Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study

Marcelo E Bigal, Lars Edvinsson, Alan M Rapoport, Richard B Lipton, Egilius L H Spierings, Hans-Christoph Diener, Rami Burstein, Pippa S Loupe, Yuju Ma, Ronghua Yang, Stephen D Silberstein

Summary

Background Benefits of calcitonin-gene related peptide (CGRP) inhibition have not been established in chronic migraine. Here we assess the safety, tolerability, and efficacy of two doses of TEV-48125, a monoclonal anti-CGRP antibody, in the preventive treatment of chronic migraine.

Methods In this multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group phase 2b study, we enrolled men and women (aged 18–65 years) from 62 sites in the USA who had chronic migraine. Using a randomisation list generated by a central computerised system and an interactive web response system, we randomly assigned patients (1:1:1, stratified by sex and use of concomitant preventive drugs) to three 28-day treatment cycles of subcutaneous TEV-48125 675/225 mg (675 mg in the first treatment cycle and 225 mg in the second and third treatment cycles), TEV-48125 900 mg (900 mg in all three treatment cycles), or placebo. Investigators, patients, and the funder were blinded to treatment allocation. Daily headache information was captured using an electronic diary. Primary endpoints were change from baseline in the number of headache-hours during the third treatment cycle (weeks 9–12) and safety and tolerability during the study. Secondary endpoint was change in the number of moderate or severe headache-days in weeks 9–12 relative to baseline. Efficacy endpoints were analysed for the intention-to-treat population. Safety and tolerability were analysed using descriptive statistics. This trial is registered with ClinicalTrials.gov, number, NCT02021773.

Findings Between Jan 8, 2014, and Aug 27, 2014, we enrolled 264 participants: 89 were randomly assigned to receive placebo, 88 to receive 675/225 mg TEV-48125, and 87 to receive 900 mg TEV-48125. The mean change from baseline in number of headache-hours during weeks 9–12 was –59·84 h (SD 80·38) in the 675/225 mg group and –67·51 h (79·37) in the 900 mg group, compared with –37·10 h (79·44) in the placebo group. The least square mean difference in the reduction of headache-hours between the placebo and 675/225 mg dose groups was –22·74 h (95% CI –44·28 to –1·21; p=0·0386), whereas the difference between placebo and 900 mg dose groups was –30·41 h (–51·88 to –8·95; p=0·0057). Adverse events were reported by 36 (40%) patients in the placebo group, 47 (53%) patients in the 675/225 mg dose group, and 41 (47%) patients in the 900 mg dose group, whereas treatment-related adverse events were recorded in 15 (17%) patients, 25 (29%) patients, and 28 (32%) patients, respectively. The most common adverse events were mild injection-site pain and pruritus. Four (1%) patients had serious non-treatment-related adverse events (one patient in the placebo group, one patient in the 675/225 mg group, and two patients in the 900 mg group); no treatment-related adverse events were serious and there were no relevant changes in blood pressure or other vital signs.

Interpretation TEV-48125 given by subcutaneous injection every 28 days seems to be tolerable and effective, thus supporting the further development of TEV-48125 for the preventive treatment of chronic migraine in a phase 3 trial.

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Research and Development Department (M E Bigal MD), **Research and Scientific Affairs Department** (P S Loupe PhD), **and Statistics Department** (Y Ma MS, R Yang PhD), **Teva Pharmaceuticals, Frazer, PA, USA; Department of Internal Medicine, Lund University Hospital, Lund, Sweden** (Prof L Edvinsson MD); **The David Geffen School of Medicine at UCLA, Los Angeles, CA, USA** (A M Rapoport MD); **Department of Neurology, Albert Einstein College of Medicine, New York, NY, USA** (Prof R B Lipton MD); **Clinical Research, MedVadis Research, Boston, MA, USA** (E L H Spierings MD); **Department of Neurology, Essen Headache Center, Essen, Germany** (Prof H-C Diener MD); **Department of Anesthesia and Critical Care, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA** (R Burstein PhD); **and Department of Neurology, Jefferson Headache Center, Thomas Jefferson University, Philadelphia, PA, USA** (Prof S D Silberstein MD)

Correspondence to:
Dr Marcelo E Bigal, Global Clinical Development Migraine and Headaches, Teva Pharmaceuticals, Frazer, PA 19355, USA
marcelo.bigal@tevapharm.com

Introduction

Calcitonin gene-related peptide (CGRP) is a well characterised peptide that belongs to the calcitonin family, along with calcitonin, amylin, adrenomedullin-2, and adrenomedullin.[1] Two isoforms of CGRP are expressed throughout the central and peripheral nervous systems, where they often co-localise with other peptides in C and A delta fibres.[2,3]

The importance of CGRP in the pathogenesis of migraine is well characterised.[4–6] CGRP is ubiquitously presented at trigeminal nerve endings and ganglia as well as in higher order neurons and glia. Peripheral release of CGRP causes vasodilation and inflammation;[3] centrally, CGRP modulates pain transmission.[7,8] CGRP is suggested to have an important role at the intersection of peripheral and central migraine pathogenesis[9] and is the most actively pursued target for the acute treatment of episodic migraine.[10–14] Proof of concept for the preventive treatment of episodic migraine has been obtained with small-molecule CGRP receptor antagonists[15] and with anti-CGRP antibodies.[16–18]

Chronic migraine is defined as headaches occurring at least 15 days per month, with at least 8 days of migraine per month.[19] The disorder affects 1–3% of the adult population[20] and is the most frequent disorder seen at

Research in context

Evidence before this study

We searched MEDLINE for articles published in English using the terms "CGRP antagonists" and "migraine", with no restriction of the year of publication. We limited the search to randomised controlled trials. The findings in five studies using small molecules showed the efficacy of calcitonin gene-related peptide (CGRP) inhibition in the acute treatment of migraine. One study using a small molecule and two studies using monoclonal antibodies anti-CGRP provided proof of concept for the preventive treatment of episodic migraine. However, CGRP had not been validated as a target in chronic migraine.

Added value of this study

TEV-48125, a monoclonal antibody against the CGRP ligand, delivered subcutaneously at 675/225 mg and 900 mg led to improvements in our primary and secondary endpoint measures relative to placebo. Onset of action was fast, with significant decreases in the number of headache-hours and moderate to severe headache-days within the first month. Treatment was associated with significant decrease in consumption of acute drugs for migraine. Tolerability and safety concerns did not emerge.

Implications of all the available evidence

This study provides level 1b evidence (well conducted individual randomised controlled trial) that TEV-48125 is effective for the preventive treatment of chronic migraine. The only alternative treatment currently approved for chronic migraine is onabotulinumtoxinA.

headache clinics.[21] According to WHO,[22] chronic migraine is one of the most disabling disorders as it imposes a substantial effect on day-to-day functioning. Compared with individuals who have episodic migraine, those with chronic migraine are much more likely to be unemployed,[23] be divorced, and have psychological comorbidities, suggestive of the burden of the disease on the individual, their families, and society.[24] Despite its enormous burden, chronic migraine is underrecognised and undertreated, and only a single approved treatment option is available.[25,26]

TEV-48125 (formerly LBR-101 and RN-307) is a fully humanised monoclonal antibody that potently and selectively binds to CGRP, thereby preventing its ligation to receptors. The overall and haemodynamic tolerability of TEV-48125 has been extensively studied.[27,28] The aim of this study was to assess the safety, tolerability, and efficacy of two distinct doses of TEV-48125 for the preventive treatment of chronic migraine.

Methods

Study design and patients

In this randomised, double-blind, double-dummy, placebo-controlled study, we compared the safety, tolerability, and efficacy of two doses of TEV-48125 (675/225 mg and 900 mg) with placebo given subcutaneously once every 28 days for 3 months (appendix). The study was done at 62 sites in the USA (including headache centres, neurology clinics, and primary care sites). NCGS, an independent clinical research organisation, monitored the study to verify the appropriate inclusion of patients, adherence to protocol, and the completeness and accuracy of the case report forms entries. This study was done in parallel with a separate study of TEV-48125 for high-frequency episodic migraine, in which two other dosing schedules were tested in individuals with 8–14 days of headache per month.[29] Sites were allowed to prescreen patients with episodic and chronic migraine at the same time. Since the prescreening periods of both studies overlapped, patients who qualified for the chronic migraine study were excluded from the episodic migraine study and vice versa.

See Online for appendix

Eligible patients were men and women (aged 18–65 years) diagnosed with chronic migraine according to the International Classification of Headache Disorders (ICHD 3rd edition, beta version).[30] Complete inclusion and exclusion criteria are provided in the appendix. In short, eligible patients were permitted to have used stable doses of up to two different standard migraine preventive drugs for at least 3 months before study onset. Patients were also allowed to treat their acute migraine headaches as usual and had to show compliance (at least 80%) with the electronic headache diary during a 28 day run-in phase (appendix). Patients were excluded if they had received onabotulinumtoxinA up to 6 months before study entry, used opioids or barbiturate compounds for more than 4 days during the run-in phase, or had tried three or more preventive drugs without efficacy.

This study was done in accordance with the principles of Good Clinical Practice and with the US Food and Drug Administration (FDA) guidelines for safety monitoring. All patients provided written informed consent before enrolment. The protocol was approved by the institutional review boards for each site.

Randomisation and masking

Sex and use of concomitant preventive drugs were treated as stratification factors. Once the stratification group was determined, randomisation (1:1:1) was done by block (men and women taking concomitant preventive drugs or men and women not taking concomitant preventative drugs) to either the placebo group, the 675/225 mg group, or the 900 mg treatment group via an electronic interactive web response system (IWRS), which was accessible by the study coordinators through the eClinical Operating System portal, a Code of Federal Regulations-compliant, permissions-based

system. The randomisation list was developed centrally by dedicated staff at the clinical research organisation who had no further role in the study.

Even though investigators in phase 1 studies[31] could not distinguish between placebo and TEV-48125 from colour, viscosity, or administration characteristics, the sites involved in this study were asked to have two blinded study coordinators at each clinic visit, one for clinical assessment and one for treatment administration. Patients were masked to treatment allocation; they received the same number of injections, which were identical in packaging regardless of treatment group from masked study coordinators.

Procedures

Daily headache information was entered by the patient using an electronic diary (IWRS), which could be accessed by each site through the eClinical Operating System portal. Each day, patients were asked to record data in the diary for the previous 24 h period. The system allowed for 1 day of back-entering information and was locked thereafter. Headache and migraine frequencies were recorded by patients during the 28 day screening period and each of the three 28 day treatment cycles.

During the monthly clinical visits, patients were given instructions about completing the electronic diary, questionnaires, and safety assessments. Safety assessments included solicitation of adverse events, complete physical examinations, 12-lead electrocardiogram (ECG), and clinical laboratory measurements, including serum chemistries, haematology, urinalysis, and coagulation tests (PT, PTT, INR). Tolerability was estimated by comparison of adverse events, which were summarised by type, severity, and relation as defined by the primary site investigator to treatment, for each treatment group. We monitored the development of antibodies against TEV-48125 using a validated ELISA assay. All assessments were done before treatment drug was given at the end of the second, third, and fourth monthly study visit (marking the beginning of the first, second, and third 28 day treatment cycle, respectively). A follow-up visit for full assessment took place 28 days after the final drug administration (week 12; appendix).

TEV-48125 or placebo were given as four subcutaneous injections in the abdominal quadrants once at the beginning of each treatment cycle. Patients in the 900 mg treatment group received four active injections (225 mg TEV-48125 per injection) at the beginning of each treatment cycle. Patients in the 675/225 mg group received an initial loading dose of 225 mg TEV-48125 as three active injections and one placebo injection at the beginning of the first treatment cycle, followed by maintenance doses of 225 mg TEV-48125 as one active injection and three placebo injections at the beginning of the second and third treatment cycles. Patients receiving placebo received four placebo injections at the beginning of each treatment cycle.

Outcomes

The primary efficacy endpoint was the mean change relative to baseline in the number of headache-hours of any severity during the third treatment cycle (weeks 9–12). As part of the prespecified statistical analysis plan (SAP), headache-hours were also measured during the first and second treatment cycles.

The primary safety endpoint was safety and tolerability parameters of TEV-48125 compared with placebo.

The secondary endpoint was the mean change from baseline in the number of headache-days of at least moderate severity during the third treatment cycle relative to baseline. The number of headache-days of at least moderate severity were also assessed during the first and second treatment cycles.

A-priori defined exploratory efficacy endpoints included decreases in the following parameters during the third treatment cycle, ending at week 12: headache-hours of moderate severity; headache-days of any severity; migraine-days; and days with consumption of acute headache drugs (including triptans and other analgesics). As part of the prespecified SAP analyses, these same endpoints were measured during the first and second treatment cycles.

In accordance with FDA regulatory precedence, migraine-days and headache-days required at least 4 consecutive hours of headache or the use of specific acute migraine drugs (triptans or ergotamine compounds).[18]

Statistical analyses

Sample size and power were calculated using the PASS version 11 statistical software developed by NCSS LLC (Kaysville, UT, USA). To detect with at least 80% power a mean change from baseline in the number of headache-hours of at least 35 h (SD≤80), at least 30 h (SD≤60), or at least 25 h (SD≤40), we aimed to allocate at least 75 participants to each group.

To impute values for missing calendar day entries in a given month, scores of months with 20–27 day entries were prorated. Scores for months with less than 10 days of diary data were estimated using a modified last observation carried forward approach, calculated as the patient's previous 28 day period mean value of day entries multiplied by the ratio of the mean for all patients in the same period and divided by the mean number of day entries for all patients in the previous 28 day period. Scores for months with 10–19 days of diary data were estimated using an average of both methods.[25,26]

The primary, secondary, and exploratory efficacy endpoints were analysed using the mixed-effects model repeated measurement (MMRM) analysis method. Change from baseline in the variable of interest (eg, headache-hours) at weeks 1–4, weeks 5–8, and weeks 9–12 was the dependent variable; preventive drug use (yes or no), sex, visit number, treatment, and treatment-by-visit interaction were fixed factors; baseline value of the variable of interest and years since disease onset were

covariates; and patient was treated as a random effect. We used unstructured covariance matrix for repeated findings within patients and constructed 95% CIs for the least square mean difference between groups.

All statistical tests were two-sided at a type I error (α) of 0·05. We used the Hochberg approach to adjust for multiplicity for the analysis of the primary and secondary efficacy variables. All efficacy variables were analysed for the intention-to-treat population, which included all patients who were randomly assigned to treatment group, received at least one dose of study drug, and provided at least one endpoint measurement. We used SAS version 9.3 for all statistical analyses.

This trial is registered with ClinicalTrials.gov, NCT02021773.

Role of the funding source

The protocol was designed and the study was conducted by the funder with input from all authors. The funder was responsible for data collection, data analysis, data interpretation, and writing the Article. All authors had full access to all the data in the study and the

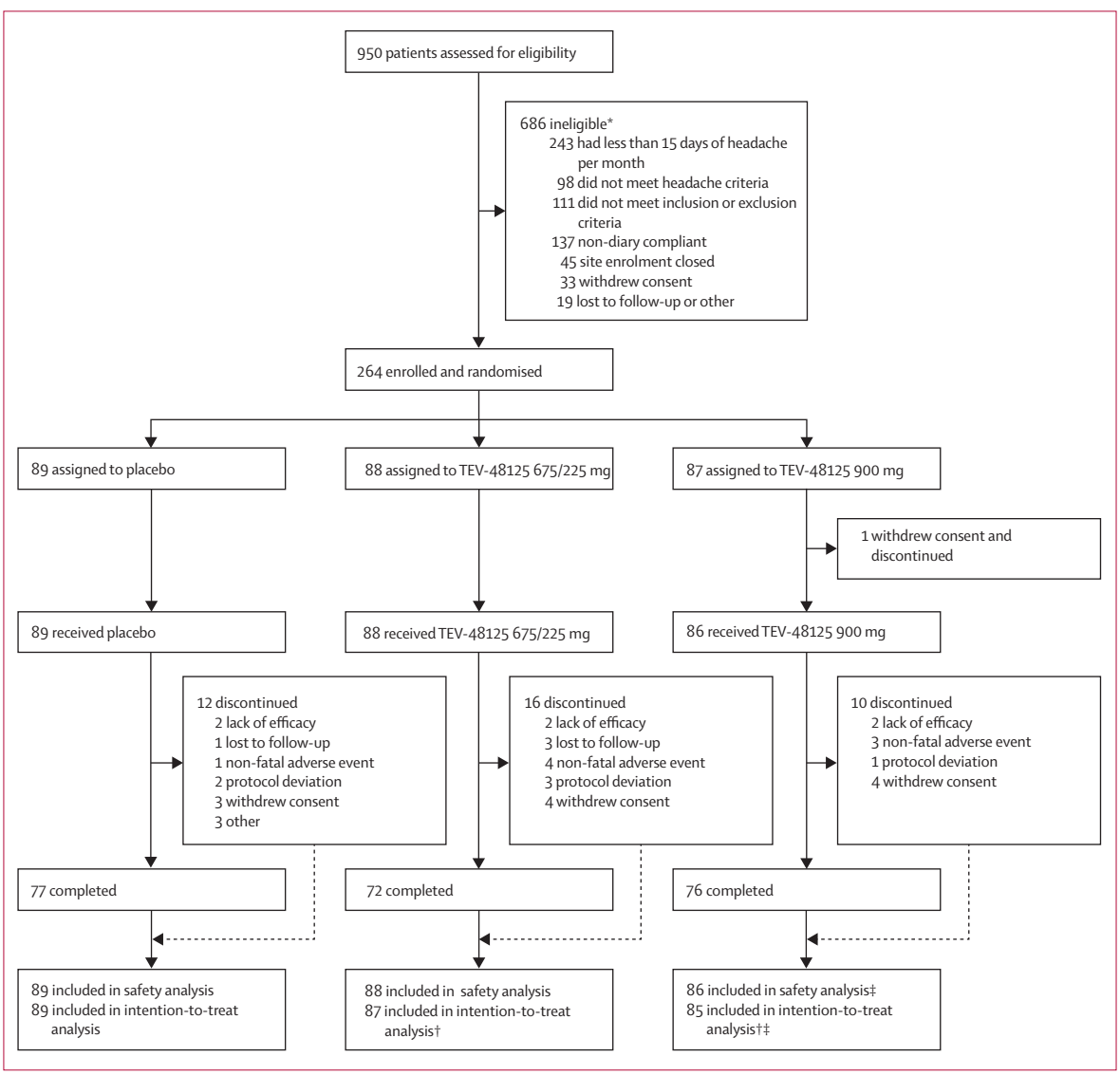

***Figure 1*: Trial profile**

*Patients were considered ineligible for the chronic migraine study if: they had less than 15 days of headaches per month for 3 months before screening; they had at least 15 days of headache per month for 3 months before screening but did not have 15 days of headaches or evidence of migraines during the 28 day run-in period; they met the headache and migraine criteria required for the chronic migraine study but did not meet one or more of the other inclusion or exclusion criteria; they were less than 80% compliant with diary entry during the 28 day run-in period; or they had miscellaneous reasons such as site closure, consent withdrawal, or loss to follow-up. †One patient in the 675/225 mg group and one patient in the 900 mg group were excluded from the intention-to-treat analysis because they withdrew from the study for personal reasons after receiving the study drug but before diary information was collected. ‡One patient in the 900 mg group withdrew after randomisation but before receiving the study drug and was not included in the safety or intention-to-treat analyses.

corresponding author had final responsibility for the decision to submit for publication.

Results

Between Jan 8, 2014, and Aug 27, 2014, we screened 950 patients with a history of chronic migraine or high frequency episodic migraine for eligibility and randomly assigned 264 patients to a treatment group: 89 entered the placebo group, 88 entered the 675/225 mg group, and 87 entered the 900 mg group (figure 1). One patient in the 900 mg group withdrew after randomisation but before receiving the study drug and was not included in the safety or intention-to-treat analyses. Two patients (one in the 675/225 mg group and one in the 900 mg group) were excluded from the intention-to-treat population because they withdrew from the study for personal reasons after receiving the study drug but before diary information was collected.

Baseline demographic and clinical characteristics were similar in the three groups (table 1). Mean overall age was 40·7 years (SD 12·0), 227 (86%) of the patients were women, 219 (83%) were white, and 106 (40%) used preventive drugs at the time of the study. Of those patients who were taking preventive drugs, 79 used one preventive drug, 25 patients used two preventative drugs, and one patient (in the placebo group) used three or more preventives. At baseline, participants had a mean of 162 headache-hours per month (SD 111·1) and had 21·1 headache-days of any duration (SD 4·3) and 16·8 migraine days (5·2) per month.

The least square mean change from baseline in the number of headache-hours of any severity during the third treatment cycle (weeks 9–12) was –37·10 headache-hours (SD 79·44) in the placebo group, –59·84 headache-hours (80·38) in the 675/225 mg group, and –67·51 headache-hours (79·37) in the 900 mg group (figure 2). The reduction in the number of headache-hours from baseline to weeks 9–12 was significantly larger in both the 675/225 mg group and the 900 mg group than in the placebo group (table 2). Patients in the placebo group had a 22% decrease in the number of headache-hours from baseline to weeks 9–12, whereas patients in the 675/225 mg group had a 38% decrease in headache-hours, and patients in the 900 mg group had a 43% decrease in headache-hours. In the MMRM analysis, both doses of TEV-48125 also significantly decreased the number of headache-hours of any severity from baseline to weeks 1–4 and weeks 5–8 (table 2).

The least square mean change in the number of moderate or severe headache-days from baseline to weeks 9–12 after the third treatment cycle was –4·2 days (SD 6·32) in the placebo group, –6·04 days (6·41) in the 675/225 mg group, and –6·16 days (6·32) in the 900 mg group (figure 2). MMRM analyses indicated that the reduction in moderate or severe headache-days was significantly larger in both dose cohorts than in the placebo group after the first treatment cycle (weeks 1–4) and third treatment cycle (weeks 9–12), but not after the second treatment cycle (weeks 5–8; table 2).

The change in moderate to severe headache-hours from baseline to weeks 9–12 did not differ significantly between either dose group and placebo; the change in mean number of headache-days and migraine-days differed from placebo in the 900 mg group but the decrease was non-significant for the 675/225 mg group. Both doses significantly decreased any acute medication consumption from baseline to weeks 9–12 relative to placebo (table 2).

A post-hoc subgroup analysis indicated that there was a significant difference in number of days on which triptans were used between the placebo group and each of the TEV-48125 dose groups (675/225 mg group *vs* placebo, least square mean –3·44, 95% CI –5·23 to –1·66, p=0·0002; 900 mg group *vs* placebo, –4·35, –6·15 to –2·55, p<0·0001, respectively). In another post-hoc analysis, we found that a greater percentage of patients in the 675/225 mg group had more than a 50% improvement in the number of days with moderate to severe headaches in weeks 9–12 than in the placebo group, and a greater percentage of patients in the 900 mg group had more than a 75% improvement in the number of days with moderate to severe headaches in weeks 9–12 than in the placebo group (appendix).

	Placebo (n=89)	TEV-48125 675/225 mg (n=88)	TEV-48125 900 mg (n=86)
Age, years	40·7 (11·5)	40·0 (11·6)	41·5 (12·9)
Height, cm	166·4 (8·1)	165·4 (8·3)	165·7 (7·6)
Weight, kg	71·3 (13·1)	74·2 (17·0)	73·0 (15·6)
Body-mass index, kg/m²	25·7 (4·5)	27·0 (5·2)	26·6 (5·3)
Sex			
Male	13 (15%)	12 (14%)	12 (14%)
Female	76 (85%)	76 (86%)	75 (86%)
Ethnic origin			
White	76 (85%)	70 (80%)	73 (84%)
Black or African American	9 (10%)	12 (14%)	9 (10%)
Asian	1 (1%)	0	0
Other	3 (3%)	6 (7%)	5 (6%)
Headache-hours of any severity per month	169·1 (113·11)	159·1 (90·73)	157·7 (108·16)
Headache-hours of at least moderate severity per month	91·90 (74·68)	90·7 (59·71)	96·20 (94·42)
Headache-days of at least moderate severity per month	13·9 (5·6)	13·8 (6·3)	13·1 (5·9)
Headache-days of any severity per month	16·5 (6·3)	16·5 (6·7)	15·9 (6·5)
Migraines-days per month	16·8 (5·0)	17·2 (5·4)	16·4 (5·3)
Days of acute drug use per month	15·7 (6·2)	15·1 (7·0)	16·2 (6·7)
Days of triptan use per month	10·0 (5·3)	9·2 (5·6)	11·8 (6·0)
Years of migraine	20·4 (13·1)	15·8 (11·2)	18·8 (12·2)
Preventive drug use			
Yes	38 (43%)	35 (40%)	33 (38%)
No	51 (57%)	53 (60%)	54 (62%)

Data are mean (SD) or number of patients (%).

Table 1: **Baseline demographic and clinical characteristics**

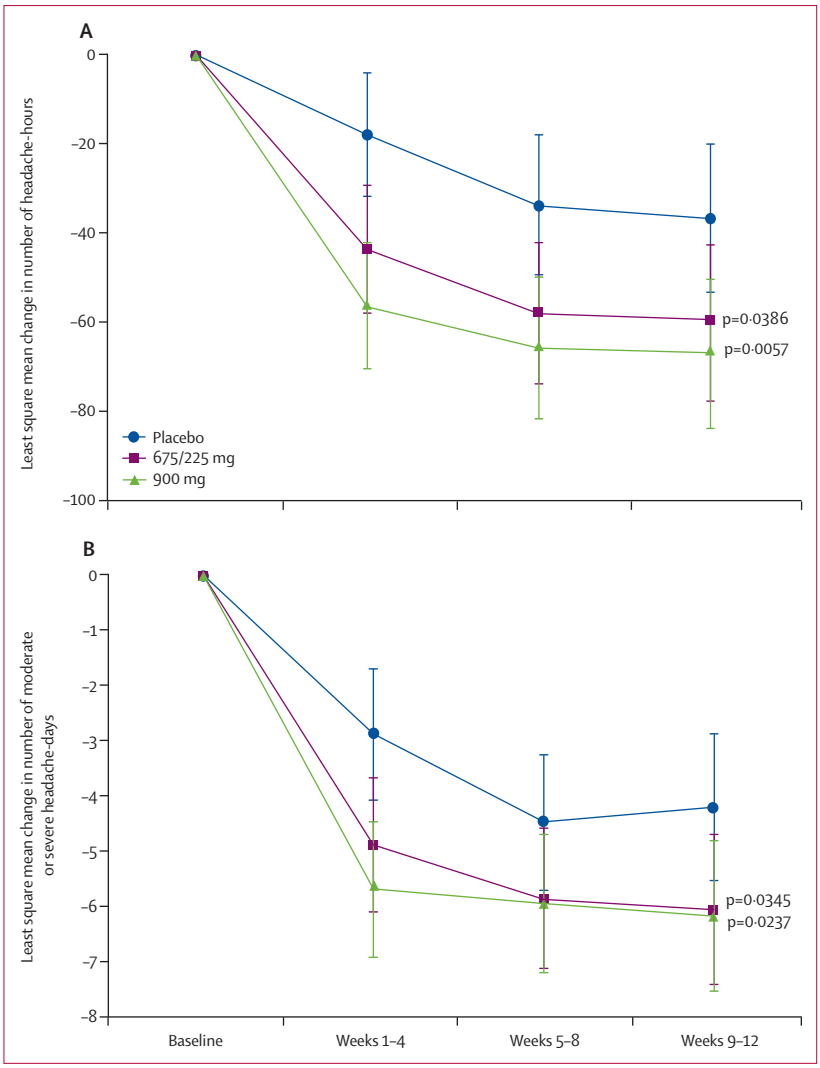

***Figure 2*: Primary and secondary efficacy analysis**
(A) Least square mean change in number of headache-hours from baseline to weeks 9–12 by treatment group (primary endpoint). (B) Least square mean decrease in number of moderate or severe headache-days from baseline to weeks 9–12 by treatment group (secondary endpoint). Error bars show 95% CI.

Treatment-emergent adverse events were reported by 36 (40%) patients receiving placebo, 47 (53%) patients receiving 675/225 mg TEV-48125, and 41 (48%) patients receiving 900 mg TEV-48125 (table 3). The most common adverse events were mild injection-site pain (three [3%] patients in the placebo group *vs* 6 [7%] patients in the 675/225 mg group *vs* 8 [9%] in the 900 mg group) and pruritus (none *vs* four [5%] *vs* two [2%]; table 3). No relevant changes in blood pressure or other vital signs were recorded. Treatment-related adverse events, most of which were minor injection-site reactions, occurred in 15 (17%) patients in the placebo group, 25 (29%) patients in the 675/225 mg group, and 28 (32%) patients in the 900 mg group.

Four patients (2%) had transient increases in liver enzyme concentrations during the treatment phase, which was considered non-treatment related. Three of these patients were receiving active drug, one of whom was diagnosed with acute hepatitis C and the other two of whom both had histories of cholecystectomy and hepatic steatosis, with past documentation of increased liver enzyme concentrations. Liver enzyme concentrations remitted to normal during the study, even after receiving additional doses of study drug.

Serious adverse events were reported by one patient in the placebo group, one patient in the 675/225 mg group, and two patients in the 900 mg group; all serious adverse events were considered non-related to the study drug (table 3). One patient with a history of nephrolithiasis had an acute kidney stone pain, which was considered by the investigator to be mild in severity. One patient developed pneumonia after having influenza, and the event was considered by the investigator to be moderate in severity. A third patient had irritable bowel syndrome, considered as severe by the investigator. Finally, a patient with a well documented history of severe depression had an episode of depression with suicidal ideation, considered severe by the investigator. All above cases resolved during the course of the study.

Two (1%) patients had antibodies against TEV-48125 before receiving study medication. After study-drug administration, we found no change in antibody concentration, and therefore the antibody response was not considered treatment emergent.

Discussion

In this phase 2b study, both doses of TEV-48125 led to improvements in the primary and secondary endpoint measures of efficacy compared with placebo. These findings for the first time validate CGRP as a therapeutic target in patients with chronic migraine. In addition to decreasing the number of headache-hours and days of moderate or severe headache, TEV-48125 improved some a-priori exploratory endpoints. We saw consistent clinical improvements as early as 1 month after starting treatment. A rapid onset of relief is a clinically important attribute because the absence of perceived effect is frequently associated with premature discontinuation of preventive drugs.[20,32] However, the speed of onset of relief might ultimately be determined by the chosen dose and by the rate of anti-drug antibody development; these parameters will be further investigated during phase 3. Finally, TEV-48125 treatment was associated with statistically significant decreases in the number of days of acute drug consumption for migraine attacks.

The choices of dose and endpoints in our study merit discussion. Our lowest dose was defined on the basis of pharmacokinetic modelling from animal studies, which suggested that subcutaneous injection of 225 mg TEV-48125 should yield a plasma concentration sufficient to block CGRP at meaningful rates, thus potentially allowing for a detectable efficacy signal, while simultaneously providing a wide clinical safety margin.[33]

	Change from baseline to weeks 1–4				Change from baseline to weeks 5–8				Change from baseline to weeks 9–12			
	Placebo (n=89) *vs* 675/225 mg (n=87)		Placebo (n=89) *vs* 900 mg (n=85)		Placebo (n=89) *vs* 675/225 mg (n=87)		Placebo (n=89) *vs* 900 mg (n=85)		Placebo (n=89) *vs* 675/225 mg (n=87)		Placebo (n=89) *vs* 900 mg (n=85)	
	Least square mean difference (95% CI)	p value	Least square mean difference (95% CI)	p value	Least square mean difference (95% CI)	p value	Least square mean difference (95% CI)	p value	Least square mean difference (95% CI)	p value	Least square mean difference (95% CI)	p value
Primary endpoint												
Headache-hours	–26·0 (–43·34 to –8·65)	0·0035	–38·76 (–56·04 to –21·48)	<0·0001	–24·22 (–44·28 to –4·15)	0·0182	–32·09 (–52·09 to –12·10)	0·0018	–22·74 (–44·28 to –1·21)	0·0386	–30·41 (–51·88 to –8·95)	0·0057
Secondary endpoint												
Moderate to severe headache-days	–2·00 (–3·50 to –0·51)	0·0088	–2·81 (–4·30 to –1·32)	0·0003	–1·38 (–2·95 to 0·19)	0·0844	–1·47 (–3·03 to 0·09)	0·0653	–1·84 (–3·54 to –0·14)	0·0345	–1·96 (–3·66 to –0·26)	0·0237
A priori exploratory endpoints												
Moderate to severe headache-hours	–18·51 (–31·8 to –5·2)	0·007	–21·58 (–34·9 to –8·3)	0·002	–17·97 (–34·0 to –2·0)	0·028	–17·21 (–33·2 to –1·3)	0·035	–13·56 (–29·3 to 2·2)	0·091	–11·25 (–26·9 to 4·4)	0·159
Headache-days	–2·13 (–3·8 to –0·5)	0·012	–2·99 (–4·7 to –1·3)	0·0004	–1·31 (–3·1 to 0·5)	0·151	–2·03 (–3·8 to –0·3)	0·026	–1·74 (–3·6 to 0·1)	0·069	–2·74 (–4·6 to –0·9)	0·004
Migraine-days	–2·07 (–3·7 to –0·5)	0·012	–2·99 (–4·6 to –1·4)	0·0003	–1·64 (–3·4 to 0·13)	0·069	–1·73 (–3·49 to 0·03)	0·054	–1·72 (–3·7 to 0·2)	0·08	–2·00 (–3·9 to –0·1)	0·041
Days using acute drugs	–1·99 (–3·6 to –0·4)	0·016	–2·15 (–3·8 to –0·5)	0·009	–2·16 (–3·9 to –0·5)	0·014	–1·39 (–3·1 to –0·3)	0·111	–2·15 (–4·0 to 0·3)	0·02	–2·04 (–3·9 to –0·2)	0·027

Data are least square mean difference (95 % CI). Data are from the mixed-effects model repeated measurement analyses, which assessed the changes in variables of interest for the placebo and active treatment groups from baseline to the 28 day post-treatment cycles (weeks 1–4, weeks 5–8, and weeks 9–12). Differences in the changes in variables of interest from baseline to weeks 9–12 between placebo and each of the active treatment groups were the primary analysis for each endpoint.

***Table 2*: Efficacy endpoints assessed as a function of treatment period**

Whereas plasma concentrations of TEV-48125 for patients in the 900 mg group were expected to exceed the therapeutic threshold early in the study, concentrations for the 225 mg arm were not expected to reach this predicted efficacy threshold until after the third dose of TEV-48125. Modelling also suggested that a single loading dose of 675 mg followed by two maintenance doses of 225 mg would largely mimic what would be achieved at steady-state with 225 mg TEV-48125, therefore providing justification for the loading dose in the lower dose group.

With respect to endpoints, we tried to measure both the quantity and severity of headaches by using complementary endpoints. As migraine evolves from episodic to chronic, the time with headache increases, but the headache often becomes less typical or severe, and some patients end with unremitting, low intensity headaches with superimposed exacerbations.[34,35] Two parameters therefore need to be assessed: a metric of total time with headaches and a metric of time with bad headaches. We used the number of headache-hours of any severity (primary endpoint) to address the first parameter and the number of moderate to severe headache-days (secondary endpoint) to address the second parameter.

TEV-48125 was well tolerated, and no safety concerns have emerged in the context of a short-duration exposure trial. Excluding local injection discomfort, no other relevant differences in the prevalence of treatment-emergent adverse events were reported between patients receiving TEV-48125 and placebo. We found no specific pattern of adverse events, which was also the case in phase 1 studies.[36] No haemodynamic or cardiovascular changes were recorded, supporting the results of the phase 1 studies and the available preclinical data.[27,28] No metabolic or immunological dysfunctions were suggested by the data. The prevalence of patients with detectable concentrations of TEV-48125 antibodies (1%), detected with an optimised assay of regulatory quality, was much lower than that detected with other monoclonal anti-CGRP antibodies (19% with LY2951742[17] and 14% with ALD403[16]). We expected to find TEV-48125 antibodies before exposure to the drug. The FDA guidance on assay development for immunogenicity testing of therapeutic proteins[37] states that a low but defined false positive incidence is desirable because it maximises detection of true positives. Other assays can be subsequently used to exclude false positive results when determining the true incidence of immunogenicity. In our study, we followed up by checking if there was any increase in TEV-48125 antibody titres or any decrease in pharmacokinetic parameters after exposure, and none was observed.

One strength of our study was the design of our clinical trial, which addressed the population with chronic migraine at large, not a less severely affected subset thereof. First, we did not exclude individuals who used other preventive drugs or establish a strict limit for acute drug use, and we even allowed some opioid therapy. Also, individuals with unremitting headaches were not

	Placebo (n=89)	TEV-48125 675/225 mg (n=88)	TEV-48125 900 mg (n=86)
Serious adverse events*	1 (1%)	1 (1%)	2 (2%)
Irritable bowel syndrome	0	0	1 (1%)
Pneumonia	0	1 (1%)	0
Depression with suicide attempt	0	0	1 (1%)
Suicide attempt	0	0	1 (1%)
Nephrolithiasis	1 (1%)	0	0
Treatment-emergent adverse events that occurred in more than 2% of patients in any group†			
Injection-site pain	3 (3%)	6 (7%)	8 (9%)
Headache	0	1 (1%)	4 (5%)
Injection-site erythema	0	1 (1%)	3 (4%)
Injection-site pruritus‡	0	4 (5%)	2 (2%)
Injection-site oedema	0	0	2 (2%)
Injection-site reaction	0	1 (1%)	2 (2%)
Injection-site bruising	2 (2%)	1 (1%)	1 (1%)
Paraesthesia	0	4 (5%)	0
Sinusitis	1 (1%)	4 (5%)	0
Urinary tract infection	1 (1%)	4 (5%)	2 (2%)
Nasopharyngitis	4 (5%)	1 (1%)	1 (1%)
Back pain	1 (1%)	1 (1%)	3 (4%)
Blurred vision	0	2 (2%)	0
Migraine	0	2 (2%)	0
Depression	0	0	2 (2%)
Insomnia	0	2 (2%)	1 (1%)
Myalgia	2 (2%)	0	1 (1%)
Constipation	0	1 (1%)	2 (2%)
Gastronenteritis	1 (1%)	2 (2%)	0
Neck pain	0	0	2 (2%)
Tooth abscess	2 (2%)	1 (1%)	2 (2%)
Ligament sprain	1 (1%)	0	2 (2%)
Food poisoning	2 (2%)	0	0
Patients with at least one treatment-emergent adverse event	36 (40%)	47 (53%)	41 (48%)
Patients with at least one treatment-related adverse event	15 (17%)	25 (29%)	28 (32%)

Data are number of patients (%). Treatment-emerging adverse events includes adverse events considered to be related as well as those not considered to be related to treatment. Treatment-related adverse events are treatment-emergent adverse events that are considered related to treatment by the investigator. *None of the serious adverse events were considered to be treatment-related by the site investigators. ‡One patient could have more than one event; for example, two patients in the 675/225 mg group and two patients in 900 mg group had both injection-site pain and injection-site pruritus.

Table 3: **Adverse events**

excluded. All of these factors were exclusionary in past trials of chronic migraine[25,26] and in the episodic migraine trials of other anti-CGRP antibody treatments.[16,17] Second, the primary endpoint (headache-hours) reflects the outcome of the disease in clinical practice, where individuals often have a substantial decrease in the duration of their daily headaches before experiencing headache-free days.[38,39] This endpoint has been used in past studies as a secondary measure.[25,26] Our secondary endpoint is the traditional decrease in number of days of moderate or severe headache.[40] Analyses were adjusted for multiplicity and missing data with the same rigour as for a registration trial. Finally, for some measurements (eg, headache-hours at early timepoints), we showed a dose-response.

This study also has limitations. First, we did not use quality-of-life questionnaires and have no data on the effect of TEV-48125 on patient well-being or disability. Second, the toxicology data available when this study was initiated showed the effects of only 3 months of consecutive exposure; thus, we limited the study duration to 3 months. Third, patients were not followed after their last visit, and data on duration of effect were not collected. Fourth, we were able to discern the number of migraine days defined by the ICHD-3 by asking about the number of hours of headache and moderate or severe headache and associated migraine symptoms. However, we did not measure whether specific numbers of hours of the day met the criterion for migraine, and we were therefore unable to define an individual's number of migraine-hours on any given day. These limitations will largely be addressed in a phase 3 study, which will have a substantially longer duration, follow-up after the last dose, and meticulous documentation of quality of life.

This study improves our understanding of chronic migraine pathogenesis. Peripheral CGRP concentrations are increased in patients with chronic migraine compared with patients with episodic migraine,[41] and we have validated CGRP as a target for this disease state. Only 0·1–0·5% of antibodies cross the intact blood–brain barrier.[42] Even if sporadic disruption of the blood–brain barrier exists, the amount of antibody penetrating the barrier during migraine attacks would be substantially lower than what would be required for meaningful CGRP inhibition. We believe that anti-CGRP antibodies exert their effect by targeting peripheral structures (including the trigeminal ganglia) involved in migraine pathophysiology.[43] Nonetheless, since anti-CGRP antibodies target CGRP that is being released outside of the blood–brain barrier, and since several other central and peripheral targets have been identified as of importance in migraine,[44] we do not suggest that all individuals with migraine would respond to anti-CGRP therapies.

Chronic migraine is a disease with substantial unmet needs. The two dosing regimens used in this phase 2 study show the efficacy and tolerability of TEV-48125 for patients with this disease. These findings support the clinical development of TEV-48125 in a phase 3 trial as a preventive treatment for chronic migraine.

Contributors

MEB designed the study, interpreted data, and drafted and finalised the Article. LE, AMR, RBL, ELHS, H-CD, RB, and SDS contributed to overseeing the data, discussed contents of the Article, and participated in the writing of the Article. YM and RY created the statistical analysis plan for the study and analysed data. PSL interpreted data, prepared tables and figures, and participated in writing the Article.

Declaration of interests

MEB, PSL, YM, and RY are employees of Teva Pharmaceuticals. LE has consulted for Teva Pharmaceuticals and Eli Lilly and reports a grant from

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