



Candesartan versus placebo for migraine prevention in patients with episodic migraine: a randomised, triple-blind, placebo-controlled, phase 2 trial

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Summary

Background Effective and well-tolerated preventive treatments for migraine remain few, and the angiotensin receptor blocker candesartan has shown promise in small studies. This study aimed to evaluate the safety, tolerability, and efficacy of candesartan for the preventive treatment of episodic migraine.

Methods This randomised, triple-blind, placebo-controlled, parallel-group, phase 2 trial was done at nine hospitals across Norway and one large hospital in Estonia, selected for their neurological services and research capacity. Adults aged 18–64 years, experiencing between two and eight migraine attacks (with or without aura) per month were randomly assigned (1:1:1) to receive oral candesartan 16 mg, candesartan 8 mg, or placebo daily for 12 weeks. Acute migraine medication was permitted during the trial but the use of other preventive treatments were prohibited. Participants, site personnel, and the trial statistician were all masked to treatment allocation. The primary endpoint was the change in the mean number of migraine days per 4 weeks from baseline to weeks 9–12, analysed in the intention-to-treat population (participants with at least one post-baseline measurement during the masked treatment period). Safety analyses included all participants who received at least one dose of the trial drug. This trial is registered with ClinicalTrials.gov (NCT04574713; Oct 5, 2020) and is completed.

Findings Between April 9, 2021, and April 12, 2024, 1340 individuals were assessed for eligibility, 806 were deemed ineligible, and 534 were enrolled in the trial. Of these, 77 were excluded, and 457 participants were randomly assigned to candesartan 16 mg (n=156), candesartan 8 mg (n=150), or placebo (n=151). The mean age of the trial population was 38·7 years (SD 10·0); 391 (86%) participants were female and 66 (14%) were male. The mean number of migraine days was 5·7 (SD 2·5) at baseline. By weeks 9–12, the reduction in migraine days was 2·04 days (95% CI 1·65–2·41 p<0·0001) in the candesartan 16 mg group compared with 0·82 days (0·38–1·23; p=0·0003) in the placebo group ((difference between groups –1·22 [95% CI –1·75 to –0·70]; p<0·0001). The most common adverse event with candesartan 16 mg was dizziness, reported in 46 (30%) of 156 participants, compared with 19 (13%) of 151 in the placebo group. Serious adverse events were reported in four (3%) participants in the candesartan 16 mg group and one (1%) participant in the placebo group. Adverse events leading to discontinuation occurred in four (3%) participants in both the candesartan 16 mg and placebo groups.

Interpretation Daily administration of candesartan 16 mg is effective and well tolerated as a preventive treatment for episodic migraine. These findings support its role as a clinically meaningful and evidence-based option for migraine prevention. However, further clinical trials and real-world data from registry studies are necessary to assess its long-term efficacy.

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Introduction

Migraine is a chronic neurological disorder characterised by a recurrent, often unilateral throbbing headache that worsens with physical activity and is frequently accompanied by photophobia, phonophobia, nausea, and vomiting.¹ Preventive medication is essential to reduce migraine-related disability,² yet effective, well-tolerated, and affordable options remain limited for this debilitating

condition that affects more than 1 billion people worldwide.³ Limited efficacy, side-effects, and high cost of available therapies are key barriers to adequate preventive treatment.⁴ Although calcitonin gene-related peptide (CGRP)-targeted treatments have shown efficacy, their use is constrained by costs, access, and guidelines reserving them for patients who do not respond to first-line options, such as beta blockers, antidepressants, and antiepileptic

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Research in context

Evidence before this study

In a systematic search of PubMed conducted on March 20, 2025, using the terms “migraine,” “preventive” or “prevention,” and “angiotensin-II receptor blockers” or “candesartan” for clinical studies published in English in the past 20 years, we identified three clinical trials: two investigating the effect of candesartan and one investigating the effect of telmisartan. Of the two studies on candesartan, one compared its efficacy with placebo, while the other compared it with propranolol. Although both studies established that candesartan is effective and well-tolerated for migraine prevention, their findings are constrained by small sample sizes, single-centre settings, and cross-over designs. Consequently, the evidence for candesartan’s efficacy in migraine prevention remains weak.

Added value of this study

Preventive medication plays a crucial role in alleviating migraine-related disability; however, effective, tolerable, and affordable treatment options remain limited. Current therapies often fall short due to their inadequate efficacy, potential side-effects, and high costs, leading to insufficient preventive care for individuals with migraine. This randomised, triple-blind, placebo-controlled, phase 2 trial is the largest of its kind and the first to use a parallel-group design. The trial

demonstrates that daily administration of candesartan 16 mg over 12 weeks is both effective and well-tolerated in individuals with episodic migraine. Efficacy was also observed with candesartan 8 mg indicating that a lower dose might be sufficient for responsive patients. With demonstrated efficacy, low costs, high tolerability, low toxicity, and easy administration and follow-up, candesartan emerges as a compelling option for migraine prevention.

Implications of all the available evidence

Although direct comparisons are limited by differences in study populations and settings, the observed efficacy of candesartan in this trial appears consistent with that reported for other preventive treatments, including calcitonin gene-related peptide monoclonal antibodies. Candesartan, an angiotensin-II receptor blocker currently approved for the treatment of hypertension, heart failure, and kidney disease, represents a promising option for repurposing as a preventive treatment for migraine. Leveraging its well-established safety profile might reduce the cost and time associated with developing new migraine therapies. This approach could enhance global access to migraine treatment, including in low-resource settings, and contribute to mitigating the individual and societal burden of migraine.

drugs. The evidence base for many first-line therapies remains weak, with few high-quality trials available. Only a small proportion of patients with episodic migraine have access to even minimally adequate treatment,⁵ and poor adherence to oral migraine preventive treatments due to adverse effects further contributes to underutilisation.^{6,7} These challenges are particularly pronounced in primary care settings, where general practitioners in many countries have limited access to the full range of migraine preventive therapies.^{8,9}

Candesartan, an angiotensin II type 1 receptor blocker, has been shown to be effective and well-tolerated for migraine prevention in multiple studies,^{10–16} including two randomised, placebo-controlled crossover trials that showed that a daily dose of 16 mg can significantly reduce migraine frequency.^{12,13} Real-world data further supports its clinical utility, with high treatment retention even among patients with chronic migraine and those for whom previous preventive treatments were ineffective.^{14–16} The favourable adherence profile, established safety, and broad availability of candesartan make it a strong candidate for long-term use in routine care. In a treatment landscape increasingly dominated by CGRP-targeted treatments, where cost, access, and adherence remain substantial challenges, candesartan offers a practical and accessible oral alternative. Despite being supported by only moderate evidence (level C) for migraine prevention, primarily due to scarce documentation and the absence of large, multicentre

trials, candesartan is recommended in several international guidelines.^{17–20}

To strengthen the evidence base and improve clinical decision making regarding both efficacy and tolerability, we conducted a randomised clinical trial that aimed to compare candesartan with placebo for the prevention of episodic migraine. In the absence of previous dose-finding studies, this trial also evaluated two doses of candesartan—8 mg and 16 mg—reflecting real-world prescribing practices, where lower doses are often used due to tolerability concerns, particularly hypotensive side-effects. The selected dose range is supported by pharmacokinetic data demonstrating dose-proportional exposure between 8 mg and 16 mg, with a once-daily dosing profile.²¹

Methods

Study design

This randomised, triple-blind, placebo-controlled, parallel-group, phase 2 clinical trial was conducted at nine hospitals across Norway, geographically distributed to ensure national coverage, and one hospital in Estonia. Hospitals were eligible if they provided neurological services, had the capacity for data collection, and agreed to participate. Participating sites included University Hospital of North-Norway (Tromsø), Nordland Hospital (Bodø), St Olavs University Hospital (Trondheim), Molde Hospital (Molde), Haukeland University Hospital (Bergen), Oslo University Hospital Ullevål and Rikshospitalet (Oslo), Akershus

University Hospital (Lørenskog), Hospital of Southern Norway (Kristiansand), and Tartu University Hospital (Tartu). The aim was to investigate the efficacy of candesartan as a migraine preventive treatment. The phase 2 classification reflects the exploratory nature of the study and its focus on assessing preliminary efficacy in a rigorously controlled setting. The protocol was approved by the regional committee for medical research ethics (REK 63527), the responsible data protection officer, and the Norwegian Medicines Agency (EudraCT No. 2019-003386-18). The trial was conducted in compliance with Guidelines of the International Headache Society for controlled trials of preventive treatment in episodic migraine,²² designed and reported according to CONSORT standards and was registered on ClinicalTrials.gov (NCT04574713; Oct 5, 2020) and is completed. An independent data monitoring committee oversaw procedures throughout the duration of the trial. The full Statistical Analysis Plan was finalised before the database lock and is available in the appendix (pp 11–26). The following protocol deviations were made: doses of acute migraine medication were prespecified as a secondary endpoint but were excluded from the final analyses due to inconsistent and unreliable reporting; the protocol specified comparisons among all three treatment groups (candesartan 16 mg, candesartan 8 mg, and placebo) but as outlined in the statistical analysis plan, a direct comparison between the 16 mg and 8 mg doses was performed in the intention-to-treat population.

Participants

Adults aged 18–64 years with a history of episodic migraine for at least 12 months before screening were eligible for participation. Sex was recorded as either male or female, based on participant self-report at the time of enrolment. Data on gender identity, ethnicity, and race were not collected in this trial. The diagnosis of migraine, with and without aura, was evaluated by a neurologist at the screening visit and was defined according to the International Classification of Headache Disorders, 3rd edition.¹ Participants were required to report between two and eight migraine attacks per month and fewer than 15 headache days per month on average during the 3 months preceding screening and during a 4-week baseline period using a prospective daily headache diary, with at least 90% adherence in completing daily entries required. Exclusion criteria included migraine onset after age 50 years, interval headache indistinguishable from migraine, consistent absence of response to any acute migraine medication, current use of migraine preventive drugs or any antihypertensive drugs, any previous use of candesartan, or having tried three or more migraine preventive drugs in the past 10 years. Individuals with hepatic or renal disease, hyperaldosteronism, alcohol or illicit drug dependency, or other complex medical conditions that, at the discretion of the investigator, could impair the participant's ability to comply with study

procedures, provide informed consent, or accurately report outcomes (eg, a high burden of comorbidities or significant psychiatric illness) were excluded. The use of potassium supplements or potassium-sparing diuretics such as spironolactone was not permitted. Pregnant or lactating individuals were excluded, and all participants of childbearing potential were required to use an effective and medically approved method of contraception throughout the trial. Participants were referred by general practitioners or neurologists, or self-referred, most commonly through targeted social media campaigns. The patient organisation HodepineNorge (Headache Norway) contributed to recruitment of participants. All participants provided written informed consent before any study procedures were initiated.

Randomisation and masking

Eligible participants were randomly assigned (1:1:1) to receive either 16 mg candesartan, 8 mg candesartan, or placebo. Randomisation was performed by staff at the Unit for Applied Clinical Research at the Norwegian University of Science and Technology using block randomisation with blocks sizes of nine and 18. The staff responsible for randomisation were not otherwise involved in the trial. Stratified randomisation was not implemented because the relatively large sample size was expected to ensure baseline balance, and the prespecified analysis model included adjustments for any potential baseline imbalances. To maintain masking, the randomisation list was provided directly to the drug manufacturer (Kraggerø Tablettproduksjon, Kraggerø, Norway), which encapsulated both active treatments and placebo in identical opaque capsules. Each medicine box was labelled with a unique trial medicine number linked to the randomisation list and shipped to study sites. Allocation concealment was ensured by assigning the lowest available medicine box number to eligible participants after baseline data collection. This number was recorded in both the electronic case report and the hospital records. The trial was triple-blinded: participants, site personnel, and the trial statistician were all masked to treatment allocation. Emergency unmasking was permitted only when necessary for participant safety, with all instances documented along with justification and context.

Procedures

The total trial duration for each participant was 141 days and included a screening visit (day 1); a 4-week baseline period; a randomisation visit (day 29); a 12-week treatment period; a 4-week follow-up period; and a final visit (day 141). Follow-up telephone calls occurred 2 weeks after the screening visit, and 2 weeks and 8 weeks after the randomisation visit. All study personnel were affiliated with neurological departments that included clinicians with expertise in headache disorders. Participants were evaluated by a neurologist (either registrar or consultant),

See Online for appendix

at the screening, randomisation, and final visits to ensure consistent, expert evaluation.

The trial capsules were identical in appearance, and participants were instructed to take one capsule daily throughout the 12-week treatment period. The trial drug was dispensed by a neurologist at the randomisation visit. Medication for the treatment of migraine attacks was permitted during the trial, including triptans, opioids, analgesics, non-steroidal anti-inflammatory drugs, and antiemetic agents. Adherence to the trial regimen was monitored by site personnel. The following were considered protocol violations: completing the headache diary on fewer than 25 days per 28-day interval during both the baseline and treatment periods; consuming the trial drug on fewer than 76 days during the treatment period; and initiating new headache preventive or anti-hypertensive treatments. Blood pressure was measured at three predefined time points during the trial: the inclusion visit; the randomisation visit; and the final visit. To minimise the risk of unmasking, no blood pressure measurements were taken during the treatment period. Blood pressure was measured as a clinical parameter and was not designated as a study outcome. No specific blood pressure thresholds were required for trial entry. If elevated blood pressure was observed, participants were advised at the final visit to consult their general practitioner for further evaluation. No laboratory investigations were included in the trial protocol.

Electronic case report forms utilising third-party software (webCRF) were used to record trial-related information during site and telephone visits. Efficacy assessments were recorded by the participant prospectively in a headache diary. Participants were required to make daily entries in the headache diary, including days without headaches. Each participant received the diary at the screening visit, along with training in making diary entries by site personnel. Data collected during the 28 days following the screening visit were used to evaluate eligibility criteria, baseline migraine and headache values, and diary adherence. In Norway, participants used an electronic headache diary (eDiary) on their smartphones, while those in Estonia used a paper diary with identical questions. The diary design ensured that participants were prompted to answer additional questions only if they reported a headache, such as headache duration, maximum intensity, non-headache associated symptoms, and use of medication for the treatment of migraine attacks. They were required to classify each headache as a migraine or not. Data from additional health-related outcome measures were also collected from the diary, such as absence from work and whether the absence was due to their migraine or headache. At the final visit, participants were asked to evaluate their subjective experience with the efficacy of the trial drug using a 7-point scale, ranging from “extremely unsatisfied” to “extremely satisfied.” They were also asked to rate the burden of the experienced side-effects of the trial drug on

a 5-point scale, which included options from “not at all” to “high”.

Microsoft Copilot powered by GPT-4, was used to support refinement of manuscript sections, primarily during the review process, by enhancing clarity, structure, and alignment with journal style. Prompts focused on improving consistency with reporting standards for randomised trials. All artificial intelligence-generated content was reviewed and edited by the authors for accuracy and appropriateness.

Outcomes

The primary objective was to compare candesartan 16 mg with placebo. The primary endpoint was the change in the mean number of migraine days per 4 weeks from baseline to weeks 9–12 of the treatment period. At the screening visit, participants were instructed to record headaches with the onset, continuation, or recurrence of their typical migraine as a migraine day. A migraine day was defined as any calendar day self-reported as a migraine in the headache diary. Any headache calendar day on which acute migraine-specific medication was used was counted as a migraine day. Secondary endpoints included differences between all three treatment groups in change from baseline to weeks 9–12 in the mean number per 4 weeks of migraine days, any headache days, headache intensity, days using acute migraine medication, 50% responder rate (ie, proportion of participants with a 50% or more reduction in migraine days compared with baseline), and days missed from work. A health economic analysis comparing overall costs between the placebo and treatment groups (16 mg and 8 mg) was also planned as a secondary outcome. Adverse events were reported by participants after commencement of the trial drug and until the final visit. The severity and causality of each adverse event were determined by a masked investigator. The secondary safety endpoints were to assess the safety and tolerability of candesartan, and to evaluate if adverse events were dose-dependent by comparing the frequency of adverse events between participants receiving candesartan 16 mg and those receiving candesartan 8 mg.

Statistical analysis

The statistical analysis plan was finalised and signed on Aug 9, 2024, following database lock earlier the same day, ensuring all analyses were prespecified and unbiased. We estimated the required sample size using a two-sample t-test. A total of 123 participants per group was calculated to provide 80% power to detect a mean difference in change from baseline in mean migraine days per 4 weeks of 1.0 between groups (change of 4.2 vs 3.2), assuming a standard deviation of 2.8 for the change in both groups and a two-sided significance level of 5%. To account for an anticipated dropout rate of 20%, we aimed to recruit 150 participants per treatment group. No formal power calculation was made for the secondary endpoints. Patient demographics were summarised using descriptive

statistics; categorical variables were reported as absolute counts and percentages, and continuous variables as means with SDs. The primary and secondary efficacy endpoints were analysed using a mixed-effects logistic model to account for the correlation of repeated measures within participants. This analysis utilised the observed data with no imputation of missing values. The fixed effect of time-and-group had levels corresponding to baseline and the combinations of group and period for post-baseline periods, comprising ten levels in total. Participant identification was taken as a random effect. Conditional odds of migraine from the mixed-effects logistic model were transformed to population-averaged number of migraine days per 28 days using the fitted model and assuming approximate normality of log-odds estimates. 95% CIs and p values were reported for the difference per 28 days between trial groups. The 50% or higher responder rates were compared with Fisher's exact

test. The primary and secondary efficacy analyses were conducted in the intention-to-treat population, which included all participants who underwent randomisation and had at least one post-baseline measurement for migraine days per 4-weeks during the masked treatment period. No interim analyses were performed, and no formal stopping guidelines were defined in the protocol. Safety analyses were performed in the safety analysis set, which included all randomly assigned participants who had taken at least one capsule of the trial drug. The per-protocol population was defined as a subset of the intention-to-treat population who completed the trial without major protocol violations and remained on their assigned treatment throughout the study. This dataset was used for sensitivity analyses. Health economic analysis based on the data will be published separately. Statistical analyses were conducted using R version 4.3.3 and SPSS version 25.0.

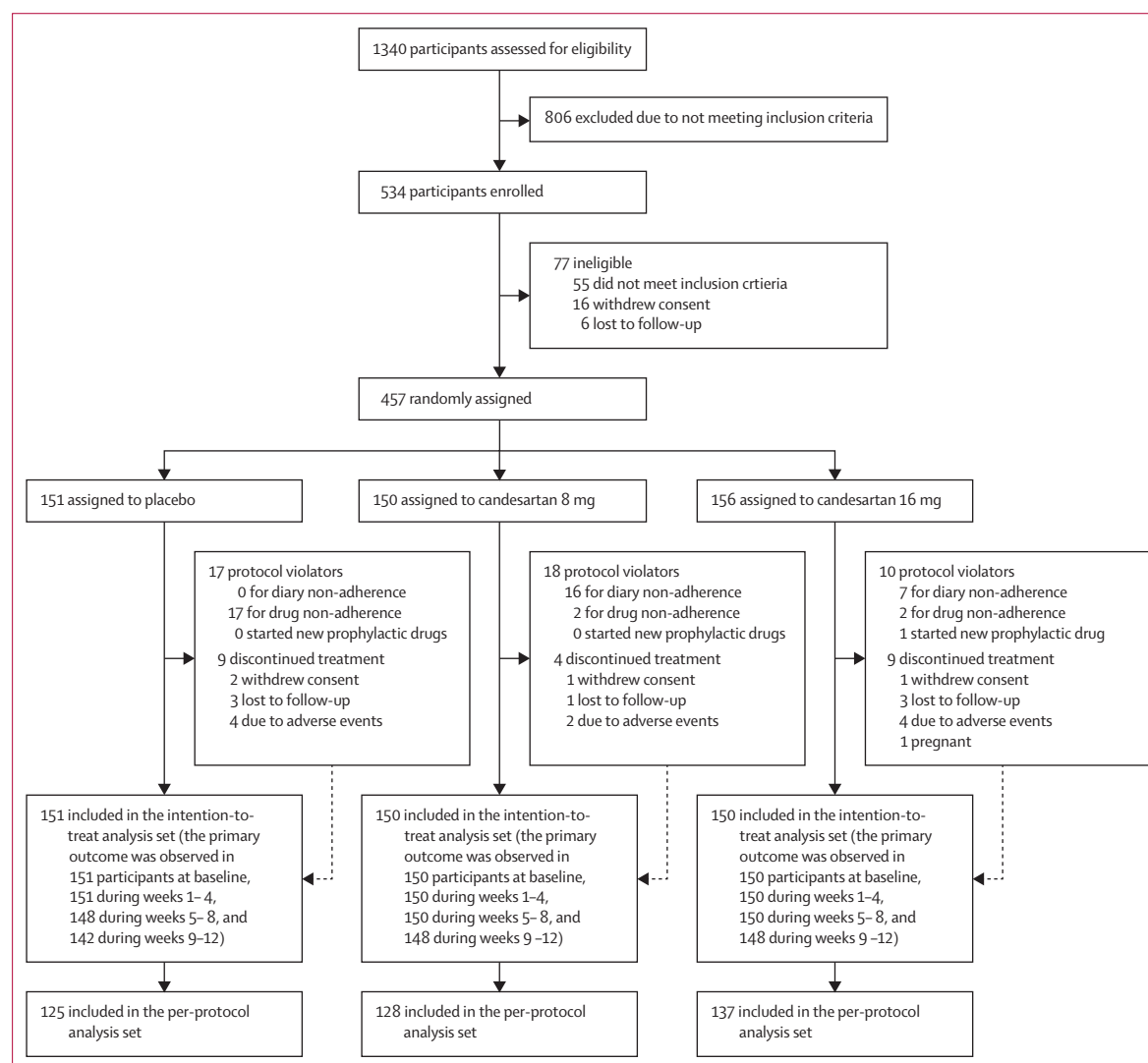


Figure 1: Trial profile

	Placebo (n= 151)	Candesartan 8mg (n=150)	Candesartan 16 mg (n=156)	Total (n=457)
Sex				
Female	122 (81%)	133 (89%)	136 (87%)	391 (86%)
Male	29 (19%)	17 (11%)	20 (13%)	66 (14%)
Age, years	38.4 (10.4; 18–63)	38.9 (9.5; 18–62)	38.8 (11.0; 19–62)	38.7 (10; 18–63)
Blood pressure, mm Hg				
Systolic	129 (14; 99–171)	130 (14; 104–173)	128 (14; 97–175)	129 (14; 97–175)
Diastolic	82 (12; 45–116)	84 (11; 55–109)	81 (10; 57–110)	83 (11; 45–116)
Pulse, beats per min	74 (12; 50–110)	73 (12; 42–109)	73 (12; 46–108)	73 (12; 42–116)
Migraine subtype				
Migraine with aura	25 (17%)	29 (19%)	24 (15%)	78 (17%)
Migraine without aura	89 (59%)	94 (63%)	95 (60%)	278 (61%)
Both migraine with and without aura	35 (23%)	27 (18%)	34 (22%)	96 (21%)
Missing	2 (1%)	0	3 (2%)	5 (1%)
Acute headache medication use	151 (100%)	146 (97%)	155 (99%)	452 (99%)
Triptans	134 (89%)	130 (87%)	142 (91%)	406 (89%)
Paracetamol, NSAIDs, opioids, and combinations medication	102 (68%)	92 (61%)	99 (64%)	293 (64%)
Previous preventive treatment				
Naive	125 (83%)	124 (83%)	129 (83%)	378 (83%)
One preventive drug	22 (15%)	21 (14%)	24 (15%)	67 (15%)
Two preventive drugs	4 (3%)	5 (3%)	3 (2%)	12 (3%)
Assessment of migraine during baseline period				
Migraine days per 4 weeks	5.9 (2.4)	5.5 (2.5)	5.8 (2.5)	5.7 (2.5)
Headache days per 4 weeks	8.1 (3.1)	8.3 (3.3)	8.4 (3.6)	8.3 (3.3)
Days of triptan use per 4 weeks	4.1 (2.9)	3.5 (2.7)	3.7 (2.8)	3.8 (2.8)
Days of analgesic use per 4 weeks	2.7 (2.8)	3.1 (3.1)	3.0 (3.1)	2.9 (3.0)
Days with work absence per 4 weeks	2.0 (3.1)	2.4 (3.3)	2.5 (3.9)	2.3 (3.4)

Data are mean (SD; range), mean (SD), or n (%). Percentages might not total 100 because of rounding. All percentages are calculated using the number of participants in each treatment group as the denominator. Sex was recorded as male or female based on self-report. Gender identity, race, or ethnicity data were not collected. Migraine subtype was reported by the investigator at the inclusion visit. One participant could report having several subtypes. NSAID=non-steroidal anti-inflammatory drug.

Table 1: Baseline characteristics

Role of the funding source

The funder had no role in the study design or conduct, data collection, data analysis, data interpretation or writing of the report.

Results

Between April 9, 2021 and April 12, 2024, 1340 individuals were assessed for eligibility, 806 were deemed ineligible because they did not meet the inclusion criteria, and 534 were enrolled in the trial. Of these, 77 were excluded, and 457 participants were randomly assigned to receive placebo (n=151), candesartan 8 mg once a day (n=150), or candesartan 16 mg once a day (n=156) (figure 1). All randomly assigned participants who received at least one dose of the trial drug were included in the intention-to-treat population. Following randomisation, 22 (5%) discontinued the trial and 45 (10%) did not follow the protocol correctly. Overall, 390 (85%) completed the trial per protocol, with similar completion rates across all treatment groups.

Baseline demographics and clinical characteristics were well balanced across the three treatment groups (table 1).

The mean age of the trial population was 38.7 years (SD 10.0), 391 (86%) were female and 66 (14%) were male. At screening, 406 participants (89%) reported using triptans for acute migraine management and 67 (15%) participants had previously used one preventive migraine drug while 12 (3%) had tried two preventive drugs. During the baseline period, participants across all groups reported a mean of 5.7 migraine days (SD 2.5) and 8.3 headache days (SD 3.3) per 4-week interval, with an average of 3.8 days (2.8) per 4 weeks involving the use of acute migraine-specific medications (triptans). The mean systolic blood pressure at baseline was 129 mmHg (SD 14; range 97–175) and the mean diastolic blood pressure was 83 mmHg (SD 11; range 45–116; table 1). Further details regarding vital measurements, neurological assessments, previous preventive treatment, and comorbid conditions are provided in the appendix (pp 2–6).

Candesartan 16 mg significantly reduced mean monthly migraine days over the 12-week treatment period compared with placebo, meeting the primary endpoint (table 2; figure 2). From baseline to weeks 9–12, participants in the 16 mg group reported a mean change

	Placebo (n=151)		Candesartan 8 mg (n=150)		Candesartan 16 mg (n=156)	
	Effect size (95% CI)	p value	Effect size (95% CI)	p value	Effect size (95% CI)	p value
Primary efficacy end point (week 9–12)						
Migraine days per 4 weeks						
Change from baseline in mean number of days	–0.82 (–1.23 to –0.38)	0.0003	..	..	–2.04 (–2.41 to –1.65)	<0.0001
Difference vs placebo	..	..	..	..	–1.22 (–1.75 to –0.70)	<0.0001
Secondary efficacy end points (week 9–12)						
Migraine days per 4 weeks						
Change from baseline in mean number of days	–0.82 (–1.23 to –0.38)	0.0003	–2.20 (–2.58 to –1.81)	<0.0001	..	..
Difference vs placebo	..	..	–1.39 (–1.92 to –0.87)	<0.0001	..	..
Difference vs candesartan 8 mg	..	..	..	..	0.17 (–0.32 to 0.64)	0.50
Headache days per 4 weeks						
Change from baseline	–1.30 (–1.78 to –0.81)	<0.0001	–2.63 (–3.07 to –2.17)	<0.0001	–2.53 (–2.97 to –2.07)	<0.0001
Difference vs placebo	..	..	–1.33 (–1.95 to –0.70)	<0.0001	–1.23 (–1.85 to –0.61)	0.0001
Difference vs candesartan 8 mg	..	..	..	..	0.10 (–0.49 to 0.69)	0.74
Days with triptan use per 4 weeks						
Change from baseline	–0.39 (–0.73 to –0.03)	0.03	–1.46 (–1.78 to –1.12)	<0.0001	–1.31 (–1.63 to –0.98)	<0.0001
Difference vs placebo	..	..	–1.07 (–1.52 to –0.62)	<0.0001	–0.92 (–1.37 to –0.47)	<0.0001
Difference vs candesartan 8 mg	..	..	..	..	0.15 (–0.26 to 0.56)	0.47
More than 50% reduction from baseline in migraine days per 4 weeks						
Number of patients	40/142 (28%)	..	74/148 (50%)	..	73/149 (49%)	..
Odds ratio vs placebo	..	..	2.54 (1.52 to 4.28)	0.0002	2.44 (1.46 to 4.11)	0.0003
Difference vs candesartan 8 mg	..	..	..	..	0.96 (0.59 to 1.55)	0.91
Days with work absence						
Change from baseline	–0.32 (–0.69 to 0.09)	0.12	–0.62 (–0.95 to –0.26)	0.0008	–0.18 (–0.56 to 0.21)	0.35
Difference vs placebo	..	..	–0.30 (–0.79 to 0.19)	0.23	0.14 (–0.38 to 0.66)	0.60
Difference vs candesartan 8 mg	..	..	..	..	0.43 (–0.04 to 0.93)	0.07

The intention-to-treat analysis set included all participants who underwent randomisation, had a baseline period of headache diary data that could be evaluated, and had at least one post-baseline measurement for migraine days per 4 weeks during the masked treatment period.

Table 2: Primary and secondary efficacy endpoints

of –2.04 [95% CI –2.42 to –1.65]; $p<0.0001$) migraine days per 4 weeks compared with a change of –0.82 (–1.23 to –0.38; $p=0.0003$) migraine days in the placebo group. In the secondary analyses, participants receiving 16 mg also experienced a change of –2.53 [95% CI, –2.97 to –2.07]; $p<0.0001$) headache days per 4 weeks, compared with –1.30 [95% CI –1.78 to –0.81]; $p<0.0001$) headache days in the placebo group. Days with triptan use were significantly reduced in the 16 mg group (mean change –1.31 days [95% CI –1.63 to –0.98]; $p<0.0001$) versus placebo (–0.39 days [95% CI –0.73 to –0.03]; $p=0.03$). No significant differences were observed in days absent from work between the candesartan 16 mg and placebo groups (0.14 days [95% CI –0.38 to 0.66]; $p=0.60$). The proportion of participants achieving a 50% or more reduction in monthly migraine days was 49% (73 of 149) in the 16 mg candesartan group compared with 28% (40 of 142) in the placebo group.

In the secondary analyses, participants receiving candesartan 8 mg experienced significant changes in mean monthly migraine days (mean change –2.20 days

[95% CI –2.58 to –1.81]; $p<0.0001$) but not compared with the 16 mg group ($p=0.50$; table 2, figure 2). Participants receiving candesartan 8 mg also experienced significant changes in mean monthly headache days (–2.63 days [95% CI –3.07 to –2.17]; $p<0.0001$) and days with triptan use (–1.46 days [95% CI –1.78 to –1.12]; $p<0.0001$) compared with placebo, with no significant differences compared with the 16 mg group (0.15 days [95% CI –0.26 to 0.56]; $p=0.74$). The more than 50% responder rate in the 8 mg group was significantly higher than placebo (50% vs 28%), but not different from the 16 mg group (49%). The odds of being a responder were 2.44 [95% CI 1.46–4.11]; $p=0.0003$) times greater in the 16 mg group and 2.54 [95% CI 1.52–4.28]; $p=0.0002$) times greater in the 8 mg group, compared with the placebo group, but ORs were not significantly different between the two candesartan dose regimens (OR 0.96 [95% CI 0.59–1.55]; $p=0.91$). No significant differences in work absences were observed between the 8 mg group and either placebo or the 16 mg group (–0.30 days [95% CI

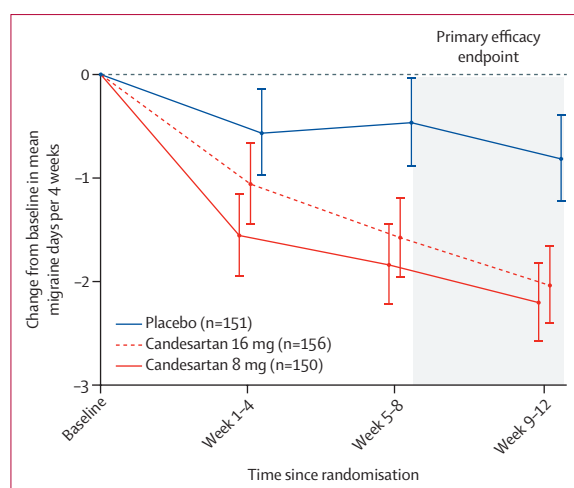


Figure 2: Changes from baseline in migraine days per 4 weeks
Bars indicate 95% CIs.

	Placebo (n=151)	Candesartan 8 mg (n=150)	Candesartan 16 mg (n=156)	Total (n=457)
One or more adverse events	65 (43%)	91 (61%)	95 (61%)	251 (55%)
Total number of adverse events* (number per participant)	136 (0.9)	185 (1.2)	195 (1.3)	516 (1.1)
Total number of adverse events related to trial drug* (number per participant)	37 (0.3)	74 (0.5)	83 (0.5)	194 (0.4)
Adverse events reported in more than 2% of participants in any trial group (events/total events)				
Dizziness	19 (13%)	42 (28%)	46 (30%)	107 (23%)
Respiratory tract infection	17 (11%)	15 (10%)	21 (14%)	53 (12%)
COVID-19	12 (8%)	13 (9%)	11 (7%)	36 (8%)
Sore throat	8 (5%)	4 (3%)	3 (2%)	15 (3%)
Nausea	6 (4%)	4 (3%)	4 (3%)	14 (3%)
Tiredness	3 (2%)	4 (3%)	6 (4%)	13 (3%)
Serious adverse events	1 (1%)	2 (1%)	4 (3%)	7 (2%)
Serious adverse events related to trial drug	0	0	1 (1%)	1 (0%)
Adverse events leading to trial discontinuation	4 (3%)	2 (1%)	4 (3%)	10 (2%)

Data are n (%), unless otherwise specified. All percentages are calculated using the number of participants in each treatment group as the denominator. The investigator assessed the potential relationship between each adverse event and the trial drug. *More than one adverse event could be reported by the participant.

Table 3: Adverse events in the safety population

−0.79 to 0.19], $p=0.23$; 0.43 days [95% CI −0.04 to 0.93; $p=0.07$)).

The sensitivity analyses conducted on the per-protocol analysis set showed similar results for the primary and secondary efficacy endpoints (appendix p 9). A significant reduction in work absences was observed in the candesartan 8 mg group compared with the candesartan 16 mg group (−0.68 days [95% CI −1.17 to −0.21]; $p=0.0050$). However, when compared with placebo, there was no significant difference in work absence days per 4 weeks (0.23 days [95% CI −0.30 to 0.70]; $p=0.38$ for 16 mg and −0.45 days [−0.94 to 0.03]; $p=0.060$ for 8 mg).

A total of 457 participants were included in the safety analysis set (figure 1). Common treatment-emergent adverse events in all three trial groups (incidence of more than 2% in any group) were dizziness, respiratory tract infection, COVID-19, sore throat, nausea, and tiredness (table 3). The incidence of dizziness was higher in participants who received candesartan 16 mg (46 [30%] of 156) and 8 mg (42 [28%] of 150), compared with placebo (19 [13%] of 151). Four participants (3%) from the candesartan 16 mg group, two (1%) participants from the 8 mg candesartan group, and four (3%) participants from the placebo group discontinued the trial due to adverse events. Among these, dizziness was reported as the cause of discontinuation in one participant in the placebo group, one participant in the 8 mg candesartan group, and two participants in the 16 mg candesartan group (appendix p 10). Overall, most adverse events were characterised by investigators as mild, and there was no imbalance in the incidence of moderate or severe events among the three trial groups.

Serious adverse events were reported in four (3%) participants who received candesartan 16 mg (intoxication with quetiapine, infectious arthritis, sepsis, and syncope with cerebral concussion), in two (1%) participants who received candesartan 8 mg (appendicitis and metrorrhagia which was later diagnosed as ovarian cancer), and one (<1%) participant who received placebo (acute diverticulitis; appendix p 10). The investigator deemed that the syncope case, which led to a cerebral concussion and hospital admission without the need for cerebral imaging, was related to the trial drug. All other serious adverse events were either considered unrelated or had a doubtful relationship to the trial drug. One participant required unmasking due to an unplanned pregnancy that occurred during the treatment phase while receiving candesartan 16 mg. The participant subsequently withdrew from the trial and was closely monitored throughout the pregnancy and postpartum period. The pregnancy resulted in the birth of a healthy child.

At the final visit, most participants across all three groups reported that the perceived burden of side-effects from the trial drug was minimal or absent: 121 (78%) of 156 in the candesartan 16 mg group, 124 (83%) of 150 in the 8 mg group, and 132 (87%) of 151 in the placebo group (figure 3A). Regarding perceived efficacy, 56 (36%) of 156 participants in the 16 mg group and 58 (39%) of 150 in the 8 mg group reported being extremely or very satisfied with the migraine preventive effect, compared with 23 (15%) of 151 in the placebo group (figure 3B). Of the 457 participants included in the study, 27 (6%) did not complete the participant-reported outcomes: 10 in the candesartan 16 mg group, five in the 8 mg group, and 12 in the placebo group.

Discussion

In this randomised, placebo-controlled trial candesartan 16 mg once daily significantly reduced the number of

monthly migraine days during the treatment period (mean reduction 2·04 days) compared with placebo (0·82 days), supporting its role as an effective preventive therapy for adults with episodic migraine.

A reduction of 2 or more monthly migraine days is regarded as clinically meaningful in episodic migraine, particularly among individuals with moderate baseline attack frequency. This threshold aligns with the placebo-adjusted reductions reported in trials of CGRP-targeted therapies and supports the relevance of our findings. A recent position statement from the International Headache Society advocates for more ambitious treatment goals, such as achieving migraine freedom or maintaining a very low migraine frequency, and notes that while a 50% or more reduction in monthly migraine days remains a key benchmark, it might not fully address the residual burden of disease or restore quality of life.²³ In our study, 49% of participants receiving candesartan 16 mg achieved a 50% or more reduction in monthly migraine days, compared with 28% in the placebo group. Although cross-trial comparisons should be interpreted with caution, these findings are consistent with 50% responder rates reported for other oral and injectable migraine preventive treatments.^{24,25} The observed therapeutic gain of approximately 20% aligns with previous findings, including a 24% gain reported for topiramate²⁶ and a 19–23% improvement in 50% responder rates seen in pivotal studies of CGRP monoclonal antibodies, comparing placebo to the highest active dose in episodic migraine.^{27–30}

Analysis of the secondary endpoint indicated candesartan 8 mg once daily was similarly effective in reducing monthly migraine days (mean reduction of 2·20 days), suggesting that a lower dose might be adequate for patients who respond to treatment. Although this study was not powered to compare dosing regimens, candesartan 8 mg performed numerically better than the 16 mg dose. Both dosing regimens were associated with significant reductions in mean monthly headache days and triptan use compared with placebo over the 12-week treatment period. No significant differences in work absence were observed between treatment groups and placebo. This could reflect the relatively short study duration or the possibility that reductions in headache frequency do not necessarily translate into improved work attendance. Presenteeism, which could have provided additional insight into productivity, was not assessed.

The frequency of adverse events was higher in the two treatment groups (61% in the 16 mg group and 61% in the 8 mg group) than in the placebo group (43%). However, participants across all three groups reported that the trial drug was generally well tolerated. The proportion of participants who discontinued the trial due to inadequate tolerability was 2%, which is lower than observed in previous randomised controlled trials^{12,13} and observational studies.¹⁵ Participants in the candesartan 16 mg group began with a daily dose of 16 mg from the

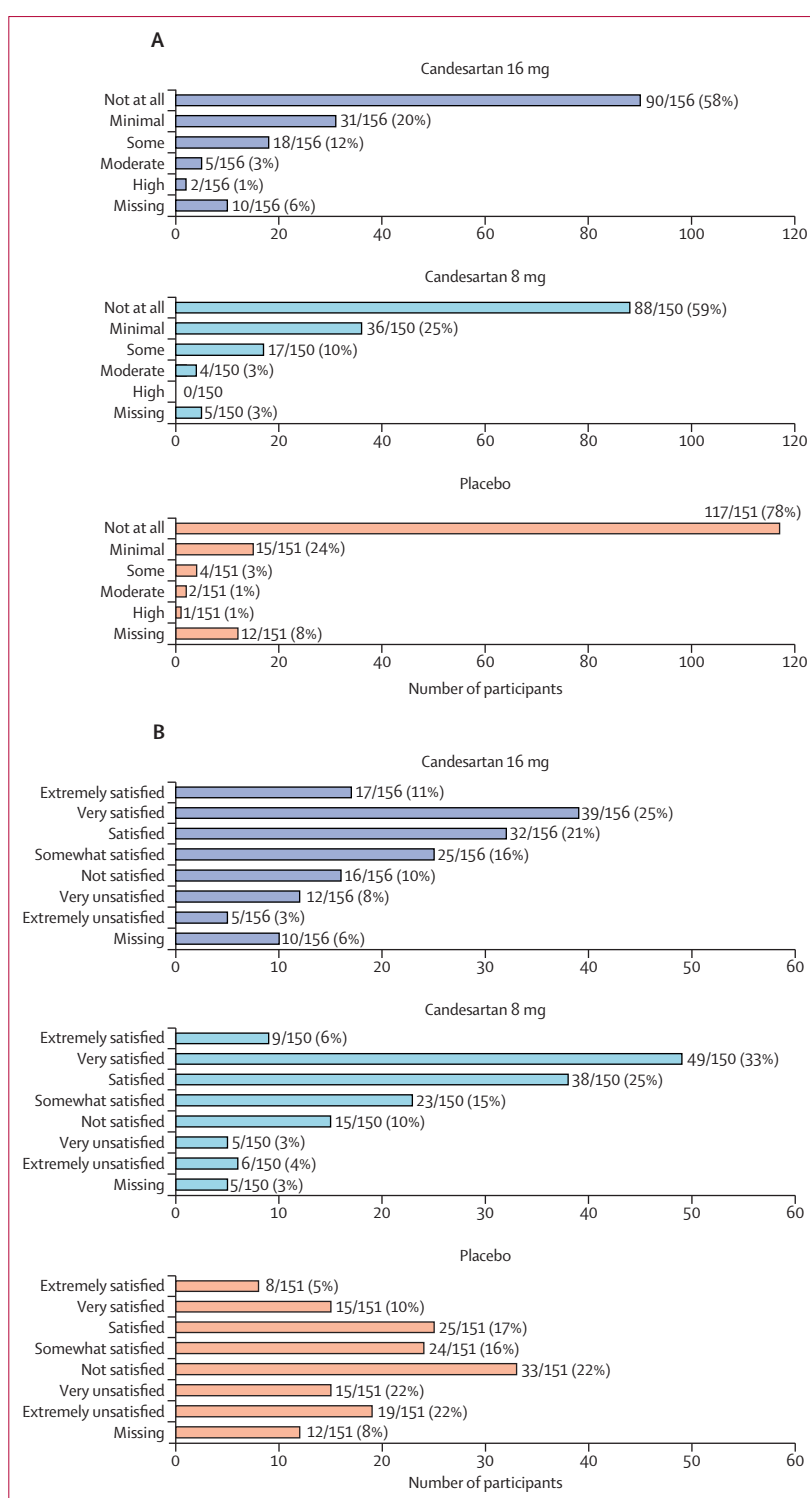


Figure 3: Participant-reported perceived burden of side-effects (A) and efficacy (B) of trial drug
Of the 457 participants included in the study, 27 (6%) did not complete the participant-reported outcomes: ten in the candesartan 16 mg group, five in the 8 mg group, and 12 in the placebo group.

start of the trial, without any dose escalation. This approach did not result in a significantly higher dropout rate due to adverse events, which was 1% for the 16 mg group, compared with less than 1% for the 8 mg group and 1% for the placebo group. The comparable dropout rates across all treatment groups underscore the safety and tolerability of candesartan as a preventive treatment for episodic migraine, even when starting at a higher dose.

Triptan use in our study was higher than previously reported in population-based studies and clinical trials.^{27,28,31} This might be partly explained by the exclusion of triptan non-responders, which could have skewed the sample toward individuals with a history of effective triptan use. Additionally, we cannot rule out the possibility that our recruitment strategy introduced bias against the inclusion of triptan-naïve participants.

Our trial is the third and largest of its kind, and the first to employ a parallel-group design, which confirms the efficacy and tolerability of candesartan in migraine prevention. Given its demonstrated efficacy, high tolerability, low toxicity, ease of administration, and affordability, candesartan should be included in migraine prevention guidelines as a first-line treatment. The drug's prescription capability extends beyond neurologists to general practitioners in primary care settings, where most migraine patients receive treatment. Additionally, it merits consideration for inclusion on the World Health Organization's list of essential medicines. Such recognition would significantly enhance access to migraine preventive treatments, also in populations with limited access to newer, more expensive treatments, ultimately reducing the individual and societal detrimental consequences of migraine.

A limitation of this trial is the relatively short 12-week treatment duration, which might have constrained the assessment of the long-term efficacy of candesartan. The observed migraine trajectory suggests that extended treatment could offer further insights into sustained benefits and potential of candesartan to stabilise migraine patterns over time. Recruitment via self-referral and social media might have introduced selection bias but allowed for broader inclusion beyond specialist care. To enhance generalisability, future trials in primary care settings are encouraged. Eligibility criteria (between two and eight attacks per month) might have underrepresented individuals with high-frequency or shorter duration migraines, and the exclusion of those with 15 or more headache days per month further limits applicability to chronic migraine populations. Individuals with significant comorbidities, such as medication overuse headache, or those who had not benefitted from three or more preventive treatments, were also excluded. However, real-world evidence suggests that candesartan might still be effective in more treatment-resistant populations.^{14,16} Participants aged 65 years or older were not included, in accordance with International Headache Society

recommendations due to increased comorbidities and altered drug metabolism in older adults. However, this limits the generalisability of our findings to older individuals. Additionally, the absence of data on gender identity and race or ethnicity restricts the ability to assess differential treatment effects across diverse populations. To preserve masking, blood pressure was not monitored during the treatment period, limiting our ability to assess treatment-related changes. We did not include measures of general or headache-specific quality of life; incorporating patient-reported outcomes in future studies could capture the broader effect of treatment on patients' daily lives. The precise mechanism by which candesartan prevents migraine remains unclear, as is the case for most oral migraine preventives. However, its target, the renin-angiotensin system, has roles beyond cardiovascular regulation, including potential involvement in central pain processing.³² Further studies are needed to elucidate the mechanism of action of candesartan in migraine prevention.

In this trial, candesartan 16 mg administered once daily for 12 weeks was effective and well tolerated as a preventive treatment for episodic migraine. Efficacy was also observed with the 8 mg dose, suggesting that a lower dose could be sufficient for patients who respond to treatment. Compared with existing treatment options, candesartan's favourable safety and tolerability profile might encourage better adherence in a condition with substantial unmet need. Further clinical trials and real-world data from registry studies are necessary to assess its long-term efficacy, particularly in chronic migraine.

Contributors

ET and LJS designed the study. LRØ, GBG, IA, M-HB, CL, KBA, BSW, AHA, ICL, MGB, MB, BM, KGV, KIM, KA, ANK, ABØ, HMLV, JL, KE, HE, BB, MBL, JHØ, and LJS acquired the data. LRØ, ØS, TW, SG, and ET contributed to analysis and data interpretation. LRØ, TW, SG, LJS, and ET drafted the manuscript. LRØ, TW, ØS, GBG, IA, SG, M-HB, CL, KBA, BSW, AHA, ICL, MGB, MB, BM, KGV, KIM, KA, ANK, ABØ, HMLV, JL, KE, HE, BB, MBL, JHØ, LJS, and ET provided critical revision of the manuscript. ØS and LRØ did the statistical analysis. ET and LJS obtained funding for the study. All authors participated in data interpretation, manuscript preparation, and final publication decisions and attest to the accuracy and completeness of the data and adverse event reporting, as well as the adherence of the trial to the protocol. LRØ and ØS had full access to all the data in the study, verified the underlying data, and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors confirm that they had access to all data in the study and accepted responsibility for the decision to submit the manuscript for publication.

Declaration of interests

LRØ has received advisory board honoraria from Roche. TW has received honoraria from TEVA, Roche, Lilly, Lundbeck and has stocks in two MedTech companies (Vilje Bionics and Keimon Medical). GBG has received honoraria for lectures and presentation from Novartis, TEVA, and Lundbeck. M-HB has received advisory board honoraria from Jazz Pharmaceuticals, Angelini Pharma, Lundbeck, Pfizer, and Eisai, and honoraria for lectures from Eisai, AbbVie, Angelini Pharma, Novartis, Pfizer, BestPractice (funded by the pharmaceutical industry), and Organon. Her institution (University of Bergen) has received fees from contract research conducted for Novartis and is listed as a marketing authorisation holder for valproate. CL has received honoraria for study board membership from Lundbeck Pharma and for lectures and

presentations from Abbvie Pharma, Lundbeck, Novartis, and Roche. KBA has received speaker-fees from Biogen, Lundbeck, TEVA, Novartis, and Roche, and has also received honoraria for participation in advisory boards sponsored by TEVA, Biogen, Lilly, and Novartis. AHA reports unrestricted research grants from Boehringer Ingelheim; honoraria for lectures from BMS and Pfizer, Teva, Abbvie, Lundbeck, and Novartis; and participation in advisory boards for Lundbeck and Abbvie. KGV has received personal honoraria for participation in advisory boards for Lundbeck, TEVA, Pfizer, Novartis, and personal honoraria for lectures for Lundbeck, TEVA, Pfizer, and Novartis. HMV has received speaker honoraria from Angelini Pharma Nordics. KE has received speaker honoraria from Novartis. LJS is the director of Lifting The Burden, an international charitable organisation running the Global Campaign Against Headache and a research committee member of the Norwegian Brain Council, a charitable organisation. ET has received personal fees for lectures and advisory boards from Novartis, Eli Lilly, Abbvie, TEVA, Roche, Lundbeck, Pfizer, Biogen, and Organon. ET is a consultant for and holds stocks and intellectual property in Man & Science and Nordic Brain Tech, and holds shares in Keimon Medical. ET has received non-personal research grants from European Commission, Norwegian Research Council, KlinBeForsk, and Nordic Innovation, and has conducted commissioned (non-personal) research for Lundbeck. All other authors declare no competing interests.

Data sharing

The study protocol and statistical analysis plan are provided in the appendix. The data supporting the findings of this study are available from the corresponding author upon reasonable request. Due to patient confidentiality, only de-identified data will be shared. For inquiries, please contact Lise Rystad Øie at lise.r.oie@ntnu.no.

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