Challenges and complexities in designing cluster headache prevention clinical trials: A narrative review

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[Correction added on 7th April 2022, after first online publication: The degree for Richard Wenzel was corrected.]

Abstract

Objective: To provide a review of challenges in clinical trials for the preventive treatment of cluster headache (CH) and highlight considerations for future studies.

Background: Current guidelines for preventive treatment of CH are largely based on off-label therapies supported by a limited number of small randomized controlled trials. Guidelines for clinical trial design for CH treatments from the International Headache Society were last issued in 1995.

Methods/Results: Randomized controlled clinical trials were identified in the European and/or United States clinical trial registries with a search term of “cluster headache,” and manually reviewed. Cumulatively, there were 27 unique placebo-controlled prevention trials for episodic and/or chronic CH, of which 12 were either ongoing, not yet recruiting, or the status was unknown. Of the remaining 15 trials, 5 were terminated early and 7 of the 10 completed trials enrolled fewer patients than planned or did not report the planned sample size. A systematic search of PubMed was also utilized to identify published manuscripts reporting results from placebo-controlled preventive trials of CH. This search yielded 16 publications, of which 7 were registered. Through critical review of trial data and published manuscripts, challenges and complexities encountered in clinical trials for the preventive treatment of CH were identified. For example, the excruciating pain associated with CH demands a suitably limited baseline duration, rapid treatment efficacy onset, and poses a specific issue regarding duration of investigational treatment period and length of exposure to placebo. In episodic CH, spontaneous remission as part of natural history, and the unpredictability and irregularity of cluster periods across patients present additional key challenges.

Conclusions: Optimal CH trial design should balance sound methodology to demonstrate efficacy of a potential treatment with patient needs and the natural history of the disease, including unique outcome measures and endpoint timings for chronic versus episodic CH.

Abbreviations: CCH, chronic cluster headache; CGRP, calcitonin gene-related peptide; CH, cluster headache; ECH, episodic cluster headache; IHS, International Headache Society; PACAP38, pituitary adenylate cyclase-activating peptide; RCT, randomized controlled trial; VIP, vasoactive intestinal peptide.

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INTRODUCTION

The 1-year cluster headache (CH) prevalence (53 per 100,000)1 is similar to other major disabling neurological disorders, such as multiple sclerosis (21 per 100,000)2 and Parkinson’s disease (106 per 100,000).2 Episodic cluster headache (ECH) is characterized by an average of 1 to 2 cluster periods per year with a mean cluster period duration of 4 to 9 weeks.3-10 A circannual periodicity is delineated by periods of remission5 ranging from 3 months up to a period of years (Figure 1).11,12 Chronic cluster headache (CCH) is characterized by active cluster cycles lasting anywhere between 1 and 10 years,8,11 with brief (<3 months) or no remission periods (Figure 1).11 While patients with CCH may not experience remissions, they may report a circannual pattern of lessening and worsening of attack frequency.5 Cluster headache has a substantial impact on quality of life with high levels of associated disability and frequent suicidal ideation.13-21 Considering both the debilitating clinical symptoms and the burden to quality of life, there remains a large unmet need for additional therapeutic options.

The excruciating pain and cranial autonomic symptoms, often occurring with a circadian and circannual rhythm, have been linked to activation of the trigeminovascular and cranial parasympathetic systems and the hypothalamus.12,22,23 This activation is associated with a release of neuuropeptides: calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), and pituitary adenylate cyclase-activating peptide (PACAP38).12,22,24,25 Intravenous infusion of CGRP,22 VIP,25 and PACAP3825 can induce CH attacks. Interestingly, the attack induction rate after CGRP infusion is lower in CCH patients (50%) compared to ECH patients (89%) suggesting there may be subtle pathophysiological differences between subtypes.22 Based on retrospective reports of attack frequency in the month prior to CGRP infusion, it was postulated that attack frequency in CCH may signal a susceptibility threshold to CGRP attacks, with higher attack frequency associated with increased susceptibility to CGRP provocation.22 However, the authors cautioned these data should be interpreted in light of the acknowledged limitations.22 Additional evidence suggesting subtle pathophysiological differences between patients with ECH and CCH include differences in response to the same treatment, as seen in examples from clinical trials to date with lithium26,27 (efficacious in CCH but not ECH) and galcanezumab28,29 (efficacious in ECH but not CCH) in preventive treatment, as well as non-invasive vagus nerve stimulation for acute treatment (efficacious in ECH but not CCH).30,31 However, some CH treatments, particularly acute treatments such as subcutaneous and intranasal triptans and oxygen are efficacious in both ECH and CCH,32-36 although some studies have reported differences in the magnitude of response.32,33,35

Treatments to interrupt cluster periods or reduce the frequency of attacks (i.e., preventive treatment) are generally based on recommendations from treatment guidelines.37,38 However, these guidelines are based on a small number of randomized controlled trials (RCTs) supplemented with data from uncontrolled trials.37,38 A lack of RCTs has resulted in a limited selection of medications approved for CH prevention, which has led to off-label prescription of agents with limited efficacy evidence.39 Table 1 lists a summary of current trial design recommendations in the International Headache Society (IHS) guidelines for controlled trials of preventive drugs in CH.40 Currently there are no CH preventive treatments approved by the European Medicines Agency; some locally approved preventive treatments vary by country and primarily include lithium and pizotifen. In the United States, only galcanezumab has been approved for the treatment of ECH.41

With this scenario in mind, we undertook this review to provide an overview of challenges and complexities encountered in clinical trials for the preventive treatment of CH and highlight considerations for future studies.

METHODS

Prevention trials for CH were identified via two methods: (1) a search of the European42 and/or US clinical trial registries43; and (2) a PubMed database search. As of September 2021, the search term “cluster headache” returned 27 unique results in the European clinical trial registry42 from which 13 randomized,
controlled prevention trials for ECH and/or CCH were identified with manual review (Table 2). In the US clinical trial registry,\(^{43}\) as of September 2021, a search for "cluster headache" returned 86 unique trials. A filter was then applied to restrict results to adults and older adults and to interventional trials, which yielded 66 results. An additional filter was applied for the status of recruitment (terminated, completed, recruiting, or not yet recruiting) in a sequential manner, and manual review was conducted to identify randomized, placebo-controlled prevention trials within each recruitment status category. Cumulatively there were 27 unique placebo-controlled prevention trials for ECH and/or CCH posted to the European\(^{42}\) and/or United States clinical trial registries\(^{43}\) of which 12 were either ongoing, not yet recruiting, or the status was unknown. Of the remaining 15 trials, 5 were terminated early and 7 of the 10 completed trials enrolled fewer patients than planned or did not report the planned sample size (Table 2).

To identify additional trials, a systematic review was performed via the PubMed database using the following search criteria: (cluster headache) AND ("1980/01/01"[Date – Publication]: "3000"[Date – Publication]) NOT review AND double blind). The search resulted in 114 potential publications. After manual review of all 114 publications (removing those that were not for CH [ECH

| Category                        | Recommendations                                                                                                                                                                                                 |
|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Patient selection               | • Diagnosis for enrollment should be made with strict adherence to the current IHS criteria  
• Patients with other headache types can be included if they can differentiate cluster headaches from other headaches  
• The expected duration of the cluster period must be longer than the expected time to onset of action of the drug and the pre-defined follow-up period for assessing efficacy |
| Blinding                        | • Trials should use a double-blind design                                                                                                                                                                           |
| Placebo control                 | • Placebo is recommended for comparative efficacy trials of a new drug  
  ◦ This helps control for spontaneous remission, assumed to occur at similar rates for both placebo and active drug |
| Crossover versus parallel       | • Parallel design recommended  
• Crossover designs have several drawbacks  
  ◦ Loss of blinding  
  ◦ High discontinuation rates due to headache recurrence during washout period  
  ◦ Prolonged study due to washout periods  
  ◦ Increased risk of spontaneous remission |
| Stratification                  | • Consideration should be given to stratifying patients by sex and CH type  
• For ECH, patients should be stratified by how long they have been in the current cluster period prior to randomization  
  ◦ Intended to avoid differences in cluster period duration between patients  
  ◦ Intended to create groups with similar rates of spontaneous remission |
| Randomization                   | • Rolling randomization, occurring in small blocks  
• To control for extended recruitment periods  
• To control for limited frequency of active cluster periods in ECH  
• Treatment order should be counterbalanced |
| Duration of treatment periods   | • Treatment duration in prophylaxis trials should be at least 2 weeks and should account for time to optimize the dose and the expected time for observable treatment effects to occur  
• Prolonged treatment periods should be avoided given the risk of spontaneous remission in ECH and, importantly, to avoid exposing patients to a lengthy treatment period with placebo or an ineffective preventive |
| Dosage                          | • Dosage in phase 3 studies should be based on efficacy and safety; ideally, derived from dose-finding studies  
• In absence of pharmacological background for efficacy, dosage should be determined by balancing efficacy and safety |
| Symptomatic treatment during prophylaxis trials | • In absence of a contraindication or interaction, patients should use usual treatment for acute attacks  
• Types of acute therapy should be constant for each patient |
| Control visits                  | • At minimum, patients should be seen monthly |
| Evaluation of results           | • Simple attack report forms to record data relevant to the main objectives of the trial should be used  
• Number of attacks should be recorded daily  
• Autonomic symptoms should be recorded at times of primary interest  
• Number of attacks that required acute treatment per week should be recorded  
• A global evaluation of therapy should be used to indicate patient satisfaction with the treatment (e.g., poor, moderate, good, excellent)  
• Primary efficacy criterion should be frequency of attacks per week |

Abbreviations: CH, cluster headache; ECH, episodic cluster headache; IHS, International Headache Society.

\(^{44}\)These highlights are specific to recommendations relevant to preventive treatment trials and do not include acute treatment trials. |
| Registry number | Timeline | Status | Treatment arms | Baseline (days) | Planned enrollment | Actual enrollment | Subtype | Primary endpoint met |
|----------------|----------|--------|----------------|----------------|-------------------|------------------|---------|---------------------|
| **Completed trials** | | | | | | | | |
| NCT00033839 | • January 2002–July 2003 | • Completed | Civamide Placebo | NR | 60 | 60 | ECH | NR |
| NCT00069082 | • August 2003–January 2004 | • Completed | Civamide Placebo | NR | 30 | 2 | ECH | NR |
| NCT00662935, Fontaine et al., 2010 | • May 2005–March 2008 | • Completed | Deep brain stimulation (on/off) Crossover | Prospective (7) | NR | 12 | Refractory CCH | No |
| NCT00804895, Leroux et al., 2011 | • December 2008–October 2009 | • Completed | Verapamil add-on: Cortivazol Placebo | Retrospective (3) | 44 | 43 | ECH/CCH | Yes |
| NCT02310828 | • December 2013–October 2020 | • Completed | Acetium Placebo | Yes, but not described | 100 | 60 | ECH/CCH | NR |
| EudraCT 2014–005429–11 NCT02438826, Dodick et al., 2020 | • June 2015–August 2019 | • Completed | Galcanezumab Placebo | Prospective (14–17) | 162 | 237 | CCH | No |
| NCT03397563 | • January 2018–August 2019 | • Completed | CPAP Sham CPAP | Prospective (28) | NR | 30 | CCH | NR |
| **Completed trials with halted recruitment** | | | | | | | | |
| EudraCT 2011–006204–13 Obemann et al., 2021 | • April 2013–January 2018 | • Completed | Verapamil add-on: Prednisone Placebo | Retrospective (3) | 144 | 118 | ECH | Yes |
| EudraCT 2015–000149–22 NCT02397473, Goadsby et al., 2019 | • May 2015–June 2018 | • Completed | Galcanezumab Placebo | Prospective (10–15) | 162 | 109 | ECH | Yes |
| EudraCT 2004–002737–39 NCT00184587, Tronvik et al., 2013 | • March 2005–December 2009 | • Completed | Candesartan Placebo | None | 64 | 40 | ECH | No |
| **Terminated trials** | | | | | | | | |
| EudraCT 2016–003278–42 NCT02945046 | • January 2017–May 2019 | • Terminated | Fremanezumab Placebo | Prospective (7) | 300 | 169 | ECH | No |
| Registry number | Timeline | Status | Treatment arms | Baseline (days) | Planned enrollment | Actual enrollment | Subtype | Primary endpoint met |
|-----------------|----------|--------|----------------|-----------------|--------------------|------------------|---------|---------------------|
| EudraCT 2016–003171-21 NCT02964338 | ● January 2017–July 2018 | ● Terminated<br>● Interim analysis demonstrated futility | Fremanezumab<br>Placebo | Prospective (≥4 weeks) | 300 | 259 | CCH | No |
| NCT00203190 | ● September 2004–June 2006 | ● Terminated<br>○ Reason unknown | Topiramate<br>Placebo | Yes; not described | 60 | NR | ECH/CCH | NR |
| EudraCT 2004–004999–36 Pageler et al., 2011 | ● August 2006–December 2007 | ● Terminated early<br>○ Slow recruitment<br>○ Protocol violations | Frovatriptan<br>Placebo | Prospective (4–7) | 80 | 11 | ECH | No |
| EudraCT 2012–003729–62 NCT02209155 | ● November 2013–March 2018 | ● Terminated<br>○ Poor recruitment | R-verapamil<br>Placebo | Prospective (7) | 30 | 1 | ECH | No |

**Ongoing trials**

| Registry number | Timeline | Status | Treatment arms | Baseline (days) | Planned enrollment | Actual enrollment | Subtype | Primary endpoint met |
|-----------------|----------|--------|----------------|-----------------|--------------------|------------------|---------|---------------------|
| EudraCT 2011–003513–41 | ● October 2011– | ● Recruiting | Verapamil add-on: Telmisartan<br>Placebo | NR | 48 | N/A | ECH/CCH | N/A |
| NCT02981173 | ● November 2016– | ● Recruiting | Psilocybin<br>Placebo<br>Crossover | Yes, but not described | 24 | N/A | ECH/CCH | N/A |
| NCT03781128 | ● January 2019– | ● Recruiting | LSD<br>Placebo<br>Crossover | Yes, but not described | 30 | N/A | ECH/CCH | N/A |
| EudraCT 2018–002224–17 NCT04014634 | ● August 2019– | ● Recruiting | GON<br>Methylprednisolone<br>Placebo | Retrospective (3) | 80 | N/A | ECH | N/A |
| EudraCT 2018–003148–21 NCT03944876 | ● November 2019– | ● Recruiting | Botulinum toxin type A to sphenopalatine ganglion<br>Placebo | Yes, but not described | 112 | N/A | Refractory CCH | N/A |
| EudraCT 2020–001969–37 NCT04688775 | ● December 2020– | ● Recruiting | Eptinezumab; Placebo | Prospective (3) | 304 | N/A | ECH | N/A |
| NCT04814381 | ● April 2021– | ● Recruiting | Ketamine + Magnesium sulfate<br>Placebo | Prospective (7) | 90 | N/A | CCH | N/A |

(Continues)
| Registry number       | Timeline                  | Status             | Treatment arms                                      | Baseline (days)    | Planned enrollment | Actual enrollment | Subtype   | Primary endpoint met |
|-----------------------|---------------------------|--------------------|----------------------------------------------------|--------------------|--------------------|-------------------|-----------|----------------------|
| EudraCT 2020– 004399–16 NCT04970355 | • April 2021-- | • Recruiting       | Erenumab Placebo                                   | Prospective (7–10) | 118                | N/A               | CCH       | N/A                  |
| NCT05023460           | • August 2021--           | • Not yet recruiting | Transcutaneous electrical nerve stimulation (TENS) Occipital nerve stimulation (ONS) Placebo | Prospective (1 month) | 40                 | N/A               | CCH       | N/A                  |

| Not recruiting or unknown |
|---------------------------|---------------------------|--------------------|----------------------------------------------------|--------------------|--------------------|-------------------|-----------|----------------------|
| NCT02637648               | • December 2015--         | • Unknown          | Sodium oxybate Placebo                              | Prospective, (NR)  | 60                 | N/A               | ECH/CCH  | N/A                  |
| NCT04570475               | • Estimated to begin recruiting May 2021 | • Not yet recruiting | Vitamin D Placebo                                   | Prospective (7)    | 220                | N/A               | ECH/CCH  | N/A                  |
| NCT01341548               | • Estimated to begin recruiting November 2023 | • Not yet recruiting | Civamide Placebo                                    | Prospective (3)    | 180                | N/A               | ECH       | N/A                  |

Abbreviations: CCH, chronic cluster headache; CPAP, continuous positive airway pressure; ECH, episodic cluster headache; EU, European Union; GON, great occipital nerve blockade; LSD, lysergic acid diethylamide; N/A, not applicable; NR, not reported; R, optically pure.

a Source links for randomized, controlled clinical trials: EudraCT, The EU Clinical Trials Register contains information on interventional clinical trials on medicines conducted in the EU, or the European Economic Area which started after 1 May 2004. ClinicalTrials.gov: With input from the Food and Drug Administration and others, the National Institutes of Health National Library of Medicine developed clinicaltrials.gov, and the first version was made publicly available on February 29, 2000.

b Candesartan cilexetil.

c Planned interim sample size re-estimation resulted in an increase in sample size.
| Study                                      | Treatment (N) and treatment duration                                                                 | Baseline (days unless otherwise indicated) | Primary efficacy endpoint (Met/Not met)                                                                 | Secondary efficacy outcomes                                                                 | Reasons for termination or for missing primary endpoint (where applicable) |
|--------------------------------------------|-----------------------------------------------------------------------------------------------------|-------------------------------------------|-------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| **ECH trials**                             |                                                                                                     |                                           |                                                                                                       |                                                                                            |                                                                                   |
| **Completed trials**                       |                                                                                                     |                                           |                                                                                                       |                                                                                            |                                                                                   |
| Leone et al., 2000                         | Verapamil 360 mg/day (15)                                                                             | Prospective (5)                          | Reduction in attack frequency in weeks 1 and 2 compared with baseline                                    | Number of abortive agents/days                                                                | Pilot study                                                                      |
|                                             | Placebo (15) Duration: 14 days                                                                         |                                           |                                                                                                       | 50% response rate                                                                            | Small sample size                                                                |
| Saper et al., 2002                         | Civamide 50 µg (25 µg per nostril) (18)                                                                | Retrospective (3)                        | CFB in weekly CH frequency across entire post-treatment period                                        | Weekly change in headache frequency                                                          | Other preventive treatments not permitted                                                                                        |
|                                             | Placebo (10) Duration: 7 days + 20-day post-treatment period                                          |                                           |                                                                                                       | Mean pain intensity                                                                         | Retrospective baseline (authors state they plan to use prospective baseline for future studies) |
| **Completed trials with halted recruitment**|                                                                                                     |                                           |                                                                                                       |                                                                                            |                                                                                   |
| Tronvik et al., 2013                       | Candesartan 16 mg 1st week, 32 mg 2nd and 3rd weeks (19)                                               | Week 1 treatment considered ‘pseudo-baseline’ | Change in attack frequency in week 3 compared to week 1                                              | Days and hours with CH                                                                       | Pseudo-baseline was selected in attempt to minimize risk of spontaneous remission |
| EudraCT                                    | Placebo (13) Duration: 3 weeks + 1-week follow-up                                                    |                                           |                                                                                                       | Attack duration                                                                             | Acute medications limited to subcutaneous sumatriptan and oxygen                     |
| NCT00184587                                |                                                                                                     |                                           |                                                                                                       | Oxygen or sumatriptan use                                                                    | Recruitment stopped after 5 years due to recruitment difficulty                     |
| Obermann et al., 2021                      | Verapamil + Prednisone (53)                                                                           | Retrospective (3)                        | Mean number of attacks within first week of treatment                                                | Number of attacks                                                                           | The a priori statistical method suggested to not be the appropriate test for the data |
| EudraCT                                    | Verapamil + Placebo (56)                                                                              |                                           | (Met)                                                                                                 | Number of days with attacks                                                                   |                                                                                   |
|                                             | Prednisone initiated at 100 mg/day x 5 days, then tapered                                           |                                           |                                                                                                       | Episode cessation                                                                           |                                                                                   |
|                                             | Verapamil initiated at 40 mg/TID x 3 days, then titrated up to 360 mg/day                             |                                           |                                                                                                       | Acute medication intake                                                                     |                                                                                   |
|                                             | Duration: 17 days + 11-day follow-up                                                                  |                                           |                                                                                                       | Responder rate (≥50% reduction in number of daily attacks)                                    |                                                                                   |
|                                             |                                                                                                     |                                           |                                                                                                       | Trigeminal autonomic symptoms                                                                |                                                                                   |
|                                             |                                                                                                     |                                           |                                                                                                       | Impact on quality of life (SF-12; HIT-6; ADS)                                                |                                                                                   |
|                                             |                                                                                                     |                                           |                                                                                                       | Mean pain intensity                                                                         |                                                                                   |
|                                             |                                                                                                     |                                           |                                                                                                       |                                                                                            |                                                                                   |

(Continues)
### TABLE 3 (Continued)

| Study                              | Treatment (N) and treatment duration                                      | Baseline (days unless otherwise indicated) | Primary efficacy endpoint (Met/Not met)                                                                 | Secondary efficacy outcomes                                                                 | Reasons for termination or for missing primary endpoint (where applicable) |
|------------------------------------|--------------------------------------------------------------------------|-------------------------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Goadsby et al., 201929            | • Galcanezumab 300 mg (49) • Placebo (57) • Duration: 56 days            | • Prospective (10–15)                     | • Overall mean CFB in weekly attack frequency across weeks 1–3 ◦ (Met)                                 | • Percentage of patients with ≥50% reduction in attack frequency at week 3                  | • Recruitment halted before planned sample size reached ◦ Lower than expected number of patients entering active cluster period during screening |
| EudraCT 2015–000149–22 NCT02397473 |                                                                          |                                           |                                                                                                        |                                                                                              |                                                                                  |
| Terminated trials                 |                                                                          |                                           |                                                                                                        |                                                                                              |                                                                                  |
| Steiner et al., 199727            | • Slow-release lithium carbonate 800 mg (13) • Placebo (14) • Duration: 7 days | • Retrospective (length not defined)       | • Percent of patients whose attacks ceased in the first week ◦ (Not met)                              | • Attack modification (reported as substantially better in 1 week)                          | • Terminated early due to futility ◦ Difficult recruitment (restrictive entry criteria) ◦ Acute treatment with sumatriptan use excluded ◦ Greater than expected placebo response ◦ Lithium dose titration not possible |
| Pageler et al., 201146            | • Frovatriptan 5 mg (5) • Placebo (6) • Duration: 14 days + 7-day follow-up | • Prospective (4–7)                      | • Reduction in mean attack frequency during 2-week treatment period ◦ (Not met)                       | • Mean attack frequency per week in week 1, week 2, and 1-week follow-up period ◦ Mean pain intensity ◦ Total attack duration ◦ Autonomic symptoms presence/absence ◦ Oxygen use frequency ◦ Additional drug treatment ◦ Quality of life (SF-36) ◦ Treatment satisfaction                             | • Terminated early (after 13 months) ◦ Excluded use of multiple classes of acute treatment ◦ Infeasibility (11 of 80 enrolled) ◦ Slow recruitment ◦ Major protocol violations |
| EudraCT 2004–004999–36            |                                                                          |                                           |                                                                                                        |                                                                                              |                                                                                  |
| Results only published on clinical trial registries | • R-verapamil • Placebo • Duration: 2 weeks                             | • Prospective (7)                        | • Change in average daily frequency of attacks during first 2 weeks of treatment ◦ (Not met)         | • Change in average daily frequency of attacks during first week ◦ Change in attack intensity ◦ Change in attack duration ◦ Change in consumption of abortive agents ◦ Patient treatment acceptability ◦ Change in headache severity index ◦ Change in HIT-6 disability score ◦ Number of responders | • Only 1 patient enrolled ◦ No results interpreted |
| EudraCT 2012–003729–62 NCT02209155 |                                                                          |                                           |                                                                                                        |                                                                                              |                                                                                  |
| Study | Treatment (N) and treatment duration | Baseline (days unless otherwise indicated) | Primary efficacy endpoint (Met/Not met) | Secondary efficacy outcomes | Reasons for termination or for missing primary endpoint (where applicable) |
|-------|-----------------------------------|------------------------------------------|---------------------------------------|-------------------------------|-------------------------------------------------------------------|
| Results only published on clinical trial registries | • Fremanezumab  
a. High dose (55)  
b. Low dose (55)  
• Placebo (59)  
• Duration: 4 weeks | • Prospective (7) | • Mean CFB in weekly average number of attacks during first 4 weeks  
◦ (Not met) | • Percentage of patients with ≥50% reduction from baseline in weekly average number of attacks  
• Mean CFB in weekly number of attacks  
• Mean CFB in weekly average number of days with cluster-specific acute headache medication  
◦ Triptans, ergot, or oxygen use  
• Number of patients with perceived improvement in pain | • Study terminated due to futility  
• Up to 2 other concomitant preventives permitted  
◦ If on stable dose at study onset/ remained on stable dose through double-blind period  
• Suggestion of improved efficacy in high dose group based on a post-hoc analysis of change in weekly attack frequency at 3 weeks |
| EudraCT  2016-003278-42 | NCT02945046 | | |
| CCH trials | Completed trials | |
| Evers et al., 1998 | • Misoprostol 600 µg  
• Placebo  
• Crossover design: 8 total patients  
• Duration: 2 weeks for each treatment period | • Prospective (2 weeks) | • Number of attacks during each 2-week period  
◦ (Not met) | • Duration of untreated attacks  
• Global impression of patient | |
| Fontaine et al., 2010 | NCT00662935 | • Unilateral hypothalamic deep brain stimulation  
• Sham stimulation  
• Crossover design: 11 total patients  
• Duration: 1-month for each treatment period | • Prospective (1 week) | • Number of attacks during the last week of each treatment period  
◦ (Not met) | • Subcutaneous sumatriptan administration during last week  
• Attack intensity  
• Patient satisfaction  
• HAD sub-scores  
• SF-12 scores  
• Changes in thirst, appetite, libido, sleep-wake cycles, and behavior | |
| Hakim SM, 2011 | NCT01831582 | • Warfarin 2 mg  
• Placebo  
• Crossover design: 34 patients total  
• Duration: 12-weeks for each treatment period (2-week washout) | • Prospective (6 weeks)(2-week washout; 4-week baseline) | • Occurrence of remission lasting ≥4 weeks  
◦ (Met) | • Status of CH  
• Impact on quality of life (HIT-6) | |
| (Continues) | | | | | |
### TABLE 3 (Continued)

| Study | Treatment (N) and treatment duration | Baseline (days unless otherwise indicated) | Primary efficacy endpoint (Met/Not met) | Secondary efficacy outcomes | Reasons for termination or for missing primary endpoint (where applicable) |
|-------|--------------------------------------|--------------------------------------------|----------------------------------------|----------------------------|---------------------------------------------------------------|
| Dodick et al., 2020<sup>28</sup> EudraCT 2014–005429-11 NCT02438826 | Galcanezumab 300 mg (117) Placebo (120) Duration: 12 weeks | Prospective (14–17) | Mean CFB in weekly attack frequency across weeks 1–12 (Not met) | Mean percentage of patients with ≥50% reduction from baseline in weekly attack frequency | Up to 6 other preventives permitted if stable dose 2 months prior to study and remained on treatment through double-blind period |
|       |                                      |                |                                       | Percentage of patients with a sustained response | |
| Completed trials with halted recruitment |                                      |                |                                       |                             | Mechanism of action may not be as effective in CCH compared to ECH |
|       |                                      |                |                                       |                             | Study length may not have been long enough to see an effect |
| Terminated trials |                                      |                |                                       |                             | |
| Results only published on clinical trial registries EudraCT 2016–003171-21 NCT02964338 | Fremanezumab, 675/225/225 mg (88) Fremanezumab, 900/225/225 mg (87) Placebo (84) Duration: 8 weeks | Prospective ≥4 weeks | Mean CFB in number of attacks up to week 12 (Not met) | Percentage of patients with ≥50% reduction in monthly attacks | Up to 2 other preventive medications permitted if on stable dose at start of and throughout study |
|       |                                      |                |                                       | Mean CFB in monthly average number of attacks | Futility assessment revealed primary endpoint unlikely to be met |
|       |                                      |                |                                       | Mean CFB in overall weekly average days with use of triptans or ergot compounds | |
|       |                                      |                |                                       | Mean CFB in weekly average days oxygen was used to treat CCH | |
|       |                                      |                |                                       | Number of participants with perceived improvement in CH-associated pain from baseline | |
| Mixed (ECH & CCH) trials |                                      |                |                                       |                             | |
| Completed trials |                                      |                |                                       |                             | |
| Monstad et al., 1995<sup>56</sup> | Sumatriptan 100 mg (89) Placebo (79) | Prospective (7) | 50% reduction from baseline in attack frequency (Not met) | 50% reduction in final 4 days of treatment week compared to final 4 days in baseline attack severity during treatment period | Not possible to individualize dose and interval of oral sumatriptan over 7-day treatment period |
| Leone et al., 1996<sup>54</sup> | Melatonin 10 mg (10) Placebo (10) Duration: 14 days | Prospective (7) | Within-group change in mean daily attack frequency (Met) Mean daily analgesic consumption (Not met) | Response rate | |
| Study                        | Treatment (N) and treatment duration                  | Baseline (days unless otherwise indicated) | Primary efficacy endpoint (Met/Not met)                                      | Secondary efficacy outcomes                                                                 | Reasons for termination or for missing primary endpoint (where applicable) |
|-----------------------------|------------------------------------------------------|-------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Ambrosini et al., 200552    | • Single suboccipital betamethasone (13)             | • Prospective (7)                         | • Disappearance of attacks within 72 hours for first week (sustained attack freedom) ◦ (Met) | • Disappearance of attacks within 72 hours for entire 4-week follow-up ◦ (Met)              | • Relapse timing among patients who were attack free for 4 weeks                   |
|                             | • Placebo (10)                                       |                                           |                                                                                |                                                                                            |                                                                                   |
|                             | • Duration: 4 weeks                                  |                                           |                                                                                |                                                                                            |                                                                                   |
|                             | • Prospective (7)                                    |                                           |                                                                                |                                                                                            |                                                                                   |
|                             | • Disappearance of attacks within 72 hours for entire 4-week follow-up ◦ (Met) |                                           |                                                                                |                                                                                            |                                                                                   |
|                             | • Prospective (7)                                    |                                           |                                                                                |                                                                                            |                                                                                   |
|                             | • Relapse timing among patients who were attack free for 4 weeks |                                           |                                                                                |                                                                                            |                                                                                   |
|                             | • Single suboccipital betamethasone (13)             | • Prospective (7)                         | • Disappearance of attacks within 72 hours for first week (sustained attack freedom) ◦ (Met) | • Disappearance of attacks within 72 hours for entire 4-week follow-up ◦ (Met)              | • Relapse timing among patients who were attack free for 4 weeks                   |
|                             | • Placebo (10)                                       |                                           |                                                                                |                                                                                            |                                                                                   |
|                             | • Duration: 4 weeks                                  |                                           |                                                                                |                                                                                            |                                                                                   |
|                             | • Prospective (7)                                    |                                           |                                                                                |                                                                                            |                                                                                   |
|                             | • Disappearance of attacks within 72 hours for entire 4-week follow-up ◦ (Met) |                                           |                                                                                |                                                                                            |                                                                                   |
|                             | • Prospective (7)                                    |                                           |                                                                                |                                                                                            |                                                                                   |
|                             | • Relapse timing among patients who were attack free for 4 weeks |                                           |                                                                                |                                                                                            |                                                                                   |
| Leroux et al., 201155       | • Suboccipital cortivazol (21)                       | • Retrospective (3)                       | • Reduction in mean attacks/day to ≤2 by 2-4 days after third injection ◦ (Met)  | • Number of attacks, day 1-15                                                          | • 50% attack frequency reduction at day 15                                          |
| NCT00804895                 | • Placebo (22)                                       |                                           |                                                                                |                                                                                            | • Remission rate at day 30                                                          |
|                             | • Add on to verapamil (ECH) or current preventive (CCH) |                                           |                                                                                |                                                                                            | • Delay to remission                                                                |
|                             | • Duration: 2 to 6 days (3 injections given 48-72 hours apart) |                                           |                                                                                |                                                                                            | • Percentage of patients with ≤2 attacks/day                                         |
| Completed trials with halted recruitment |                                           |                                           |                                                                                |                                                                                            |                                                                                   |
| El Amrani et al., 200253    | • Sodium valproate 1000–2000 mg/day (50)             | • Prospective (7)                         | • Percentage of patients with ≥50% reduction in weekly average number of attacks ◦ (Not met) | • >75% reduction in attack frequency ◦ Percentage of patients reporting much/very much improved ◦ Percentage of attack-free days ◦ Mean pain intensity ◦ Mean attack duration ◦ Acute medication use | • Enrollment stopped early ◦ Slow recruitment ◦ Recent preventive therapy use was exclusionary ◦ Placebo had similar (high) response rates ◦ No difference in secondary endpoints ◦ Spontaneous remission suspected ◦ Patients with ECH enrolled late in cluster period |
|                             | • Placebo (46)                                       |                                           |                                                                                |                                                                                            |                                                                                   |
|                             | • Duration: 2 weeks                                  |                                           |                                                                                |                                                                                            |                                                                                   |
|                             | • Prospective (7)                                    |                                           |                                                                                |                                                                                            |                                                                                   |
|                             | • Percentage of patients with ≥50% reduction in weekly average number of attacks ◦ (Not met) |                                           |                                                                                |                                                                                            |                                                                                   |
| Terminated trials           | No applicable results                                |                                           |                                                                                |                                                                                            |                                                                                   |

Abbreviations: ADS, Allgemeine Depressionsskala; CCH, chronic cluster headache; CFB, change from baseline; CH, cluster headache; ECH, episodic cluster headache; HAD, Hospital Anxiety and Depression Scale; HIT-6, Headache Impact Test 6; R, optically pure; SF-12, 12-Item Short Form Survey; SF-36, 36-Item Short Form Survey; TID, three times daily.

*Results could have been published in either an academic journal, EudraCT, or clinicaltrials.gov. Using the PubMed database, we included the search criteria (Cluster headache) AND (“1980/01/01”[Date - Publication]: “3000”[Date - Publication]) NOT review AND double blind). This resulted in 114 potential publications. After manual review of all 114 publications to confirm the publication, we removed any studies that were not for cluster headache (ECH or CCH), that were open label or were not true randomized controlled trials, or any study that did not assess preventive treatment as a primary efficacy outcome. If results were not published in an academic journal, but published results were found on EudraCT or clinicaltrials.gov, those results are also listed in the above table.*
or CCH or both ECH and CCH), that were open label or were not true RCTs, or any study that did not assess preventive treatment as a primary efficacy outcome) the search yielded 16 unique publications (7 ECH, 27,29,44–48 4 CCH, 28,49–51 and 5 mixed ECH/CCH 52–56) (Table 3). An additional 3 studies had results published online only on the clinical trial registries mentioned above (2 ECH and 1 CCH), resulting in 19 clinical trials with published results, which are presented in Table 3.

Challenges and complexities in the design of RCTs for prevention of attacks in cluster headache

Guidelines and recommendations

Guidelines for designing and conducting controlled clinical trials for CH treatment were last published in 1995 and modeled after the 1991 IHS guidelines for migraine (Table 1). In migraine treatment, guidelines for controlled trials have undergone more recent updates that reflect new developments in migraine treatment, including recommendations for the preventive treatment of episodic migraine or chronic migraine and recommendations for acute migraine therapy. A discussion of the challenges and complexities in the design of RCTs for prevention of attacks in CH follows. A summary of the authors’ considerations and suggestions to aid in alleviating these challenges and complexities is shown in Table 4.

Some of the major barriers encountered by RCTs for CH preventive treatments include slow recruitment and/or patient retention. The phenomenon of spontaneous remission in ECH poses a unique challenge in RCTs of preventive treatments. Once natural resolution of the cluster period begins, differentiating this effect from therapeutic intervention becomes increasingly difficult, if not impossible. Furthermore, between-treatment efficacy comparisons in RCTs are hindered by heterogeneity of primary outcome measures and the timing of endpoint measurements after randomization. While failure of a specific RCT may provide valuable information about a treatment or hypothesis, the failure of multiple RCTs to adequately test their hypotheses because of issues related to recruitment, retention, protocol deviations, or inadequate study design, becomes a barrier to drug development.

Cluster period characteristics in ECH

The episodic nature of attacks, spontaneous remission, variation in attack frequency, and typical cluster period duration 3,5,7,8,11,40 make CH (particularly the ECH subtype) challenging to study. These features also present key challenges for enrolling and retaining patients 27,29,45–48,52,53,60 and for assessing between-treatment group differences. Patients experience unpredictable, relatively brief, active periods separated by periods of remission 3–12; thus, there is a limited window of opportunity to study therapeutic interventions. Patients in remission must enter an active period before treatments can be studied, and initiation of the active treatment should begin as soon as reasonably possible after an active period begins. This clashes, however, with the need to obtain a proper prospective baseline period during which patients are often asked to refrain from taking preventive drugs. On one side, this can lead to the loss of patients during the run-in period, and on the other side, to the risk of spontaneous remission occurrence during the double-blind period, causing a convergence of attack frequencies for the placebo and active treatment groups. Thus, rapid evidence of treatment efficacy is extremely important, not only to patients but also to investigators, if a treatment effect is to be detected. For both ECH and CCH, between-patient heterogeneity in the number of attacks per day and number of weeks in an active cluster period may further complicate identifying meaningful between-treatment group differences in attack frequency, despite attempts to adjust for baseline. Additionally, some patients experience a more gradual increase and reduction of frequency and severity, which also presents challenges when assessing attack frequency. Current guidelines suggest measures to help control for interpatient variability and the impact of spontaneous remission, such as rolling randomization and stratification by length of the active cluster period prior to enrollment (Table 1), but lack of findings in past RCTs (Tables 2 and 3) suggest that it may still be difficult to successfully and fully control for variability even when implementing these measures.

Symptom severity

Given the excruciating pain experienced in CH attacks, 11 CH prevention trials should allow acute medications to treat the individual attack in order to be ethical to patients, to improve enrollment, and to minimize dropout (Table 1). Some older prevention trials have limited the number of acute treatment options (Table 3), and these restrictions appear to have had an impact on enrollment and patient retention. Extreme pain and failure of conventional treatments may also contribute to the use of non-approved drugs or experimental substances with limited data (e.g., lysergic acid diethylamide or psilocybin). Patients with CH usually seek treatment urgently at the beginning of a cluster period, starting a transitional and/or preventive therapy. As the use of other preventive therapies, non-approved drugs or substances with limited efficacy and/or safety data are often exclusion criteria in RCTs, patients may be unable or less likely to enroll in a clinical trial or they may be subsequently withdrawn due to major protocol deviations. For both ECH and CCH, it may be useful for clinical trial sites to engage patients in a thoughtful discussion (following informed consent) to explain the challenges presented to trials when these substances are used. If possible, sites may also consider obtaining an agreement (verbal or written) that participants...
**TABLE 4** Trial design considerations and suggestions for future studies on CH preventive-treatments

| Category                          | Considerations for RCT design                                                                 | Justification                                                                 |
|----------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| **Patient selection**            | • CCH                                                                                         | • CCH                                                                         |
|                                  |   ◦ Consideration of treatment history refractoriness should be made,                      |   ◦ To maximize probability of detecting a                                      |
|                                  |     similar to migraine treatment studies                                                   |     ◦ To enroll the desired patient population                                  |
|                                  |   ◦ Consideration should be given to limiting the percentage of patients                   |     ◦ CCH and ECH                                                              |
|                                  |     who are treatment refractory                                                              |     ◦ To help ensure study results are                                          |
|                                  |   ◦ Definition of refractoriness should be provided by experts to avoid                      |     applicable to the broader CH patient                                       |
|                                  |     exclusion of otherwise eligible patients                                                  |                                                 |
|                                  | • CCH and ECH                                                                                 |                                                 |
|                                  |   ◦ Enroll more diverse populations                                                         |                                                 |
| **Study site selection**         | • CCH and ECH                                                                                 | • CCH and ECH                                                                 |
|                                  |   ◦ Study site selection may be expanded to include, non-headache                          |   ◦ To maximize eligible sample of patients                                     |
|                                  |     centers, with verification of the CH diagnosis, using third party                       |   ◦ To increase patient awareness of trials                                    |
|                                  |     confirmation and electronic medical records                                              |                                                 |
|                                  |   ◦ Site eligibility should be based on number of active (e.g., seen within               |                                                 |
|                                  |     ≤2 years) patients with CH at that site                                                  |                                                 |
|                                  |   ◦ Clinicians and clinical trial sites should consider working in                         |                                                 |
|                                  |     conjunction with CH support and advocacy groups (e.g., Clusterbusters, OUCH UK,       |                                                 |
|                                  |     American Migraine Foundation) to                                                         |                                                 |
|                                  |     increase patient awareness and improve recruitment and enrollment                       |                                                 |
| **Incorporation of a baseline**  | • CCH and ECH                                                                                 | • CCH and ECH                                                                 |
| period**                         |   ◦ Limiting the length of the prospective baseline period to 5-7 days                      |   ◦ To avoid the onset of spontaneous                                          |
|                                  |   ◦ A plea should be made to well-organized CH support and advocacy                        |     remission, particularly in ECH, by                                         |
|                                  |     groups to ask patients, who are willing to enter clinical trials, to                   |     minimizing the overall length of                                         |
|                                  |     maintain a daily diary to facilitate drug development                                     |     prospective baseline and the treatment                                        |
|                                  |   ■ Such a plea may obviate the need for a lengthy prospective                             |     period                                                                 |
|                                  |     baseline by providing a reliable retrospective baseline                                   |   ◦ To maximize enrollment                                                     |
|                                  |   ◦ In the presence of a diary, a historical baseline plus a shorter                       |   ◦ To improve the effectiveness of patient                                     |
|                                  |     prospective baseline period may be acceptable                                            |     diaries and reliability of diary data                                        |
| **Placebo or other comparator**  | • CCH and ECH                                                                                 | • CCH and ECH                                                                 |
|                                  |   ◦ Allowance for effective acute treatments is a must in placebo-                         |   ◦ To minimize pain severity for patients                                      |
|                                  |     controlled trials                                                                        |     and improve patient retention                                              |
|                                  |   ◦ Limit exposure to potentially ineffective comparator (either placebo                    |   ◦ To ensure the treatment groups are                                         |
|                                  |     or standard-of-care) to the minimal time needed to assess efficacy                     |     balanced; maximize probability of                                         |
|                                  |   ◦ Permit patients who have had prior preventive treatment failures                      |     detecting a true treatment effect, if                                          |
|                                  |   ◦ Stratify treatment randomization by number of prior treatment                             |     one exists                                                                |
| **Primary efficacy**             | • CCH and ECH                                                                                 | • CCH and ECH                                                                 |
| outcome measure**               |   ◦ A standardized preferred efficacy outcome measure should be                         |   ◦ To ensure the outcome is relevant to                                         |
|                                  |     recommended, such as reduction of attacks over a period of weeks in                    |     clinicians and the CH population                                           |
|                                  |     association with persistence of the effect over longer periods                          |                                                 |
|                                  | • ECH                                                                                         | • CCH                                                                         |
|                                  |   ◦ A standardized preferred efficacy outcome measure should be                         |   ◦ To standardize clinical trials                                              |
|                                  |     recommended, such as early termination of an active cycle, or                         | • ECH                                                                         |
|                                  |     reduction in attack frequency                                                           |   ◦ To standardize clinical trials                                              |
|                                  |   ◦ Assessment of attack frequency (numerical reduction or proportion                     |   ◦ To maximize the probability of                                           |
|                                  |     of responders) should be ascertained early in the ECH episode,                         |     assessing the primary outcome prior to                                        |
|                                  |     preferably within 1 to 3 weeks of treatment, depending on the                        |     the onset of spontaneous remission                                           |
|                                  |     expected onset of action of the investigational treatment                             | • CCH and ECH                                                                  |
|                                  |   ◦ CCH and ECH                                                                               |   ◦ To ensure the outcome is relevant to                                         |
|                                  |   ◦ Outcomes MUST be biologically AND pragmatically appropriate                           |     clinicians and the CH population                                           |
|                                  |   ◦ Expert consensus on the optimal timing of assessments should be defined               |                                                 |
|                                  |   ◦ An expert consensus on a magnitude of reduction in attack                              |                                                 |
|                                  |     frequency indicating a clinically meaningful response needs to be                     |                                                 |
|                                  |     defined and incorporation of patient-reported improvement should be                   |                                                 |
|                                  |     considered                                                              |                                                 |

(Continues)
### TABLE 4 (Continued)

| Category | Considerations for RCT design | Justification |
|----------|--------------------------------|---------------|
| Secondary outcomes | • CCH  
  ○ Similar to primary outcomes, secondary outcomes for CCH should be assessed in a period of weeks as well as persistence of the effect over longer periods  
  ○ ECH  
  ○ We suggest optimal timing for outcome assessment for ECH is within 2–3 weeks of treatment onset  
  ○ CCH and ECH  
  ○ Expert consensus on the optimal timing of assessments should be defined  
  ○ We suggest patient and/or clinician perception of improvement as a key secondary outcome  
  ○ Other secondary outcome measures to be considered for both ECH and CCH, including:  
    ▪ Acute medication use  
    ▪ Limited assessments to acute treatments specific to CH (subcutaneous or intranasal triptans and oxygen) and measure within patient to reduce variability  
    ▪ Quality of life. Disability, sleep disruption outcomes may be considered but are limited by the lack of validation in the CH population  
  ○ Validated scales should be developed for these outcomes specific to patients with CH | • CCH  
  ○ Endpoints should be assessed at multiple timepoints, particularly for CCH, given the long duration of bouts, with minimal periods of remission  
  ○ ECH  
  ○ To maximize the probability of assessing the secondary outcomes prior to the onset of spontaneous remission  
  ○ CCH and ECH  
  ○ To standardize clinical trial measurements  
  ○ To emphasize the patient voice and provide data relevant to the CH condition |
| Concomitant preventive therapies | • CCH  
  ○ Concomitant preventive therapies should be considered, must be stable for study period, and should not include corticosteroids or interventional procedures (e.g., occipital or trigeminal nerve blocks)  
  ○ Randomization to treatment should be stratified by baseline concomitant preventive therapy.  
  ○ ECH  
  ○ Concomitant preventive therapies should not be permitted during the assessment of efficacy (primary and key secondary outcomes) | • CCH  
  ○ Given patients with CCH may experience partial relief from their current therapies, but still qualify for the study, allowance of concomitant therapies is ethical and will likely improve recruitment  
  ○ Given the established efficacy of corticosteroids, their use should be excluded during the assessment period for the primary and key secondary outcomes  
  ○ ECH  
  ○ To maximize the probability of detecting a true treatment effect of the investigational preventive treatment |
| Spontaneous remission | • CCH  
  ○ Understanding of patient history of spontaneous remission is important  
  ○ ECH  
  ○ Limit prospective baseline periods to minimal duration as noted above  
  ○ Limit length of efficacy assessments to minimal time needed based on the expected onset of action for the investigative treatment  
  ○ Enroll patients with consistent ECH episode duration that is of sufficient length to exceed the key efficacy endpoints and that have good response to the allowed acute CH treatments | • CCH  
  ○ To minimize potential of spontaneous remission (although it is much less common for patients with CCH)  
  ○ ECH  
  ○ To minimize potential of spontaneous remission during assessment of the primary and key secondary outcomes  
  ○ To minimize time spent for patients exposed to placebo or an ineffective treatment  
  ○ To maximize the number of enrolled patients who will experience an active bout during the clinical trial period |
will not use these types of excluded substances, which may not be detectable in a urine drug screen. If a sponsor or investigator feels compelled to allow these substances, consideration should be given to the suggestions outlined in Table 4 for concomitant preventive therapies.

The appropriate comparator for a new investigational treatment in an RCT may be placebo, standard-of-care, or both. However, patients who get rapid preventive effects from another therapy are not likely to be the target patient for RCTs; patients who historically do not have a reliable or rapid onset preventive treatment option are the patients of most interest in RCTs evaluating a new investigational preventive therapy. Consideration should be given to the number of allowed preventive treatment failures and/or stratification by the number of prior treatment failures. For RCTs in CCH, consideration should also be given to the allowable percentage of patients who may be treatment refractory.\(^70\) As long as acute treatments are permitted, placebo-controlled trials are possible and remain necessary to characterize the drug effect and control for spontaneous remission. Evaluation of a newer preventive treatment compared to an older standard preventive treatment can also provide useful information. In all RCTs, regardless of whether placebo or standard-of-care is chosen as the comparator, it is essential to ensure limited exposure to a potentially ineffective treatment to the minimal time needed to assess efficacy of the new investigational preventive therapy. Just as the severe pain of CH may limit enrollment and retention in RCTs, a lengthy prospective baseline period only adds to the patient burden.

Some trials have allowed concomitant preventive therapies (primarily CCH and mixed ECH/CCH studies), the most successful of which include oral or injectable steroids that were included as add-ons to concurrent preventive or verapamil.\(^49,52,55\) Other trials permitting the use of non-steroid concomitant preventive treatments have failed to meet their primary endpoint.\(^28,49,50,60\) Whether the concomitant preventive treatment contributed to the failure of these studies to meet their primary endpoint is difficult to ascertain.

Other potential reasons for failure, such as treatment duration, dosage or dosing frequency, or incorrect method of administration, are equally plausible.\(^28,49,50,60\)

For CCH, we believe concomitant preventive therapies should not be considered in an RCT; this is possible with an appropriate trial design that allows acute treatments and limits time on placebo. For CCH, concomitant preventives should be allowed, provided patients have been on a stable dose prior to enrollment and the dose is maintained for the double-blind study period. Corticosteroids or interventional procedures (e.g., occipital or trigeminal nerve blocks) should not be allowed.

### Study site selection

Guidelines recommend conducting studies at multiple centers to increase the population size and ensure the study is appropriately powered.\(^30\) Using headache centers as study sites, with headache specialists on staff, ensures study quality and appropriate patient selection.\(^27–29,45–47,50,52,54,55\) However, exclusively using headache centers may limit the number of eligible patients and challenge feasibility of completing the trial. If non-headache centers were included, verification of the CH diagnosis (and any other comorbid headache conditions) may be accomplished by implementing third-party confirmation with a headache specialist. Electronic medical records may make it easier to utilize non-headache centers, as they aid in quickly and accurately identifying patients with a documented diagnosis of CH (assuming records have been coded correctly). Therefore, site eligibility should be based on the number of active patients with CH at that site (e.g., seen within ≤2 years), preferably after outreach to patients to determine interest in a clinical trial. This method is currently utilized in many headache clinics. Furthermore, if clinicians work in conjunction with CH support and advocacy groups (e.g., Clusterbusters, OUCH UK, American Migraine Foundation), there is a possibility of increasing patient awareness of available clinical trials and improving recruitment and enrollment, particularly if organized and/or co-chaired by CH support groups or patient advocacy organizations.
Incorporation of a baseline period

As shown in Tables 2 and 3, the efficacy of CH preventive treatments in RCTs is often determined by comparing the change in attack frequency from baseline (prospective or retrospective) for each treatment group. Currently, clinical trial results have not demonstrated a clear advantage between prospective or retrospective baseline periods, nor is there an expert consensus on optimal trial design. Many RCTs use a prospective baseline period; however, this can limit patient enrollment and retention if too lengthy due to not having access to the investigational treatment during the prospective baseline. Prior to bout stabilization, some patients experience an escalation in attack frequency and severity, which may complicate assessing a prospective baseline period; any prospective baseline period should not begin until the typical cluster cycle has started. In response to recommendations against using a prospective baseline, one placebo-controlled study utilized a pseudo-baseline design where baseline was defined as the first week of active treatment (see Tronvik et al.48 listing in Table 3). However, this study failed to meet its primary endpoint due to the absence of a significant difference between active and placebo groups when attack frequency during week 3 of treatment was compared to the pseudo-baseline period.48

Another option is a retrospective baseline, for which some may advocate. However, few patients with CH maintain a diary outside of a clinical study; therefore, documentation of daily-attack frequency is often based on a patient’s historical recall. Nevertheless, in clinical experience, patients with CH are remarkably accurate when it comes to frequency and duration of attacks. To improve the use of retrospective baseline periods, we believe a plea could be made to well-organized CH support and advocacy groups to ask patients who are interested in participating in clinical trials, to maintain a diary to facilitate drug development for the treatment of CH and obviate the need for a prospective baseline. In the presence of a diary, a historical baseline plus an ultra-short prospective baseline of 2–3 days, to document the patient’s retrospective estimate is accurate, should be acceptable.

Primary efficacy outcome

To be worthy of consideration, efficacy outcomes in preventive treatment RCTs for CH should theoretically be both biologically and pragmatically appropriate. Although prevention of a CH cycle is the ideal outcome, demonstrating prevention in an RCT is difficult given the current lack of a reliable biomarker and can likely be detected only in a clinical practice setting. Thus, for ECH, early termination of a cycle (within days) followed by suppression or reduced frequency of attacks are the preferred outcomes of preventive therapy. For CCH, reduction in frequency is a more appropriate endpoint. Indeed, reduction in CH attack frequency has been used as the primary outcome in the majority of the placebo-controlled RCTs for both ECH and CCH (Table 3). Although clinical experience suggests any reduction in attack frequency represents a positive outcome, defining the magnitude of reduction indicative of a clinically meaningful response remains to be determined (either by specific methods, such as an anchor-based approach or by expert consensus). By default, many studies have used a 50% response in both ECH and CCH (Table 3), and 30%, 75%, and 100% responses may be useful secondary endpoints to explore. Documenting CH frequency is another challenge, which can be facilitated by patient diaries. For diaries to be useful, patients must maintain a high level of diary-entry compliance. This should be feasible with electronic diaries, particularly if outcomes are measured early (at 2 or 3 weeks). Real-time data entry allows attack frequency and compliance to be more easily monitored. A daily diary is also beneficial for collecting other headache features that may be useful secondary outcomes, such as cranial autonomic symptoms, sleep disruption, and acute medication use. Each of these outcomes faces the same key challenge: outcome measurement is extremely difficult if there is not a high level of diary-entry compliance. The adoption of diaries with automatic reminders or reminders activated by missed data entry represent a potential strategy for improving data completeness.

Determining the appropriate timing to assess attack frequency relative to baseline is another challenging facet of this outcome. The timing of endpoints relating to attack frequency is important for both ECH and CCH but can be particularly difficult to determine in ECH trials because assessments must occur prior to the natural onset of spontaneous remission. Thus, observations over a prolonged period are problematic for ECH trials. Primary endpoint assessment timing in past clinical trials has included a range of time points including days, 1 week, 2 weeks, 3 weeks, 4 weeks, and up to 12 weeks. Enrollment criteria that take into account the current length of time in an active cluster period and the expected timing of spontaneous remission based on previous cluster periods may be helpful for optimizing assessment of efficacy endpoints.

We suggest a primary efficacy outcome of active cluster period termination or reduced attack frequency for ECH. This outcome should be evaluated within 2 to 3 weeks of treatment. Rapid onset of treatment effect is essential for ECH. Thus, we believe this timing would be a compromise between allowing some time for an intervention to be effective but not so long that the utility and value of a treatment for patients with ECH is called into question. Slightly different outcomes will likely be needed in the case of CCH. We suggest a reduction of attacks over a period of weeks in association with the persistence of the effect over longer periods.

Secondary outcomes

Secondary efficacy outcomes in CH prevention trials include patient or clinician perception of improvement, pain severity and/or duration, acute treatment use, the proportion of patients considered responders (e.g., ≥50% reduction in attack frequency), and remission (Table 3). While patient or clinician perception of improvement (e.g.,
Patient Global Impression of Improvement) are widely accepted as useful outcomes, there is no consensus on the optimal timing or frequency of patient/clinician perception; we would suggest the same timepoint as the primary efficacy parameter, within 2 to 3 weeks of treatment onset. Assessing improvements in pain severity or duration is complicated by the necessity of allowing acute treatments that might reduce pain severity and attack duration, a factor that clearly complicates accurately measuring this outcome in prevention trials. The restricted 5-point (0–4) scale, commonly used to assess pain severity in CH RCTs, makes it difficult to interpret average reductions from the standpoint of being clinically meaningful. Endpoints related to changes in acute medication use have the potential to be unreliable because of between-patient heterogeneity in attack frequency; however, if assessed within patients, this concern may be alleviated. The reliability of the measures seems higher intra-individually, as CH patients seem to be able to perceive clearly and report when an acute medication is more or less effective on their attacks in routine practice. However, it must be noted that patients with CH often use a variety of acute treatments for pain relief including treatments which may treat a less intense headache (e.g., non-steroidal anti-inflammatory drugs). Targeting medications or treatments used specifically for acute CH treatment, such as subcutaneous or intranasal triptans or oxygen, may provide a better picture of treatment efficacy. If not the designated primary outcome, response rates are an important secondary outcome, and as discussed in the primary outcome section, more than one response rate may be considered. There is no expert consensus on a standard definition for remission, but we would suggest a 7-day period free of cluster attacks.

Sleep disruption, quality of life, and psychological/psychosocial outcomes are also assessed as secondary outcomes and are appropriate given the high disease burden (Table 3). Challenges inherent in these outcomes include the scarcity of validated scales for CH (unlike migraine); however, there has been at least one quality of life scale developed and validated specific to patients with CH. Secondary outcome measures for CCH will likely be the same as those for patients with ECH.

Placebo response

The placebo response in CH trials can be considerable; one review article reports rates of 14% and 43% from two preventive studies. A substantial response in the placebo group was observed in the clinical trials reported herein (Table 3); however, as previously noted, the improvement in the placebo group in CH trials was likely due to spontaneous remission and placebo effect. Challenges raised in this paper, including lengthy prospective baseline and treatment periods, increase the risk of spontaneous remission. Thus, minimal duration baseline periods or novel trial designs that allow elimination of baseline periods and enrich the patient population most likely to respond to treatment (e.g., patients with good disease control with acute treatments or patients with consistent duration of CH cycles of at least 6 weeks, etc.) are needed to help reduce placebo response.

Statistical considerations

When making suggestions for designing and conducting RCTs in CH, statistical considerations are also important. In the measurement of some outcomes, low diary compliance or non-completers may contribute to a smaller sample size than intended. Thus, statistical methods to assess efficacy should be selected based on the ability to accommodate missing data while still achieving an accurate estimate. For example, a mixed model with repeated measures could be used to assess longitudinal data, such as reduction in weekly attack frequency (generally treated as continuous in the literature although attack counts themselves are natural numbers), from baseline to each weekly interval post baseline. Alternatively, a missing data imputation method could be used, such as the mean change from baseline to last observation carried forward, in which case the treatment effect can be estimated using an analysis of covariance model. Reporting reduction in attack counts as a percentage of patients meeting a defined response threshold (≥x%) can be estimated for each treatment using a categorical, pseudo-likelihood-based repeated measures analysis of longitudinal binary outcomes. As mentioned above, the ≥x% response threshold should be defined based on a clinically meaningful reduction in attack frequency. Accounting for various confounding factors is also critically important. Examples of variables to be considered as potential confounders include sex, baseline attack frequency, length of current bout, history of treatment responsiveness, and concomitant medication use.

CONCLUSIONS

This report highlights challenges and potential considerations for RCTs in the preventive treatment of CH. One simple, yet vitally important suggestion, is to ensure all results are published, regardless of study outcomes. This will help ensure forward movement in identifying and improving preventive treatments for CH. Many RCTs in CH are terminated for futility, suggesting there is ample room to improve the design and conduct of RCTs involving patients with CH. Many questions remain, particularly regarding the selection and timing of outcomes. Optimal RCT design should be driven by both patient needs and by the natural history of the disease. Analysis of the literature and expert consensus suggest that outcome measures and the endpoint timings might need to be different for ECH and CCH. For ECH, prevention of the active period is the strongest outcome measure for trials evaluating the efficacy of preventive treatment; however, this is almost impossible to verify due to the lack of reliable prodromal biomarkers or prediction tools. This leaves us with the second-best option, termination of the active period within a given period of time in the range of days. An alternative option is represented by the reduction in weekly attacks, which must be ascertained early (within the first- or second-week posttreatment onset) to avoid the possibility of patients entering spontaneous remission periods. Multiple secondary outcome measures should be captured including the use of acute medications specific for CH...
and their efficacy, quality of life, patient satisfaction, and disability. In the case of CCH, the most appropriate outcome measure is represented by the reduction of attacks over a period of weeks in association with the persistence of the effect over longer periods. Secondary outcome measures will likely be the same as those for patients with ECH.

Equally important are considerations regarding patient selection and trial design. For both CCH and ECH, study sponsors, investigators, and coordinators should strive to enroll diverse patient populations. This will help ensure the study results are applicable to the broader CH population. For ECH, trial design is difficult due to the episodic nature of active clusters, punctuated by spontaneous remission periods and accompanied by the extreme pain severity experienced repeatedly during an active cluster period. This requires the allowance of adequate acute treatments specific for CH (kept stable from pre-enrollment to treatment period, within-patient) for relief during clinical trials and either limiting or forgoing completely medication-free prospective baseline periods. For CCH, consideration of treatment history refractoriness (as has been applied to some migraine treatment studies) may be beneficial, but the definition of refractory would need to be clearly made to avoid exclusion of otherwise eligible participants. The observations outlined in this review based on recent successes and difficulties of clinical trials of preventive treatments for ECH and CCH may be useful considerations for the design of future clinical trials.

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DWD reports the following conflicts within the past 12 months: Consulting: Amgen, Atria, Cerecin, Cooltech, Ctrl M, Allergan, Biohaven, GSK, Lundbeck, Eli Lilly, Novartis, Impel, Satsuma, Theranica, WL Gore, Genentech, Nocira, Perfood, Praxis, AYYA Biosciences, Revance. Honoraria: Vector psychometric Group, Clinical Care Solutions, CME Outfitters, Curry Rockefeller Group, DeepBench, Global Access Meetings, KLJ Associates, Academy for Continued Healthcare Learning, Majallin LLC, Medlogix Communications, MJH Lifesciences, Miller Medical Communications, WebMD Health/Medscape, Wolters Kluwer, Oxford University Press, Cambridge University Press. Research Support: Department of Defense, National Institutes of Health, Henry Jackson Foundation, Sperling Foundation, American Migraine Foundation, Patient Centered Outcomes Research Institute (PCORI). Stock Options/Shareholder/Patents/Board of Directors: Ctrl M (options), Aural analytics (options), ExSano (options), Palion (options), Healint (Options), TheraNica (Options), Second Opinion/Mobile Health (Options), Epfen (Options/Board), Necora (options), Matterhorn (Shares/Board), Ontologics (Shares/Board), King-Devick Technologies (Options/Board), Precon Health (Options/Board), AYYA Biosciences (Options), Atria Health. Patent 17189376.1-1466:vTitle: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis. PJG reports the following conflicts: Grants: Celgene. Grants and personal fees: Eli Lilly and Company, electroCore, and Atria. Personal fees: Lundbeck, Aeon Biopharma, Allergan/Abbvie, Biohaven Pharmaceuticals, Epalex Corporation, GlaxoSmithKline, Impel NeuroPharma, Inc, Novartis, Pfizer, Praxis, Santanta Therapeutics Biotechnology, Sanofi, Satsuma Pharmaceuticals, Inc, Teva Pharmaceutical Industries Ltd, and Dr Reddy’s Laboratories. Owning stock options and consulting: Trigemina, Inc. In addition, PJG has a patent Magnetic stimulation for headache licensed to eNeura without fee; fees for advice through Gerson Lehrman Group and Guidepoint; fees for educational materials from Medergy, Medlink, PrimeEd, UptoDate, WebMD; and fees for publishing from Oxford University Press, Massachusetts Medical Society, and Wolters Kluwer. MA is a consultant, speaker, or scientific advisor for AbbVie, Allergan, Amgen, Alder, Eli Lilly and Company, Lundbeck, Novartis, and Teva; a primary investigator for AbbVie, Amgen, Eli Lilly and Company, Lundbeck, Novartis, and Teva trials. MA reports no ownership interest and does not own stocks of any pharmaceutical company. CT reports the following potential conflicts of interest: Scientific Consulting: Allergan/AbbVie, Eli Lilly and Company, Novartis, Teva, and Lundbeck. Honoraria for Scientific Presentations: Allergan/AbbVie, Eli Lilly and Company, Novartis, Teva, Lundbeck, and WebMD Health/Medscape. Research Support: Italian Ministry of Health, Migraine Research Foundation, European Commission. TO, H-PH, JNB, RW, PK, RC, and JMM are all employees and shareholders at Eli Lilly and Company.

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