p<0·0001). Adverse events were reported in 110 (39%) of 282 patients, 83 (44%) of 190 patients, and 88 (47%) of 188 patients in the placebo, 70 mg, and 140 mg groups, respectively. The most frequent adverse events were injection-site pain, upper respiratory tract infection, and nausea. Serious adverse events were reported by seven (2%), six (3%), and two (1%) patients, respectively; none were reported in one patient in any group or led to discontinuation. 11 patients in the 70 mg group and three in the 140 mg group had anti-erenumab binding antibodies; none had anti-erenumab neutralising antibodies. No clinically significant abnormalities in vital signs, laboratory results, or electrocardiogram findings were identified. Of 667 patients randomly assigned to treatment, 637 completed treatment. Four withdrew because of adverse events, two each in the placebo and 140 mg groups.

Interpretation In patients with chronic migraine, erenumab 70 mg and 140 mg reduced the number of monthly migraine days with a safety profile similar to placebo, providing evidence that erenumab could be a potential therapy for migraine prevention. Further research is needed to understand long-term efficacy and safety of erenumab, and the applicability of this study to real-world settings.

Funding Amgen.

Introduction
Migraine is a primary headache disorder that can cause substantial pain and disability and has a high global burden. Chronic migraine, which is defined as headaches occurring for 15 days or more per month for 3 months or more, and migraines occurring 8 days or more per month, in a patient with a previous history of migraine, shares many features with, and can transform from, episodic migraine. Migraine therefore constitutes a spectrum of disease frequency and severity that affects quality of life and is associated with a range of comorbidities.

Chronic migraine affects approximately 1–2% of the global population, and is the most prevalent type of headache in tertiary care. Acute treatment options are available to abort migraine attacks, yet too frequent use of these can lead to medication overuse, a common problem in patients with chronic migraine. Based on the high frequency of migraine and effect on quality of life, patients with chronic migraine are good candidates for preventive therapy. However, there are few well controlled studies for migraine preventive therapies in patients with chronic migraine, with quality evidence...
Research in context

Evidence before this study
Preclinical studies dating back nearly three decades first suggested a role for calcitonin gene-related peptide (CGRP) in migraine. There has since been clinical substantiation, with proof-of-concept studies showing that monoclonal antibodies targeting the CGRP pathway have the potential to prevent migraines. A search through the Ovid SP platform using Embase (Jan 1, 1974–Oct 31, 2016) and Ovid Medline In-Process and other non-indexed citations and Epub ahead of print (Jan 1, 1946–Oct 31, 2016) using the search terms “CGRP”, “migraine”, “prevention”, “prophylaxis”, “monoclonal antibody”, and “chronic migraine”, restricted to studies in human beings and in English, identified 50 articles. Of these, five phase 2 studies of monoclonal antibodies targeting the CGRP pathway were identified: galcanezumab (LY2951742) in patients with episodic migraine; eptinezumab (ALD403) in patients with frequent episodic migraine; fremanezumab (TEV-48125) in patients with high-frequency episodic migraine and chronic migraine; and erenumab (AMG 334) in patients with episodic migraine. All studies contributed evidence for the role of CGRP in the pathogenesis of migraine, and all monoclonal antibodies investigated showed no significant adverse event or safety concerns and were seemingly well tolerated.

Added value of this study
The present study is, to the best of our knowledge, the largest phase 2 trial of an antibody targeting the CGRP pathway. It is available only for onabotulinumtoxinA,4,11 topiramate,12,13 and fremanezumab (TEV-48125).14 Other therapies such as β blockers or amitriptyline are frequently used, despite a lack of evidence in patients with chronic migraine. Oral preventive therapies available at present, including topiramate, β blockers, and amitriptyline, are often not fully efficacious or are poorly tolerated,15 which can lead to low adherence rates.16,17 One study of 8688 adults with chronic migraine estimated adherence to range from 26% to 29% at 6 months, decreasing to as low as 17% at 12 months.18 This gap in care is underscored by the availability of just one preventive treatment for adults with chronic migraine, onabotulinumtoxinA, which is approved by the US Food and Drug Administration and in receipt of a licence from the European Medicines Agency.19 Thus, a large unmet need remains.

Calcitonin gene-related peptide (CGRP) is a proinflammatory vasodilating neuropeptide implicated in the pathophysiology of migraine,20,21 with early studies showing that CGRP levels increase in jugular venous blood during migraine attacks22 and are elevated interictically in the peripheral circulation in patients with episodic migraine23 and chronic migraine.24 By contrast, normal plasma CGRP levels were reported in chronic tension-type headache.25 The CGRP pathway is a promising target for migraine therapies. Small-molecule CGRP receptor antagonists, also known as gepants, have previously shown efficacy for acute treatment of migraine, although concerns with liver toxicity from telcagepant halted clinical development.26 Studies of monoclonal antibodies as preventive therapy for migraine have shown potential with respect to efficacy and safety.14,27–31 Erenumab is the only fully human monoclonal antibody against the CGRP receptor, could be a potential new preventive therapy in patients with chronic migraine. Areas of future research should aim to identify which patients respond best to therapy and whether factors such as biomarkers, previous preventive treatment history, or presence or absence of medication overuse might predict a therapeutic response.

Evidence before this study
Preclinical studies dating back nearly three decades first suggested a role for calcitonin gene-related peptide (CGRP) in migraine. There has since been clinical substantiation, with proof-of-concept studies showing that monoclonal antibodies targeting the CGRP pathway have the potential to prevent migraines. A search through the Ovid SP platform using Embase (Jan 1, 1974–Oct 31, 2016) and Ovid Medline In-Process and other non-indexed citations and Epub ahead of print (Jan 1, 1946–Oct 31, 2016) using the search terms “CGRP”, “migraine”, “prevention”, “prophylaxis”, “monoclonal antibody”, and “chronic migraine”, restricted to studies in human beings and in English, identified 50 articles. Of these, five phase 2 studies of monoclonal antibodies targeting the CGRP pathway were identified: galcanezumab (LY2951742) in patients with episodic migraine; eptinezumab (ALD403) in patients with frequent episodic migraine; fremanezumab (TEV-48125) in patients with high-frequency episodic migraine and chronic migraine; and erenumab (AMG 334) in patients with episodic migraine. All studies contributed evidence for the role of CGRP in the pathogenesis of migraine, and all monoclonal antibodies investigated showed no significant adverse event or safety concerns and were seemingly well tolerated.

Methods

Study design and participants
We did a randomised, double-blind, placebo-controlled, phase 2 study in 69 headache and clinical research centres in North America (Canada and the USA) and Europe (Czech Republic, Denmark, Finland, Germany, Norway, Poland, Sweden, and the UK). The study comprised an...
initial screening phase (up to 3 weeks), a baseline phase (4 weeks), a double-blind treatment phase (12 weeks), and a safety follow-up phase (12 weeks).

Men and women aged 18–65 years with a history of chronic migraine (with or without aura) were enrolled. In each of the 3 months before screening, patients had to have had 15 or more headache days per month, of which 8 or more of those days were migraine days (based on medical records or self-report). The same criteria were applied during the baseline phase, with headache information recorded daily in an electronic diary. During this phase, patients had to show at least 80% compliance with the diary. Patients with overuse of triptans, ergot derivatives, analgesics, and combination drugs (any combination of those above or simple analgesics with opiates or butalbital) were permitted to participate in this study (appendix p 1). Patients were excluded if they were older than 50 years at migraine onset and if they had a history of cluster headache or hemiplegic migraine, or chronic migraine with continuous pain (ie, no pain-free periods of any duration during the 1 month before screening). Patients were also excluded from the study if they had no therapeutic response (reduction in frequency, duration, or severity of headache) with prophylaxis of more than three treatment categories (appendix p 1) after an adequate trial (at least 6 weeks of treatment at generally accepted doses). Migraine preventive drugs were prohibited during the study and 2 months before the start of the baseline phase (appendix pp 1, 2). Botulinum toxin injections in the head or neck region were prohibited during the study and for at least 4 months before the start of the baseline phase. Patients were recruited under the supervision of study investigators at each site.

An independent ethics committee or relevant institutional review board for each study centre approved the final study protocol. All patients provided written informed consent before initiation of any study procedures. Summaries of data by unmasked treatment assignment were prepared by an independent biostatistician group and presented to an independent data monitoring committee that reviewed the summaries and made recommendations regarding the safety of study participants throughout the 12-week double-blind treatment phase. The data monitoring committee included two clinicians and a biostatistician external to the sponsor.

Randomisation and masking
Eligible patients were randomly assigned (3:2:2) to receive placebo, erenumab 70 mg, or erenumab 140 mg once every 4 weeks for the 12-week double-blind treatment phase. Randomisation was stratified by region (North America vs Europe) and medication overuse (presence vs absence). Patients were assigned to treatment groups using a sponsor-generated randomisation sequence centrally executed by an interactive voice response or interactive web response system. Erenumab was packaged in 5 mL clear glass vials containing 1 mL of 70 mg/mL erenumab; placebo was presented in identical vials and stored, packaged, and formulated to match erenumab. All patients received two 1 mL injections consisting of either two placebo syringes (placebo group), one erenumab 70 mg syringe and one placebo syringe (70 mg group), or two erenumab 70 mg syringes (140 mg group). Patients, sponsor site personnel, and study personnel were all masked to treatment assignment. Sponsor study personnel who were responsible for tracking, assaying, or analysing biological samples, who did not have access to patient-level clinical data apart from the samples they were assaying and analysing, were unmasked to treatment assignments.

Procedures
During the 12-week, double-blind treatment phase, patients received two subcutaneous 1 mL injections at study centre visits on day 1, week 4, and week 8. Patients entered headache information using the electronic diary, including incidence of headache (ie, incidence of migraine with or without aura, or non-migraine headache), presence of aura, time of onset of headache, time to resolution of headache, headache severity, pain features, and other migraine symptoms, and use of acute drug treatment during aura or headaches. Based on this information, an algorithm determined whether any given calendar day qualified as a migraine day. Data on concomitant therapies were collected on the electronic diary or case report form. Adverse events observed by the investigator or reported by the patient were recorded on the case report form during the study centre visits throughout the double-blind treatment phase. A central laboratory processed complete blood count, serum chemistry, urine drug screening, and serum pregnancy testing, and samples for pharmacokinetic testing, biomarker development, and pharmacogenetics studies (collected during the study centre visits). Anti-erenumab antibody testing samples were sent to the central laboratory and then to the sponsor for analysis.

Outcomes
The primary endpoint was the mean change in monthly migraine days from the baseline phase to the last 4 weeks of the 12-week double-blind treatment phase (number of migraine days from weeks 9 to 12 of double-blind treatment minus the number of migraine days during the 4 weeks of baseline). Migraine days were assessed on the basis of headache duration, symptoms, pain features, and migraine-specific drug use on the calendar day. A migraine day was defined as any calendar day on which the patient had an onset, continuation, or recurrence of a qualified migraine. A qualified migraine was defined as a migraine headache (with or without aura) lasting for at least 4 h continuously, with reports of either two or more pain features (unilateral, throbbing, moderate-to-severe
intensity, or aggravation by exercise or physical activity) or one or more associated non-pain features (nausea or vomiting, or both photophobia and phonophobia). If a patient took an acute migraine-specific drug during aura or to treat headache during a calendar day, the day was counted as a migraine day regardless of the headache duration and pain features or associated symptoms. A headache day was defined as any calendar day on which the patient experienced a qualified migraine headache or a non-migraine headache (onset, continuation, or recurrence of the headache) lasting at least 4 h continuously, or a headache of any duration for which acute drug treatment (simple analgesics, combination analgesics, triptans, ergot derivatives, or opiates) was given to treat headache pain.

Prespecified secondary efficacy endpoints were achievement of at least 50% reduction from baseline in monthly migraine days (ie, 50% responder rate), change from baseline in days on which acute migraine-specific drugs (triptans and ergot derivatives) were used, and change from baseline in cumulative headache hours (of any severity). All endpoints were assessed using data from the last 4 weeks of the 12-week, double-blind treatment phase. Safety endpoints were adverse events, clinical laboratory values, vital signs, and anti-erenumab antibodies. The Medical Dictionary for Regulatory Activities (MedDRA, version 19.0) was used to code all adverse events, and the Common Terminology Criteria for Adverse Events (CTCAE, version 4) was used to grade events. Primary and secondary endpoints were analysed as exploratory outcomes for weeks 1–4 and 5–8 of the double-blind phase; other exploratory outcomes will be reported separately.

**Statistical analyses**
The final analysis for the study, including the double-blind treatment phase and the safety follow-up phase, was done at the end of the study. Descriptive statistics by each treatment group were tabulated at each visit. We did statistical analyses according to a

---

**Figure 1: Study profile**

953 patients screened for eligibility

286 not randomly assigned
258 protocol-specified criteria
12 lost to follow-up
12 withdrawal of consent
4 decision by sponsor

667 patients randomly assigned

286 assigned to placebo
4 did not receive placebo
282 received placebo and were included in the safety analysis
1 did not complete ≥1 post-baseline monthly eDiary measurement
13 discontinued
6 at patient request
2 adverse events
2 ineligibility determined
2 lost to follow-up
1 non-compliance
281 included in efficacy analysis

191 assigned to erenumab 70 mg
1 did not receive erenumab 70 mg
190 received erenumab 70 mg and were included in the safety analysis
2 did not complete ≥1 post-baseline monthly eDiary measurement
6 discontinued
3 ineligibility determined
2 at patient request
1 lost to follow-up
1 non-compliance
188 included in efficacy analysis

190 assigned to erenumab 140 mg
2 did not receive erenumab 140 mg
190 received erenumab 140 mg and were included in the safety analysis
1 did not complete ≥1 post-baseline monthly eDiary measurement
6 discontinued
3 ineligibility determined
2 at patient request
1 lost to follow-up
2 adverse events
187 included in efficacy analysis

286 assigned to placebo

281 included in efficacy analysis

190 assigned to erenumab 140 mg

188 included in efficacy analysis

190 assigned to erenumab 70 mg

188 included in efficacy analysis

190 assigned to erenumab 140 mg

188 included in efficacy analysis

286 assigned to placebo

190 assigned to erenumab 70 mg

190 assigned to erenumab 140 mg

286 assigned to placebo

281 included in efficacy analysis

188 included in efficacy analysis

188 included in efficacy analysis
prespecified statistical analysis plan. Assuming a treatment effect of −1.9 days with a SD of 6.1, the planned sample size of 279 for the placebo group and 186 for the erenumab 70 mg group provided 85% power using a two-sample t test with a two-sided significance level of 0.04. Assuming a treatment effect compared with placebo of −2.21 days for the erenumab 140 mg group provided 85% power using a two-sample t test with a two-sided significance level of 0.01.

A sequential testing procedure, specifically the hierarchical gate-keeping procedures and Hochberg method, was used to maintain the two-sided study-wise type 1 error at 0.05 for the two erenumab doses and the primary and secondary endpoints. The test for erenumab superiority in the primary endpoint (change from baseline in mean monthly migraine days) was tested separately at a significance level of 0.04 for the erenumab 70 mg group and 0.01 for the erenumab 140 mg group. If the primary endpoint was significantly different from placebo at each dose level, the secondary endpoints were to be tested separately using the Hochberg method at the same significance levels. If the secondary endpoints were significantly different for an erenumab treatment group compared with placebo, the corresponding significance level was to be carried over to the hypothesis testing of the primary endpoint for the other erenumab treatment group, if it was not significantly different from placebo under the original significance level (0.04 for the 70 mg group and 0.01 for the 140 mg group). If the secondary endpoints were negatively correlated, the Holm method was used for the corresponding tests rather than the Hochberg method.

For the primary endpoint at week 12, the least-squares mean at each timepoint was calculated with a linear mixed effects model including treatment group, baseline monthly migraine days, stratification factors (region [North America vs Europe] and medication overuse [presence vs absence]), scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. The continuous secondary endpoints were analysed with the same method as for the primary endpoint. We reported the least-squares mean change from baseline for each treatment group, treatment difference compared with placebo, 95% CI, and p values for pairwise comparison. For the 50% responder secondary endpoint, we used a stratified Cochran-Mantel-Haenszel test after the missing data were imputed as non-response. We reported adjusted odds ratios (OR) compared with placebo, 95% CI, and p values.

The randomisation analysis set included all patients who were randomly assigned to treatment or placebo in the study. The efficacy analysis set included patients in the randomisation analysis set who received at least one dose of investigational product and completed at least one post-baseline monthly electronic diary measurement. The safety analysis set included all randomly assigned patients who received at least one dose of investigational product. For all analyses, patients were analysed according to the randomised treatment.

This trial is registered with ClinicalTrials.gov, number NCT02066415.

Role of the funding source

The study sponsor, in collaboration with investigators, developed the protocol. The study sponsor provided study drug, managed study sites, and did the statistical analysis according to a prespecified statistical analysis plan. Site investigators collected the data and authors interpreted the data and contributed to the manuscript preparation, with support from professional medical writers, funded by Amgen. All authors had full access to the study data. All authors made the final decision to submit the manuscript for publication.

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=286)</th>
<th>Erenumab 70 mg (n=191)</th>
<th>Erenumab 140 mg (n=190)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42.1 (11.3)</td>
<td>41.4 (11.3)</td>
<td>42.9 (11.1)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>226 (79%)</td>
<td>166 (87%)</td>
<td>160 (84%)</td>
</tr>
<tr>
<td>Men</td>
<td>60 (21%)</td>
<td>25 (13%)</td>
<td>30 (16%)</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>26.3 (5.1)</td>
<td>26.0 (5.3)</td>
<td>26.0 (5.4)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>268 (94%)</td>
<td>176 (92%)</td>
<td>184 (97%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>11 (4%)</td>
<td>10 (5%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (1%)</td>
<td>4 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Other†</td>
<td>3 (1%)</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>Age at migraine onset (years)</td>
<td>20.4 (10.0)</td>
<td>21.1 (10.9)</td>
<td>21.5 (10.6)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>22.2 (12.6)</td>
<td>20.7 (12.8)</td>
<td>21.9 (11.8)</td>
</tr>
<tr>
<td>History of migraine with aura</td>
<td>124 (43%)</td>
<td>81 (42%)</td>
<td>71 (37%)</td>
</tr>
<tr>
<td>Medication overuse</td>
<td>117 (41%)</td>
<td>79 (41%)</td>
<td>78 (41%)</td>
</tr>
<tr>
<td>History of previous preventive treatment failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No drug failures‡</td>
<td>86 (30%)</td>
<td>64 (34%)</td>
<td>64 (34%)</td>
</tr>
<tr>
<td>Failure of ≥1 drug§</td>
<td>200 (70%)</td>
<td>127 (67%)</td>
<td>126 (66%)</td>
</tr>
<tr>
<td>Failure of ≥2 drugs§</td>
<td>142 (50%)</td>
<td>93 (49%)</td>
<td>92 (48%)</td>
</tr>
<tr>
<td>Previous use of preventive drug topiramate</td>
<td>150 (52%)</td>
<td>89 (47%)</td>
<td>97 (51%)</td>
</tr>
<tr>
<td>Previous use of onabotulinum toxin</td>
<td>65 (23%)</td>
<td>50 (26%)</td>
<td>43 (23%)</td>
</tr>
<tr>
<td>Baseline period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly migraine days</td>
<td>18.2 (4.7)</td>
<td>17.9 (4.4)</td>
<td>17.8 (4.7)</td>
</tr>
<tr>
<td>Monthly headache hours</td>
<td>235.3 (126.1)</td>
<td>223.6 (126.6)</td>
<td>215.1 (122.5)</td>
</tr>
<tr>
<td>Monthly headache days</td>
<td>21.3 (3.9)</td>
<td>20.5 (3.8)</td>
<td>20.7 (3.8)</td>
</tr>
<tr>
<td>Monthly migraine attacks</td>
<td>4.2 (1.7)</td>
<td>4.5 (1.7)</td>
<td>4.3 (1.6)</td>
</tr>
<tr>
<td>Monthly acute migraine-specific drug use days</td>
<td>9.5 (7.6)</td>
<td>8.8 (7.2)</td>
<td>9.7 (7.0)</td>
</tr>
<tr>
<td>Acute migraine-specific drug use</td>
<td></td>
<td>225 (79%)</td>
<td>143 (75%)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or n (%) unless otherwise stated. Table based on randomisation analysis set. Some percentages do not total 100% because of rounding. *One patient was 65 years old at screening but turned 66 before randomisation. §Excludes native Hawaiian and other Pacific Islander; multiple ethnic origins, or other. ||Triptans and ergot derivatives only.
Results

Eligibility assessments began on March 5, 2014. The double-blind treatment was given from April 3, 2014, when the first patient was randomly assigned, to Feb 23, 2016. 953 patients were screened for eligibility, and 667 patients were randomly assigned. 656 (98%) patients (281 receiving placebo, 188 receiving erenumab 70 mg, and 187 receiving erenumab 140 mg) were thus included in the efficacy analysis (figure 1). Retention rates were high, with 637 (97%) of 656 patients in the efficacy analysis set receiving the last dose of investigational product at week 8.

Baseline demographics and clinical characteristics were generally similar between groups, including the proportions of patients with a history of migraine with aura, previous preventive treatment failure, and medication overuse (table 1). There was a slightly higher proportion of female patients in the erenumab groups than in the placebo group and a small numerical difference in the mean monthly acute migraine-specific drug use days between the erenumab treatment groups at baseline (8·8 [SD 7·2] days for the 70 mg group and 9·7 [7·0] days for the 140 mg group; table 1).

At baseline, patients reported mean (SD) monthly migraine days of 18·2 (4·7), 17·9 (4·4), and 17·8 (4·7) in the placebo, erenumab 70 mg, and erenumab 140 mg groups, respectively. The erenumab 70 mg and 140 mg groups had a greater reduction in monthly migraine days from baseline during the last 4 weeks of the double-blind treatment phase compared with placebo (table 2, figure 2). The results were significant based on the prespecified hypothesis testing procedure.

During the last 4 weeks of the 12-week double-blind treatment phase, 75 (40%) of 188 patients in the erenumab 70 mg group and 77 (41%) of 187 patients in the erenumab 140 mg group achieved a 50% or greater reduction (ie, 50% responder rate) from baseline in monthly migraine days during the last 4 weeks of the double-blind treatment phase compared with placebo (figure 2, table 2). The proportion of patients experiencing adverse events was generally low, with higher proportions of female patients in the erenumab groups than in the placebo group (281 receiving placebo, 188 receiving erenumab 70 mg, and 83·8 (6·8) days for those who received erenumab 70 mg, and 82·5 (10·8) days for patients who received placebo, 82·8 (10·0) days for those who received erenumab during the double-blind treatment phase at weeks 4 and 8 suggested that both doses of erenumab resulted in greater reductions than placebo at earlier timepoints. In another exploratory analysis, increases in the 50% responder rate were also observed at week 4 and week 8 compared with placebo (appendix p 4).

Overall, 660 (99%) patients received at least one dose of investigational product and were included in the safety analysis. The mean (SD) duration of exposure during the double-blind treatment phase was 82·5 (10·8) days for patients who received placebo, 82·8 (10·0) days for those who received erenumab 70 mg, and 83·8 (6·8) days for those who received erenumab 140 mg. Of 378 patients who received erenumab, 370 (98%) received three doses (185 [97%] in the 70 mg group and 185 [98%] in the 140 mg group). The proportion of patients experiencing adverse events

### Table 2: Primary and secondary endpoints

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=281)</th>
<th>Erenumab 70 mg (n=188)</th>
<th>Difference or odds ratio (95% CI)</th>
<th>p value†</th>
<th>Erenumab 140 mg (n=187)</th>
<th>Difference or odds ratio (95% CI)</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly migraine days</td>
<td>−4·2 (0·4)</td>
<td>−6·6 (0·4)</td>
<td>−2·5 (−3·5 to −1·4)</td>
<td>&lt;0·0001</td>
<td>−6·6 (0·4)</td>
<td>−2·5 (−3·5 to −1·4)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% responder rate</td>
<td>66 (23%)</td>
<td>75 (40%)</td>
<td>2·21 (1·5 to 3·3)</td>
<td>0·0001</td>
<td>77 (41%)</td>
<td>2·31 (1·6 to 3·5)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Monthly acute migraine-specific drug treatment days</td>
<td>−1·6 (0·2)</td>
<td>−3·5 (0·3)</td>
<td>−1·9 (−2·6 to −1·1)</td>
<td>0·0001</td>
<td>−4·1 (0·3)</td>
<td>−2·6 (−3·3 to −1·8)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Cumulative monthly headache hours</td>
<td>−55·2 (5·7)</td>
<td>−64·8 (6·9)</td>
<td>−9·5 (−27·0 to 7·9)</td>
<td>0·2833</td>
<td>−74·5 (6·9)</td>
<td>−19·3 (−36·7 to −1·9)</td>
<td>0·0296</td>
</tr>
</tbody>
</table>

Data are least-squares mean (SE) or n (%) unless otherwise stated. *Difference in least-squares mean from placebo. †p values are for the placebo group vs the erenumab group. ‡Odds ratio.
and serious adverse events was similar between treatment groups (table 3). Discontinuation rates because of adverse events were low, with no patients in the erenumab 70 mg group, and only two patients each in the placebo (<1%) and erenumab 140 mg (1%) groups, withdrawing from the study because of adverse events. 281 patients reported adverse events, 83 (44%) of 190 in the erenumab 70 mg group, 88 (47%) of 188 in the erenumab 140 mg group, and 110 (39%) of 282 in the placebo group. The most frequent adverse events, reported by 2% or more of erenumab-treated patients, were injection-site pain, upper respiratory tract infection, nausea, nasopharyngitis, constipation, muscle spasms, and migraine (table 3). No adverse events were reported by more than 5% of patients in either of the erenumab groups, or by more than 6% of patients in the placebo group. Serious adverse events were reported by eight erenumab-treated patients and seven patients receiving placebo; no serious adverse events were reported by more than one patient in any of the treatment groups (table 3). No patient had a serious adverse event that led to withdrawal from the study.

There were 14 incidences of binding antibodies in the erenumab groups (11 [6%] in the 70 mg group and 3 [2%] in the 140 mg group), and no neutralising antibodies at any time. There was no association between antibody incidence and adverse events at any time during the study. Because of concerns of liver toxicity with the gepant class of CGRP receptor antagonists, patients were assessed for liver enzyme abnormalities. One patient in the erenumab 140 mg group experienced abnormal increases in alanine and aspartate aminotransferases at week 4; there were no associated adverse events reported by the patient and no interruption of treatment, and aminotransferases had returned to baseline levels by the next visit (week 8). No clinically significant abnormalities in vital signs, laboratory values, or electrocardiogram findings were recorded for any of the patients.

Discussion

In this study, two different doses of erenumab were given subcutaneously every 4 weeks, and shown to be efficacious and well tolerated in a population of patients with chronic migraine. The safety profile was similar to placebo.

Overall, patients enrolled in this study had migraine on more than half of the days in a month (mean around 18 migraine days per month during the baseline phase). Patients randomly assigned to either the erenumab 70 mg or erenumab 140 mg group experienced a mean 6-6-day reduction from baseline in monthly migraine days (2-5 days more than patients receiving placebo).
Reductions of headache frequency from baseline of more than 30% and by more than one day per month are generally thought to represent a clinically relevant change.\textsuperscript{14} The reductions in monthly migraine days in this study represent a change of more than 30%, and more than one day per month relative to patients receiving placebo. Additionally, at week 12, more patients in each erenumab dose group achieved a 50% reduction or more in migraine days from baseline compared with those in the placebo group, further confirming that erenumab can reduce the monthly burden of migraine in a substantial proportion of patients. The effect of erenumab was also substantiated by significant reductions in the number of days per month on which acute migraine-specific drugs were used in the erenumab groups compared with the placebo group, which were in accordance with the range of reductions in acute migraine-specific drug days during the phase 2 trial of fremanezumab (TEV-48125), a monoclonal anti-CGRP ligand antibody, in patients with chronic migraine.\textsuperscript{14}

There was no statistically significant difference between the erenumab groups and the placebo group for the secondary endpoint of cumulative headache hours. Headache hours was previously used as an endpoint to assess efficacy in patients with chronic migraine, notably in the PREEMPT 1 and 2 trials of onabotulinumtoxinA,\textsuperscript{11,14,15} and the phase 2 trial of fremanezumab (TEV-48125).\textsuperscript{14} Measurement and interpretation of this endpoint are not without limitations, and comparisons across trials are difficult because of different methods of capturing, computing, and analysing headache hours: importantly, these differences could translate into high variability of headache hour data. In our study, the placebo response was higher than expected, whereas the reductions in the erenumab groups compared with baseline were consistent with expectations. Headache hours might not be a reliable or clinically meaningful endpoint or standalone parameter, particularly in the absence of standardisation regarding when and how data are collected and analysed across studies. In the future, headache hours could be interpreted in conjunction with more robust headache-related parameters, such as headache days and responder rates.

Consistent with phase 2 results of erenumab in patients with episodic migraine,\textsuperscript{10} the present study not only shows the efficacy of erenumab in patients with chronic migraine, but also shows that it has a safety and tolerability profile similar to placebo. The positive safety profile is reflected by overall low study withdrawal rates, while the separation of response from placebo at week 4 suggests an early onset of efficacy. Between the placebo and erenumab groups there were no differences in the type or frequency of adverse events, no serious adverse events occurred in more than one patient in any of the treatment groups, and no serious adverse events were related to treatment or led to study withdrawal. Furthermore, only a small proportion of erenumab-treated patients developed drug-binding antibodies, with no observations of neutralising antibodies. Notably, there was no association between antibody incidence and adverse events at any time during the study.

Results from five other phase 2 studies have been published on the efficacy and safety of monoclonal antibodies targeting the CGRP pathway for migraine prevention,\textsuperscript{14,27–30} all of which showed efficacy, and none of which raised safety concerns. Thus there is collective affirmation that in a broad population of migraine patients, CGRP is important in the pathophysiology of migraine. Although antagonising the CGRP pathway seems to be an effective approach in migraine prevention, the continued occurrence of migraines during the study reinforces that it is probably not the only relevant pathway; for example, pituitary adenylate cyclase-activating peptide (PACAP)-38 has also been implicated in migraine pathophysiology.\textsuperscript{35} Although the specific pathogenic mechanism of CGRP in migraine is unknown, including uncertainty with respect to its site of action, it probably includes components of the trigemino-vascular system. Because of its size and structure as an antibody, the site of action for erenumab is probably limited to the periphery, which supports previous research suggesting that CNS penetration is not required for migraine prevention.\textsuperscript{35}

In the assessment of erenumab as a potentially clinically relevant migraine preventive therapy, the increases in 50% responder rate and reductions in the number of days on which acute migraine-specific drugs are taken provide complementary information to the primary endpoint of reduction in monthly migraine days. Although all aspects are important for patients with chronic migraine, the improvement in responder rate might be particularly important for patients who experience treatment failure, whereas reduction in acute migraine-specific drug days is relevant for patients with chronic migraine who concomitantly have medication overuse headache. This study provided robust representation of both subgroups of patients because it included 453 (68%) patients who had failed at least one previous preventive drug class because of lack of efficacy or poor tolerability and 327 (49%) who had failed at least two previous preventive drug classes, suggesting there could be efficacy in a treatment-resistant population. Furthermore, based on the randomisation strata, 274 (41%) patients met the criteria for medication overuse (appendix p 1). Subgroup analyses on these populations will be reported separately in another article.

A limitation of this study is that it remains to be seen how the safety, efficacy, and adherence in the 12-week double-blind treatment period is translated in the real world, over longer-term treatment. Also, although patients with comorbidities such as anxiety and depression were allowed in the study, patients with other comorbidities (eg, fibromyalgia and poorly controlled hypertension) were not, which limits the generalisability of the study results to broader populations.
Because of its favourable safety, tolerability, and efficacy profile in this study, and its once-monthly administration, subcutaneous erenumab has the potential to increase real-world adherence to treatment in patients with chronic migraine. This could address an important unmet need, because just 17–20% of patients with chronic migraine adhere to migraine preventive drugs after 1 year, and non-adherence can lead to worsening of the disorder. Chronic migraine has a significant impact on daily activities and quality of life; the key aims of preventive therapies are to reduce migraine frequency and acute drug use, and to improve patient functioning. A well tolerated preventive treatment that reduces the monthly number of migraine days in a substantial proportion of patients and reduces the number of days that acute drugs are taken could substantially lessen the personal and societal burden associated with chronic migraine.

Contributors

RL, ST, SS, and UR contributed to the protocol design. ST, MA, UR, JLB, DD, SS, and PW contributed to collection of data. DL, RL, and DM analysed the data. All authors were involved in the interpretation of the data. All authors critically reviewed and edited the manuscript.

Declaration of interests

ST reports personal fees from Amgen during the conduct of the study and reports grants and research support (no personal compensation) from Alder, Allergan, Amgen, Avanir, Dr Reddy’s Laboratories, Scion Neurostim, Teva, and Zosano; reports consultancy or advisory board fees from Acorda, Alder, Allergan, Amgen, ATB, BioVision, Dr Reddy’s Laboratories, Eli Lilly, Kimberly-Clark, Permix, Pfizer, Scion Neurostim, Teva, and Zosano; reports stock options in ATI; reports royalties from Springer; and reports salaries from Dartmouth-Hitchcock Medical Center and the American Headache Society. MA reports personal fees from Amgen during the conduct of the study, and personal fees from Allergan, Alder, ATI, Eli Lilly, and Novartis. JLB reports personal fees from Avanir, Depomed, and Pernix, and has done clinical trials for Allergan, Amgen, Colacaid, Teva, and Zosano. DD reports personal fees from Allergan, Amgen, Biogen Idec, Novartis, Bayer, and Teva. UR reports personal fees or research grants from Amgen, Eli Lilly, Novartis, Pharm Allergan, and Teva; has done clinical trials for Amgen, Eli Lilly, and Novartis; and has received personal fees from Colacaid. SS reports personal fees from Alder Biopharmaceuticals, Allergan, Amgen, Avanir, Curelatel, Depomed, Dr Reddy’s Laboratories, eNeura, ElectroCore Medical, INSYS Therapeutics, Lilly USA, LLC, Supernus, Teva, Theranica, and Trigemina Inc. PW reports research grants from Amgen. DL, DM, and RL are employees of, and own stock in, Amgen.

Acknowledgments

We thank the study investigators and patients for their participation and commitment to this work. Lucy Bee of Fishwack Communications wrote the first draft of the manuscript under the guidance of all authors. Medical writing support was provided by Lucy Bee, and by Lori Smette of Amgen.

References


