Erenumab for Chronic Cluster Headache
A Randomized Clinical Trial

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Abstract

IMPORTANCE Calcitonin gene-related peptide (CGRP) is involved in the pathophysiology of cluster headache (CH). Prophylactic pharmacologic treatment options for chronic CH (CCH) are limited. The potential effects of erenumab, a CGRP receptor antagonist monoclonal antibody, in treating CCH have not been assessed.

OBJECTIVE To evaluate the superiority of erenumab compared with placebo in the prophylaxis of CCH.

DESIGN, SETTING, AND PARTICIPANTS A 12-week, double-blind, placebo-controlled randomized clinical trial (CHERUB01) was conducted at 11 sites in Germany from December 2, 2021, to September 27, 2023. Participants (aged 18-65 years) had a diagnosis of CCH, had no previous sufficient response to standard CCH prophylactic medications approved in Germany, and had experienced at least 9 attacks during screening.

INTERVENTION Loading dose of erenumab (280 mg subcutaneously) or matching placebo in a 1:1 randomization, followed by another dose of erenumab (140 mg subcutaneously) or placebo 4 weeks later.

MAIN OUTCOMES AND MEASURES The primary end point was the reduction of mean weekly CH attacks from baseline over weeks 5 and 6. Key secondary end points were 50% responder rates and changes in Patient Global Impression of Improvement (PGI-I) scores. Safety and tolerability were also assessed. A bayesian analysis scheme was used for statistical analysis.

RESULTS This study randomized 81 participants (mean [SD] age, 48.9 [10.4] years; 60 men [74.1%]) with CCH (mean [SD], 21.5 [9.7] attacks per week) to erenumab (n = 41) or placebo (n = 40). Recruitment was stopped prematurely due to insufficient patient numbers meeting the inclusion criteria within the planned recruitment period. The primary end point was not met over weeks 5 and 6 of the double-blind phase because the mean (SD) reduction of weekly CH attacks was −7.3 (8.6) per week for erenumab and −5.9 (10.5) per week for placebo (group difference, −1.5 [95% credible interval [CrI], −5.7 to 2.8]). At weeks 5 and 6, the percentage of participants with a 50% or greater reduction in CH attacks was not significantly different between the erenumab (13 [31.7%]) and placebo (18 [45.0%]) groups (odds ratio, 0.5 [95% CrI, 0.2-1.5]). PGI-I scores were also not different between groups. More participants reported adverse events with erenumab than placebo (27 [65.9%] vs 17 [42.5%]), which were mostly of mild or moderate intensity.

(continued)

Key Points

Question Is the calcitonin gene-related peptide (CGRP) receptor monoclonal antibody erenumab effective in the treatment of patients with chronic cluster headache (CCH)?

Findings In this randomized clinical trial with 81 patients, a 280-mg subcutaneous loading dose of erenumab followed by a 140-mg subcutaneous dose 4 weeks later did not substantially reduce weekly cluster headache attacks compared with placebo. Erenumab was not superior to placebo in Patient Global Impression of Improvement scores, reduction of mean pain severity, and attack duration.

Meaning These findings suggest that blockade of the CGRP receptor has no beneficial effect in patients with CCH.

+ **Visual Abstract**

+ **Supplemental content**

Abstract (continued)

CONCLUSIONS AND RELEVANCE In this clinical trial of patients with CCH, blockade of the CGRP receptor with erenumab was not successful in the prophylaxis of attacks. Future studies should revisit the role of CGRP in CCH.

Introduction

Cluster headache (CH) is a disabling primary headache disorder characterized by unilateral pain attacks (lasting 15-180 minutes) accompanied by ipsilateral autonomic symptoms. About 20% to 30% of patients are affected by chronic cluster headache (CCH), which involves attacks occurring for at least 1 year without remission or with remission periods lasting less than 3 months.[1] The high frequency of up to 8 attacks per day necessitates effective medication prophylaxis.[2,3] In most countries, verapamil and lithium are unspecific first-choice medications for CCH prophylaxis. Monotherapy is rarely sufficient in CCH; even with combination therapies, patients often see only marginal improvement.[4] In severely affected patients, devices such as occipital nerve stimulation are used to provide some benefit.[5]

Calcitonin gene-related peptide (CGRP) is a key neurotransmitter in CH pathophysiology, with elevated levels during attacks in the ipsilateral jugular vein.[6,7] CGRP infusion can induce attacks in susceptible individuals but less frequently in CCH than in active episodic CH (ECH).[8] Triptans, which inhibit CGRP release from trigeminal afferents, effectively abort CH attacks in ECH and CCH.[2,6,9] Therefore, blocking the CGRP pathway may be beneficial in CCH prophylaxis.

The CGRP monoclonal antibody (mAb) galcanezumab reduced attack frequency in a randomized placebo-controlled trial involving patients with ECH (n = 106) but failed to show superiority to placebo in patients with CCH.[10] In this trial,[10] patients had a reduction of attacks over 12 weeks, but the results did not differ between galcanezumab and placebo for most end points.[11] Fremanezumab is another CGRP mAb with a binding site on the CGRP molecule that is slightly different from galcanezumab. A phase 3 trial with fremanezumab in the treatment of CCH was stopped prematurely due to lack of benefit over placebo. Both trials allowed prophylactic comedications and had notable placebo responses.[12] In contrast, clinical observations strongly indicate a benefit for CGRP mAbs and the CGRP receptor mAb erenumab in CCH prophylaxis.[13,14] A 1-year open-label trial with the only intravenously available CGRP antagonist, eptinezumab, showed good tolerability and an efficacy within the range of results for galcanezumab.[15]

Erenumab is a specific mAb that binds to and blocks the CGRP receptor with high affinity, distinguishing it from galcanezumab, fremanezumab, and eptinezumab, which target CGRP. Several trials led to the approval of erenumab for migraine prophylaxis.[16-18] Erenumab is administered monthly at subcutaneous doses of 70 or 140 mg. Higher doses up to 280 mg were tested in healthy volunteers without substantial safety concerns.[18,19] Erenumab also blocks other receptors of the CGRP family, such as the amylin-1 receptor, thereby differentiating from CGRP blockade, which could potentially lead to benefits in CCH therapy.[20,21]

Substantial evidence for CGRP's role in CCH exists, but the effects of CGRP receptor blockade in CCH have not been assessed in a clinical study.[22] Here, we report results from a randomized clinical trial to investigate erenumab in the treatment of CCH.

Methods

A 12-week, double-blind, placebo-controlled, investigator-initiated randomized clinical trial was conducted in 11 study centers in Germany between December 2, 2021, and September 27, 2023. The trial was approved by the lead ethics committee of the State of Berlin. All participating sites have extensive experience with patients with CH. The Efficacy of Erenumab in Chronic Cluster Headache (CHERUB01) trial consisted of a screening phase of 7 to 12 days (baseline), a double-blind treatment phase of 6 weeks, and a follow-up phase of 4 weeks. Here, we report data from the double-blind treatment phase. Participants provided written informed consent before study inclusion. The statistical analysis plan and the trial protocol are presented in Supplement 1. This trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Inclusion and Exclusion Criteria

Inclusion criteria required eligible patients (aged 18-65 years) to have a history of CCH for more than 12 months and to meet the *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) criteria for CCH.[1] Participants had to have sufficient CH attack treatment with triptans, oxygen, or both based on their history. Participants needed to have insufficient efficacy or tolerability or contraindications to approved CH prophylactic medications, such as verapamil and lithium, as determined by the patient. Prior therapy for CCH with a CGRP-targeted mAb generally led to study exclusion. Complete inclusion and exclusion criteria can be found in Supplement 1.

Randomization and Masking

Participants and staff were blinded to study treatment. Using interactive response technology (Calyx), participants were randomized 1:1 to erenumab or placebo, stratified by CH attack frequency (>19 attacks per week vs 9-19 attacks per week) and study site. Erenumab was supplied in 1-mL glass syringes, each with 70 mg of erenumab or identical placebo. All randomized participants received 4 subcutaneous injections of either erenumab (4 syringes of 70 mg each; 280 mg) or matching placebo on day 1. Four weeks later, participants received only 2 subcutaneous injections of erenumab (70 mg each; 140 mg) or placebo.

Procedures

Following confirmation of eligibility and study inclusion, participants recorded CH attacks using an e-diary, noting pain severity, duration, and acute attack medication until primary end point assessment. If no attack occurred, participants used the e-diary once daily for adherence. Randomized participants received study medication during the double-blind phase on day 1 and again after 4 weeks. The dose and the number of injections were reduced after 4 weeks based on pharmacokinetics (provided by Novartis) and to minimize a possible placebo response. Participants also completed patient-reported outcome questionnaires via the e-diary as needed. Following randomization, patients visited the study site in person at weeks 4, 6, and 10.

Outcomes

Data were analyzed over 7-day periods (weekly). The primary end point was the mean reduction in weekly CH attacks from baseline over weeks 5 and 6 of the double-blind phase. A CH attack was defined following the *ICHD-3* classification without modifications. Key secondary analyses included the proportion of patients achieving a 50% or greater reduction in attacks and the number of patients with scores of 1 or 2 on the Patient Global Impression of Improvement (PGI-I) scale at week 6. The 7-point PGI-I scale (with 7 indicating very much worse and 1 indicating very much better) was used to assess the pain condition at the end of the double-blind study period compared with the start of the study. Exploratory end points covered the 30% and 70% responder rates, CH attack duration reduction, and changes in mean pain severity. Pain severity was rated on a scale from 0 to 10, where 0 indicates no pain and 10 is the worst pain imaginable. Safety analysis involved counting

the numbers of adverse events (AEs) and participants discontinuing the study. Further details are listed in the trial protocol in Supplement 1.

Statistical Analysis

Bayesian statistics underpinned the planning and analysis of this study. Inference on the mean reduction in weekly CH attacks came from a bayesian posterior distribution. Success for erenumab was defined by (1) a posterior probability of any effect greater than 0 of at least 90% and (2) a posterior probability of a clinically relevant effect (ie, reduction of >3 attacks per week) of at least 50%. We aimed to recruit 118 patients in total. The trial was powered to demonstrate the superiority of erenumab over placebo by reducing a mean (SD) of 9.2 (8.6) vs 4.6 (8.6) CH attacks per week. The assumed placebo effect was derived from Dodick et al,[11] whereas the assumed double erenumab treatment effect was supported by Goadsby et al.[10] In this ECH trial,[10] a mean (SD) reduction of 8.7 (1.4) attacks per week was achieved with galcanezumab (n = 49 participants), which is in the range of the attack reduction (9.2 attacks) that we deemed meaningful. In bayesian power simulations with weakly informative priors, both success criteria were met with at least 94 randomized patients. Given the 10-week trial duration, we assumed a 20% dropout rate and adjusted recruitment numbers. No interim analysis was planned.

The primary cohort for efficacy analyses was intention to treat (ITT), including all randomized participants. The safety analysis included all patients receiving at least 1 dose of active study medication or placebo. The primary end point (change in the mean number of weekly CH attacks from weeks 5 and 6 compared with baseline) was analyzed using a bayesian linear mixed-effects model with weakly informative priors (for details on the method, see Fisch et al[23]; for technical details, see Bürkner[24]). This model included treatment group as the main predictor and clustered data by study center (random-intercept, fixed-slope model). Covariates included baseline weekly CH attacks, sex, age, and years since diagnosis. Secondary end points were analyzed similarly using logistic models for binary outcomes. We obtained 95% credible intervals (CrIs) by sampling from the posterior distributions of the model's parameters. Four Markov chain Monte Carlo chains were run with 2000 iterations each. Model convergence was checked with an $\hat{R}$ of less than 1.05 and effective sample sizes of posterior draws greater than 500. Data management and model estimation were conducted in R, version 4.3.2 (R Project for Statistical Computing), interfacing with STAN, version 2.32.2 via the brms package, version 2.21.0. Missing data were addressed through imputation, with a complete case analysis as a sensitivity check. Imputation was done in 2 ways, separating outcomes and covariates. Missing CH attacks were imputed daily: If fewer than 3 were missing in the last 7 days, a running average was used; if more than 2 were missing, we used the last 7-day average without missing values. This approach provided conservative imputed values, assuming a positive treatment effect. Missing covariates (eg, years since diagnosis) were imputed using multiple imputation (mice package for R, version 3.16.0). A CrI not including the null represented statistical significance.

The safety analysis primarily comprised descriptive statistics for AEs and severe AEs stratified by group. A mixed model, adjusted for study center and using a negative binomial link for sparse AE counts, was run to compare the number of AEs per group.

Results

Of the 102 participants with CCH assessed for eligibility, 81 were included in this study (mean [SD] age, 48.9 [10.4] years). Most participants were male (60 [74.1%] vs 21 female [25.9%]). Attack frequency was balanced at baseline, with a mean (SD) of 21.5 (9.7) attacks per week. The number of recruited patients corresponded to 86.4% (102 of 118) of the planned sample size. The first patient visit was on December 2, 2021, and the last was on September 27, 2023. The study was stopped prematurely due to an insufficient number of participants meeting the inclusion criteria (**Figure 1**). A total of 81 participants were randomized to receive erenumab (41 participants) or matching placebo (40 participants) (**Figure 2**). Both study groups were similar at baseline. The most frequent

comorbidity was depression. Participants had a mean (SD) CCH duration of 8.3 (7.1) years. Baseline and clinical characteristics are summarized in **Table 1**.

The most common exclusion reason was a lack of minimum required CH attacks. All patients exposed to at least 1 dose of study medication were included in the ITT analysis and safety population. During the double-blind phase, 11 participants (13.6%) terminated the study for various reasons but not lack of efficacy. Dropouts were evenly distributed (5 in the erenumab group and 6 in the placebo group). E-diary adherence was greater than 90% during the double-blind phase.

Efficacy End Points

The primary end point of the study was not met. The reduction of mean (SD) weekly CH attacks from baseline over weeks 5 and 6 was −7.3 (8.6) attacks per week for erenumab and −5.9 (10.5) attacks per week for placebo. The group difference for the reduction of weekly CH attacks was −1.5 (95% CrI, −5.7 to 2.8) attacks per week in favor of erenumab (**Table 2**). This difference was not statistically significant, as the CrI included zero. Achieving a clinically meaningful difference (reduction of >3 attacks per week) had a bayesian posterior probability of 24% (**Figure 3**). The mean number of

Figure 1. Trial Flow Diagram
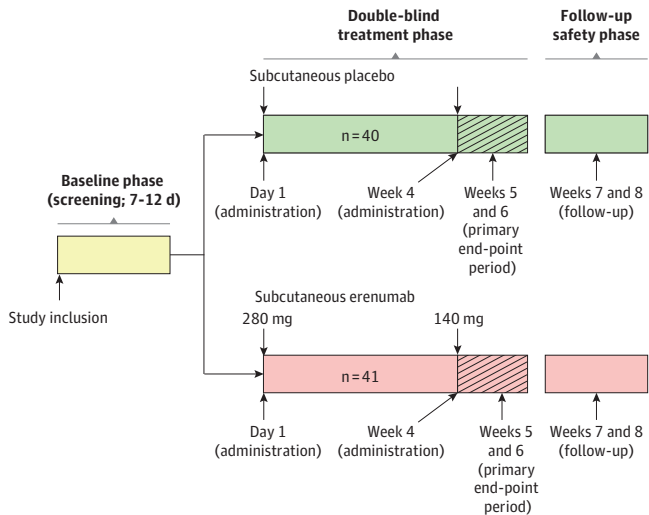

ITT indicates intention to treat.
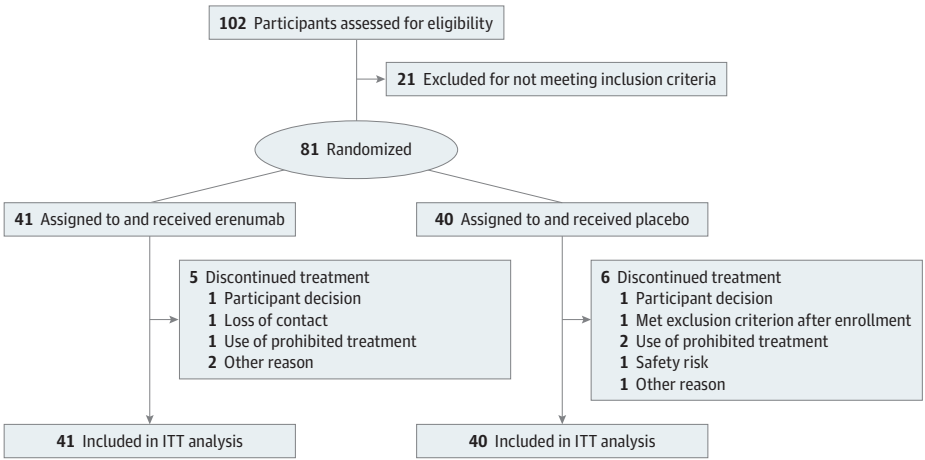
Figure 2. Study Design

weekly CH attacks over weeks 5 and 6 was 10.9 (95% CrI, 5.7-15.3) attacks per week with erenumab vs 12.9 (95% CrI, 7.6-18.4) attacks per week with placebo (Figure 3).

The reduction of weekly CH attacks of at least 50% from baseline over weeks 5 and 6 was not different between groups. In the erenumab group, 13 participants (31.7%) had a 50% or greater reduction in weekly CH attacks compared with 18 (45.0%) in the placebo group (odds ratio [OR], 0.5

Table 1. Key Baseline and Demographic Characteristics of Enrolled Patients, Randomized Set[a]

Characteristic	All participants (N = 81)	Erenumab, 280 mg/ 140 mg (n = 41)	Placebo (n = 40)
Age, mean (SD), y	48.9 (10.4)	48.3 (10.7)	49.6 (10.3)
Sex			
Male	60 (74.1)	30 (73.2)	30 (75.0)
Female	21 (25.9)	11 (26.8)	10 (25.0)
Weight, mean (SD), kg	81.2 (19.1)	83.8 (21.4)	78.5 (16.6)
Duration of CCH, mean (SD), y	8.3 (7.1)	7.6 (7.0)	9.0 (7.3)
Baseline No. of weekly CH attacks, mean (SD)	21.5 (9.7)	21.2 (9.0)	21.7 (10.6)
>19 Weekly attacks	47 (58.0)	26 (63.4)	21 (52.5)
Attack duration, mean (SD), min	40.8 (23.9)	42.0 (23.3)	39.6 (24.7)
Attack severity measured by NPRS score, mean (SD)	6.5 (1.7)	6.3 (1.6)	6.8 (1.8)
No. of acute medications, mean (SD)	24.2 (14.5)	23.7 (12.2)	24.6 (16.8)
Participants with comorbid depression	14 (17.3)	9 (22.0)	5 (12.5)

Abbreviations: CCH, chronic cluster headache; CH, cluster headache; NPRS, numeric pain rating scale.

[a] Unless specified otherwise, values are No. (%) of patients. Randomization was stratified by attack frequency (>19 attacks vs 9-18 attacks) and study site.

Table 2. Primary, Secondary, and Exploratory End Points

End point (change from baseline to weeks 5 and 6)	Erenumab group (n = 41)	Placebo group (n = 40)	Adjusted difference (95% CrI)[a]
Primary			
No. of weekly CCH attacks, mean (SD)	−7.3 (8.6)	−5.9 (10.5)	−1.5 (−5.7 to 2.8)
Secondary, No. (%) of patients			
≥50% Reduction in No. of attacks	13 (31.7)	18 (45.0)	0.7 (−1.7 to 0.4)
PGI-I score improved or very much improved at week 6 vs baseline	15 (36.6)	14 (35.0)	0.3 (−0.7 to 1.2)
Exploratory, mean (SD)			
Change in CH duration, min	−1.3 (11.0)	−0.5 (23.3)	−1.2 (−9.6 to 4.4)
Change in NPRS scale score for CH attack severity	−3.4 (2.2)	−3.8 (2.1)	0.1 (−0.6 to 0.9)
Change in No. of weekly acute CH attack medications	1.6 (25.4)	3.3 (22.0)	1.0 (−9.0 to 11.2)

Abbreviations: CCH, chronic cluster headache; CH, cluster headache; CrI, credible interval; NPRS, numeric pain rating scale; PGI-I, Patient Global Impression of Improvement.

[a] Not statistically significant.

Figure 3. Primary End Point Analysis Using Bayesian Posterior Distribution of the Estimated Difference in the Reduction of Weekly Cluster Headache Attacks With Erenumab vs Placebo
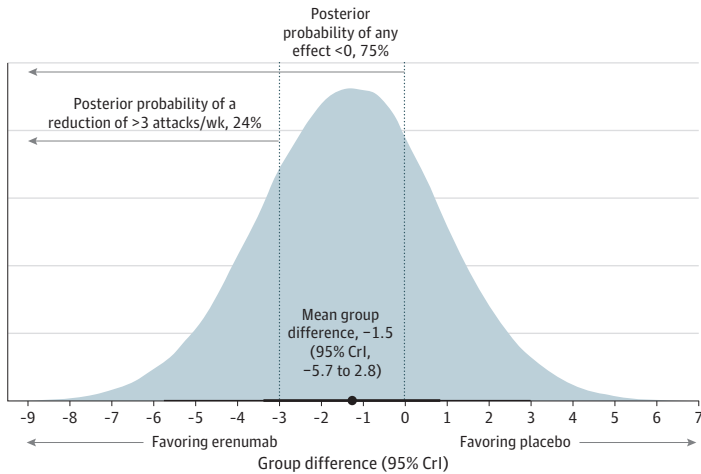
CrI indicates credible interval.

[95% CrI, 0.2-1.5]). There was also no difference in 30% (OR, 1.0 [95% CrI, 0.3-1.0]) and 70% (OR, 1.3 [95% CrI, 0.4-1.9]) responder rates in weeks 5 and 6 (eFigure in Supplement 2).

A total of 15 participants (36.6%) in the erenumab group and 14 (35.0%) in the placebo group reported improvement in PGI-I scores (PGI-I score 1 or 2) at week 6 (OR, 1.3 [95% CrI, 0.5-3.4]). For patients who completed the trial per protocol (35 in the erenumab group and 30 in the placebo group), the OR was 1.0 (95% CrI, 0.3-3.0), indicating no difference (Table 2).

Exploratory End Points

Mean (SD) attack duration at baseline was 42.0 (23.3) minutes in the erenumab group and 39.6 (24.7) minutes in the placebo group. Across weeks 5 and 6, the mean (SD) attack duration was 40.7 (28.0) minutes for the erenumab group and 39.2 (36.0) minutes for the placebo group. The change in mean (SD) attack duration was not different between groups, with −1.3 (11.0) minutes for erenumab and −0.5 (23.3) minutes for placebo (difference, −1.2 [95% CrI, −9.6 to 4.4] minutes) (Table 2).

Mean pain severity was reduced in both groups across weeks 5 and 6 compared with baseline but was not different between treatments. Attack severity assessed with numeric pain rating scale scores decreased by a mean (SD) of 3.4 (2.2) points with erenumab and 3.8 (2.1) points with placebo (adjusted difference, 0.1 [95% CrI, −0.6 to 0.9]). Despite this reduction, the mean total number of weekly acute medications for CH attacks increased in both treatment groups from baseline to weeks 5 and 6 (1.6 [25.4] vs 3.3 [22.0] for erenumab vs placebo [95% CrI, −9.0 to 11.2]).

Adverse Events

More participants reported AEs with erenumab than with placebo (27 [65.9%] vs 17 [42.5%]; OR, 3.0 [95% CrI, 1.1-8.2]). Most AEs were mild or moderate; 2 serious AEs occurred in the erenumab group (eTable in Supplement 2). The most frequent AE was upper respiratory tract infection (4 of 27 [14.8%] vs 4 of 17 [26.6%] for erenumab vs placebo). Constipation was reported only in the erenumab group (3 [11.1%]), and hypertension occurred in 2 participants treated with erenumab (7.4%) and 3 with placebo (19.9%). One severe AE involved worsening CH, leading to termination of study medication (eTable in Supplement 2).

One suspected unexpected serious adverse reaction of atrial flutter and sigmoid diverticulitis occurred with erenumab, which was resolved with medication. No deaths or pregnancies occurred in the trial. Laboratory examinations revealed no substantial pathologic findings during the double-blind phase and safety follow-up. Hematology analysis showed no notable findings, although lymphocyte counts were consistently lower in the erenumab group at baseline and week 6 without clinical implications. Mean systolic and diastolic blood pressure did not change during the trial and remained within normal limits. Electrocardiograms were without clinically significant findings.

Discussion

The CHERUB01 trial evaluated the safety and efficacy of the CGRP receptor mAb erenumab in the treatment of CCH. Erenumab did not show superiority over placebo in reducing the mean number of CH attacks, nor did it demonstrate a higher 50% responder rate. The mean attack duration was nearly unchanged over the 6-week double-blind study period, whereas mean pain intensity was reduced with no statistically significant difference between treatment groups. The safety profile of erenumab was consistent with previous observations in migraine studies, although 1 nonfatal suspected unexpected serious adverse reaction occurred. Our findings indicate that blockade of the CGRP receptor with erenumab does not provide any advantages over placebo, suggesting that the CGRP receptor is not an appropriate target for CCH treatment at least with an mAb.

To our knowledge, this is the first clinical trial with a CGRP receptor mAb used in the prophylaxis of CH and the only trial with a CGRP-targeted mAb in CCH using monotherapy, excluding confounders from additional oral prophylactic agents, because we aimed to assess the sole blockade of the CGRP receptor. Concomitant oral prophylaxis was allowed in 2 previous unsuccessful trials in

which the antibodies were directed against the CGRP peptide in contrast with our trial.[12,13] Together, the results of the unsuccessful trials of galcanezumab and fremanezumab and those of the CHERUB01 trial imply that the role of CGRP in CCH needs to be revisited. Supporting evidence for a limited role of CGRP in CCH may be the observation of lower CGRP levels in patients with CCH than in those with ECH, although a newer study could not confirm this finding.[25,26]

CHERUB01 participants received an initial 280-mg subcutaneous dose of erenumab. This dosing aimed to ensure complete CGRP receptor saturation and rapid onset of action. Higher doses of erenumab (>280 mg subcutaneously) have not been thoroughly analyzed in humans, preventing their use in an ITT analysis.[19] Participants received 4 injections of medication at randomization and 2 injections at week 4. A higher number of injections typically increases the placebo response, whereas a lower number reduces it.[27] The placebo response in our trial was similar to that in the galcanezumab CCH trial, indicating that our approach did not yield the desired effect.[11]

We opted for weeks 5 and 6 of the double-blind phase for primary end point determination mainly for 2 reasons. First, in the CCH study by Dodick et al,[11] the maximal numeric difference between galcanezumab and placebo was seen at weeks 1 and 2 and weeks 5 and 6. We deemed weeks 1 and 2 as too short to evaluate the efficacy of a medication in a chronic disease. Second, a double-blind study period of longer than 6 weeks would have exposed severely affected patients to a potential noneffective study medication.

Erenumab is a mostly peripherally acting CGRP receptor mAb.[28] It is unlikely that central nervous system (CNS) penetration is necessary to treat CH attacks based on multiple lines of evidence, including successful attack therapy with sumatriptan, which does not penetrate the blood-brain barrier.[29] However, a lack of CNS penetration may have contributed to the lack of efficacy in CCH prophylaxis. It is possible that CNS binding sites of the CGRP receptor family are relevant for CCH prophylaxis. Central sensitization in CCH may also contribute to the lack of effect of CGRP mAbs.[30]

The role of CGRP differs in migraine and CCH as evidenced by their differing responses to CGRP-targeted agents.[12,16] Intracellular mechanisms activated downstream of the CGRP receptor may explain the contrasting responses.[31] The CHERUB01 results do not match the favorable findings from clinical studies, nor do the results from the galcanezumab CCH trial.[11] For example, in a clinical study, 83% of patients with CCH had a 50% reduction in monthly attacks at month 3. Expectations in the clinical setting may drive this difference or the targeting of specific CCH subgroups.[13,14,32]

The evaluation of attack frequency alone may not adequately reflect the benefits of CCH prophylaxis. A reduction in attack duration or pain severity can provide benefit.[33] We did not find differences in attack duration or pain severity between the erenumab and placebo groups.

Strengths and Limitations

This trial has several strengths. The CHERUB01 population is typical for CCH and comparable to previous studies of the disease. All patients had previously shown an insufficient response to verapamil or lithium, suggesting our cohort had refractory symptoms. Baseline demographic and CH characteristics were closely aligned with participants in the 2 other trials involving CGRP mAbs in CCH, and the response to placebo was similar.[11,12] Participants in our trial without prophylaxis experienced a mean (SD) of 21.5 (9.7) CH attacks per week compared with approximately 19 attacks per week in a combined cohort of patients with (approximately 65%) and without (35%) prophylaxis in a previous trial with galcanezumab, suggesting that our cohort was similarly affected and not refractory.[11]

The clean trial design free of concomitant prophylactic medications allowed for a true evaluation of CGRP blockade effects without confounding factors.[34] The short double-blind trial duration of 6 weeks minimized exposure to study medication or placebo. The numeric reduction of attacks with galcanezumab in the CCH study did not differ between weeks 5 and 6 and week 12.[11] Therefore, extending the duration of the double-blind treatment phase in this study is unlikely to yield greater benefit. Another reason for selecting weeks 5 and 6 was the numeric difference in mean (SD) attack reduction at this time, which favored galcanezumab over placebo (−5.9 [0.9] vs −4.6

[0.9] attacks) in the CCH trial. This difference was not observed at later time points during the double-blind study period. The duration of the treatment period in this trial is also in line with the recommendations of Dodick et al[35] for preventive studies in CH. In neuromodulation studies using occipital nerve stimulation, there is a trend for patients to become responders over time.[5,36] However, trials involving devices are challenging to compare due to their open-label design.[5] Nonetheless, our data do not rule out the possibility of long-term benefits resulting from changes in neuroplasticity. However, open-label data from eptinezumab over 40 weeks do not show an increase in attack reduction over time.[15]

Despite not reaching the targeted sample size due to premature trial termination, the results of the CHERUB01 trial provide valuable insights. The study had to be terminated prematurely because we did not achieve the planned randomization of participants (n = 94). Monotherapy with study medication was a key limitation for recruitment. Randomization of the missing patients to the placebo (n = 7) and erenumab (n = 6) groups with a typical response would not have changed the results. Based on our result, there is no reason to believe we missed potential superresponders to erenumab due to premature termination of recruitment, which is supported by a hypothetical analysis we performed. This analysis showed that the nonrecruited patients in the erenumab group would have needed to achieve a mean reduction of 15.5 attacks per week to produce a positive group difference for the whole study. This required reduction is more than twice the actual mean attack change observed in erenumab-treated patients, demonstrating that enrolling more patients would not likely have resulted in a different study outcome.

This study has limitations. One limitation is the lack of data on the number of patients with primary CCH and those who progressed from a primary episodic form to the chronic form of the disease. To our knowledge, no such analysis has been performed previously in pharmacologic CCH prophylaxis studies. We cannot provide specifics on when the current CCH episode began, but it is evident from the diagnosis that it had been ongoing for over 12 months prior to study inclusion. Our patients had a diagnosis of CCH for more than 8 years on average. We did not record the response to steroids in the past. Furthermore, we cannot provide a detailed analysis of whether there was a lack of response to either of the 2 medications (verapamil or lithium) or any previous AE, as this inclusion criterion was based on patient judgment. It is common for patients to have difficulty recalling whether they experienced adverse outcomes with one or both medications. Therefore, we opted not to investigate the specific reasons for previous treatment failures.

The AE profile in this study with predominantly male participants aligns with the well-known AEs of erenumab in mostly female populations with migraine.[17,37,38] Despite the use of a 280-mg dose of erenumab, we did not see hypertension more frequently with erenumab than with placebo. Cardiac AEs and arrhythmia have been described previously in patients with migraine treated with an mAb, but the causality remains to be determined.[39]

Conclusions

In this randomized clinical trial, erenumab failed to show a benefit over placebo in patients with CCH, indicating that blockade of peripheral CGRP receptors has no beneficial role in the prophylaxis of CCH. To date, all double-blind controlled trials in CCH using an mAb affecting the CGRP pathway were negative, leading to the conclusion that future research should revisit the role of CGRP in CCH.

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SUPPLEMENT 1.
Trial Protocol and Statistical Analysis Plan

SUPPLEMENT 2.
eTable. Summary of Adverse Events in the Safety Analysis Population
eFigure. Illustration of 70%, 50%, and 30% Responder Rates at Weeks 5 and 6

SUPPLEMENT 3.
Nonauthor Collaborators

SUPPLEMENT 4.
Data Sharing Statement