REVIEW ARTICLE

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.

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 remission[5] 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 neuropeptides: 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 PACAP38[25] 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 lithium[26,27] (efficacious in CCH but not ECH) and galcanezumab[28,29] (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 European[42] and/or US clinical trial registries[43]; and (2) a PubMed database search. As of September 2021, the search term "cluster headache" returned 27 unique results in the European clinical trial registry[42] from which 13 randomized,
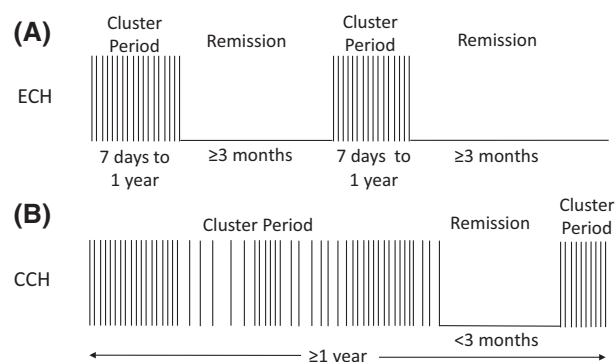

FIGURE 1 Depiction of the International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria from the International Headache Society for episodic cluster headache (ECH) and chronic cluster headache (CCH). (A) According to ICHD-3 criteria, ECH is defined as at least 2 cluster periods with a duration of 7 days to 1 year per period, with a remission period of at least 3 months between cluster periods. (B) According to the ICHD-3 criteria, CCH is defined as attacks occurring for at least a year, with no remission period or remission periods less than 3 months

TABLE 1 Summary of trial design recommendations in the International Headache Society guidelines for controlled trials of preventive[a] drugs in cluster headache[40]

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.

[a]These highlights are specific to recommendations relevant to preventive treatment trials and do not include acute treatment trials.

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

TABLE 2 List of registered, randomized, placebo-controlled clinical trials[a] for the preventive treatment of cluster headache

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[50]	• May 2005–March 2008	• Completed	Deep brain stimulation (on/off) Crossover	Prospective (7)	NR	12	Refractory CCH	No
NCT00804895 Leroux et al., 2011[55]	• 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[28]	• June 2015–August 2019	• Completed	Galcanezumab Placebo	Prospective (14–17)	162	237[c]	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 Obermann et al., 2021[45]	• April 2013–January 2018	• Completed • Recruitment halted after 5 years	Verapamil add-on: Prednisone Placebo	Retrospective (3)	144	118	ECH	Yes
EudraCT 2015–000149–22 NCT02397473 Goadsby et al., 2019[29]	• May 2015–June 2018	• Completed • Recruitment halted after 3 years	Galcanezumab Placebo	Prospective (10–15)	162	109	ECH	Yes
EudraCT 2004–002737–39 NCT00184587 Tronvik et al., 2013[48]	• March 2005–December 2009	• Completed • Recruitment halted after 5 years	Candesartan[b] Placebo	None	64	40	ECH	No
Terminated trials								
EudraCT 2016–003278–42 NCT02945046	• January 2017–May 2019	• Terminated • Interim analysis demonstrated futility	Fremanezumab Placebo	Prospective (7)	300	169	ECH	No

TABLE 2 (Continued)

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 • Interim analysis demonstrated futility	Fremanezumab Placebo	Prospective (≥4 weeks)	300	259	CCH	No
NCT00203190	• September 2004-June 2006	• Terminated ○ Reason unknown	Topiramate Placebo	Yes; not described	60	NR	ECH/CCH	NR
EudraCT 2004-004999-36 Pageler et al., 2011[46]	• August 2006-December 2007	• Terminated early ○ Slow recruitment ○ Protocol violations	Frovatriptan Placebo	Prospective (4-7)	80	11	ECH	No
EudraCT 2012-003729-62 NCT02209155	• November 2013-March 2018	• Terminated ○ Poor recruitment	R-verapamil Placebo	Prospective (7)	30	1	ECH	No
Ongoing trials								
EudraCT 2011-003513-41	• October 2011-	• Recruiting	Verapamil add-on: Telmisartan Placebo	NR	48	N/A	ECH/CCH	N/A
NCT02981173	• November 2016-	• Recruiting	Psilocybin Placebo Crossover	Yes, but not described	24	N/A	ECH/CCH	N/A
NCT03781128	• January 2019-	• Recruiting	LSD Placebo Crossover	Yes, but not described	30	N/A	ECH/CCH	N/A
EudraCT 2018-002224-17 NCT04014634	• August 2019-	• Recruiting	GON Methylprednisolone Placebo	Retrospective (3)	80	N/A	ECH	N/A
EudraCT 2018-003148-21 NCT03944876	• November 2019-	• Recruiting	Botulinum toxin type A to sphenopalatine ganglion 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 Placebo	Prospective (7)	90	N/A	CCH	N/A

(Continues)

TABLE 2 (Continued)

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.

TABLE 3 Randomized, placebo-controlled clinical trials published[a] results

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[44]	• Verapamil 360 mg/day (15) • Placebo (15)Duration: 14 days	• Prospective (5)	• Reduction in attack frequency in weeks 1 and 2 compared with baseline ○ (Met)	• Number of abortive agents/days • 50% response rate • Effect size	
Saper et al., 2002[47]	• Civamide 50 μg (25 μg per nostril) (18) • Placebo (10) • Duration: 7 days + 20-day post-treatment period	• Retrospective (3)	• CFB in weekly CH frequency across entire post-treatment period • (Not met over entire post-treatment period; did detect a significant difference in first 7 days post-treatment)	• Weekly change in headache frequency • Mean pain intensity • Presence/absence of associated symptoms • Abortive therapy uses	• Pilot study • Small sample size • Other preventive treatments not permitted • Retrospective baseline (authors state they plan to use prospective baseline for future studies)
Completed trials with halted recruitment					
Tronvik et al., 2013[48] EudraCT 2004–002737–39 NCT00184587	• Candesartan 16 mg 1st week, 32 mg 2nd and 3rd weeks (19) • Placebo (13) • Duration: 3 weeks + 1-week follow-up	• Week 1 treatment considered 'pseudo-baseline'	• Change in attack frequency in week 3 compared to week 1 ○ (Not met)	• Days and hours with CH • Attack duration • Oxygen or sumatriptan use • Treatment satisfaction • Analgesics use • Disability level • Headache severity index • Autonomic symptoms • Responder rate	• Pseudo-baseline was selected in attempt to minimize risk of spontaneous remission • Acute medications limited to subcutaneous sumatriptan and oxygen • Recruitment stopped after 5 years due to recruitment difficulty • The a priori statistical method suggested to not be the appropriate test for the data
Obermann et al., 2021[45] EudraCT 2011–006204–13	• Verapamil + Prednisone (53) • Verapamil + Placebo (56) • Prednisone initiated at 100 mg/day x 5 days, then tapered • Verapamil initiated at 40 mg/TID x 3 days, then titrated up to 360 mg/day • Duration: 17 days + 11-day follow-up	• Retrospective (3)	• Mean number of attacks within first week of treatment ○ (Met)	• Number of attacks • Number of days with attacks • Episode cessation • Acute medication intake • 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	• Recruitment halted before planned sample size reached due to recruitment difficulties • Secondary endpoints related to attack frequency, acute medication use, pain intensity significantly better in prednisone versus placebo group at day 7 ○ Improvement continued, but difference attenuated over time ○ Attenuation primarily attributed to verapamil efficacy ○ Spontaneous remission may have contributed to attenuation • No significant between-treatment differences in autonomic symptoms or quality of life measures (except HIT-6 at Day 28)

(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., 2019[29] EudraCT 2015-000149-22 NCT02397473	• 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
Terminated trials					
Steiner et al., 1997[27]	• 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., 2011[46] EudraCT 2004-004999-36	• 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
Results only published on clinical trial registries EudraCT 2012-003729-62 NCT02209155	• 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

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)
Results only published on clinical trial registries EudraCT 2016–003278–42 NCT02945046	• 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 　o (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 　o 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 　o 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
CCH trials **Completed trials**					
Evers et al., 1998[49]	• 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 　o (Not met)	• Duration of untreated attacks • Global impression of patient	• All types of acute symptomatic therapy permitted • Other preventive treatments patients were taking prior to enrollment were permitted simultaneous to treatment • No misoprostol effect seen • Authors concluded targeted mechanism of action was not involved in CCH
Fontaine et al., 2010[50] 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 　o (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	• Use of other preventive treatments permitted • Small sample size • Active stimulation period possibly too short • Randomized phase possibly conducted using non-optimal parameters • Open phase findings suggest long-term efficacy in ≥50% of patients
Hakim SM, 2011[51]	• 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 　o (Met)	• Status of CH • Impact on quality of life (HIT-6)	

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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[28] 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 • Percentage of patients with a sustained response	• Up to 6 other preventives permitted if stable dose 2 months prior to study and remained on treatment through double-blind period • 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
Completed trials with halted recruitment					
No applicable results					
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 • Mean CFB in monthly average number of attacks • 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	• Up to 2 other preventive medications permitted if on stable dose at start of and throughout study • Futility assessment revealed primary endpoint unlikely to be met
Mixed (ECH & CCH) trials					
Completed trials					
Monstad et al., 1995[56]	• 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 baselineAttack severity during treatment period	• Not possible to individualize dose and interval of oral sumatriptan over 7-day treatment period
Leone et al., 1996[54]	• 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	

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)

Ambrosini et al., 2005[52]	• Single suboccipital betamethasone (13)
	• Placebo (10)
	• Duration: 4 weeks
		• 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	

Leroux et al., 2011[55] NCT00804895	• Suboccipital cortivazol (21) • Placebo (22) • Add on to verapamil (ECH) or current preventive (CCH) • Duration: 2 to 6 days (3 injections given 48–72 hours apart)	• 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 • Remission rate at day 30 • Delay to remission • Percentage of patients with ≤2 attacks/day	
Completed trials with halted recruitment					

El Amrani et al., 2002[53]	• Sodium valproate 1000–2000 mg/day (50)
	• Placebo (46)
	• Duration: 2 weeks
		• 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

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.

aResults 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).[40] 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[57] or chronic migraine[58] and recommendations for acute migraine therapy.[59] 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.[29,46,52] The phenomenon of spontaneous remission in ECH also poses a unique challenge in RCTs of preventive treatments.[40] 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.[45,48,53,55] 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.[40] 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.[6,14,61–65] 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),[40] 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).[27,40,46,48,66] 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.[27,48] 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).[67,68] Patients with CH usually seek treatment urgently at the beginning of a cluster period, starting a transitional and/or preventive therapy in addition to acute treatments.[69] 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.[27–29,44–48,53,54] 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
	  ○ Consideration of treatment history refractoriness should be made, similar to migraine treatment studies
	  ○ Consideration should be given to limiting the percentage of patients who are treatment refractory
	  ○ Definition of refractoriness should be provided by experts to avoid exclusion of otherwise eligible patients
	• CCH and ECH
	  ○ Enroll more diverse populations
		• CCH
		  ○ To maximize probability of detecting a true treatment effect, if one exists
		  ○ To enroll the desired patient population
		• CCH and ECH
		  ○ To help ensure study results are applicable to the broader CH patient population

Study site selection	• CCH and ECH
	  ○ Study site selection may be expanded to include, non-headache centers, with verification of the CH diagnosis, using third party 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
		• CCH and ECH
		  ○ To maximize eligible sample of patients
		  ○ To increase patient awareness of trials

Incorporation of a baseline period	• CCH and ECH
	  ○ Limiting the length of the prospective baseline period to 5-7 days
	  ○ A plea should be made to well-organized CH support and advocacy groups to ask patients, who are willing to enter clinical trials, to maintain a daily diary to facilitate drug development
	    ▪ Such a plea may obviate the need for a lengthy prospective baseline by providing a reliable retrospective baseline
	  ○ In the presence of a diary, a historical baseline plus a shorter prospective baseline period may be acceptable
		• CCH and ECH
		  ○ To avoid the onset of spontaneous remission, particularly in ECH, by minimizing the overall length of prospective baseline and the treatment period
		  ○ To maximize enrollment
		  ○ To improve the effectiveness of patient diaries and reliability of diary data

Placebo or other comparator	• CCH and ECH
	  ○ Allowance for effective acute treatments is a must in placebo-controlled trials
	  ○ Limit exposure to potentially ineffective comparator (either placebo or standard-of-care) to the minimal time needed to assess efficacy
	  ○ Permit patients who have had prior preventive treatment failures
	  ○ Stratify treatment randomization by number of prior treatment failures
		• CCH and ECH
		  ○ To minimize pain severity for patients and improve patient retention
		  ○ To ensure the treatment groups are balanced; maximize probability of detecting a true treatment effect, if one exists

Primary efficacy outcome measure	• CCH
	  ○ A standardized preferred efficacy outcome measure should be recommended, such as reduction of attacks over a period of weeks in association with persistence of the effect over longer periods
	• ECH
	  ○ A standardized preferred efficacy outcome measure should be recommended, such as early termination of an active cycle, or reduction in attack frequency
	  ○ Assessment of attack frequency (numerical reduction or proportion of responders) should be ascertained early in the ECH episode, preferably within 1 to 3 weeks of treatment, depending on the expected onset of action of the investigational treatment
	• CCH and ECH
	  ○ Outcomes MUST be biologically AND pragmatically appropriate
	  ○ 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
		• CCH
		○ To standardize clinical trials
		• ECH
		  ○ To standardize clinical trials
		  ○ To maximize the probability of assessing the primary outcome prior to the onset of spontaneous remission
		• CCH and ECH
		  ○ To ensure the outcome is relevant to clinicians and the CH population

(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

TABLE 4 (Continued)

Category	Considerations for RCT design	Justification

Statistical considerations	• CCH and ECH
	  ○ Statistical methods to assess efficacy should be based on ability to accommodate missing data, while still achieving accurate estimate (e.g., mixed model with repeated measures)
	  ○ 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
	  ○ Confounding factors must be accounted for in all analyses (e.g., sex, baseline attack frequency, length of current bout, history of treatment responsiveness, concomitant medication use)
		• CCH and ECH
		  ○ Low diary compliance or non-completers may contribute to a smaller sample size than intended
		  ○ These methods can account for a smaller than intended sample size by including partial data
		  ○ Confounding factors may have an impact on treatment efficacy and thus should be accounted for in all analyses

Abbreviations: CCH, chronic cluster headache; CH, cluster headache; ECH, episodic cluster headache; IHS, International Headache Society; RCT, randomized controlled trials.

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.[45,52,55] 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 ECH, 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.[40] 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.[40] 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,[65] 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,[53] 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[40] 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[28,29,44–50,54,55,60] 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[71,72] (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.[40] 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.[27–29,44–50,52,53,55,60] 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,[73] 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 intraindividually, 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.[74] 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.[62] A substantial response in the placebo group was observed in the clinical trials reported herein[53,55] (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.

CONFLICT OF INTEREST

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), Epien (Options/Board), Nocira (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 Amgen. Personal fees: Lundbeck, Aeon Biopharma, Allergan/Abbvie, Biohaven Pharmaceuticals, Epalex Corporation, GlaxoSmithKline, Impel NeuroPharma, Inc, Novartis, Pfizer, Praxis, Santara 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.

AUTHOR CONTRIBUTIONS

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REFERENCES

1. Fischera M, Marziniak M, Gralow I, Evers S. The incidence and prevalence of cluster headache: a meta-analysis of population-based studies. *Cephalalgia*. 2008;28:614-618.
2. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396:1204-1222.
3. Allena M, De Icco R, Sances G, et al. Gender differences in the clinical presentation of cluster headache: a role for sexual hormones? *Front Neurol*. 2019;10:1220.
4. Bahra A, May A, Goadsby PJ. Cluster headache: a prospective clinical study with diagnostic implications. *Neurology*. 2002;58:354-361.
5. Gaul C, Christmann N, Schröder D, et al. Differences in clinical characteristics and frequency of accompanying migraine features in episodic and chronic cluster headache. *Cephalalgia*. 2012;32:571-577.
6. Lund N, Barloese M, Petersen A, Haddock B, Jensen R. Chronobiology differs between men and women with cluster headache, clinical phenotype does not. *Neurology*. 2017;88:1069-1076.
7. Manzoni GC, Terzano MG, Bono G, Micieli G, Martucci N, Nappi G. Cluster headache – clinical findings in 180 patients. *Cephalalgia*. 1983;3:21-30.
8. Manzoni GC, Terzano MG, Moretti G, Cocchi M. Clinical observations on 76 cluster headache cases. *Eur Neurol*. 1981;20:88-94.
9. Moon HS, Park JW, Lee KS, et al. Clinical features of cluster headache patients in Korea. *J Korean Med Sci*. 2017;32:502-506.
10. Ofte HK, Berg DH, Bekkelund SI, Alstadhaug KB. Insomnia and periodicity of headache in an Arctic cluster headache population. *Headache*. 2013;53:1602-1612.
11. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38:1-211.
12. Hoffmann J, May A. Diagnosis, pathophysiology, and management of cluster headache. *Lancet Neurol*. 2018;17:75-83.
13. Bussone G, Usai S, Grazzi L, Rigamonti A, Solari A, D'Amico D. Disability and quality of life in different primary headaches: results from Italian studies. *Neurol Sci*. 2004;25:s105-s107.
14. Buture A, Ahmed F, Mehta Y, Paemeleire K, Goadsby PJ, Dikomitis L. Perceptions, experiences, and understandings of cluster headache among GPs and neurologists: a qualitative study. *Br J Gen Pract*. 2020;70:e514-e522.
15. D'Amico D, Raggi A, Grazzi L, Lambru G. Disability, quality of life, and socioeconomic burden of cluster headache: a critical review of current evidence and future perspectives. *Headache*. 2020;60:809-818.
16. Jensen RM, Lyngberg A, Jensen RH. Burden of cluster headache. *Cephalalgia*. 2007;27:535-541.
17. Ji Lee M, Cho SJ, Wook Park J, et al. Increased suicidality in patients with cluster headache. *Cephalalgia*. 2019;39:1249-1256.
18. Jürgens TP, Gaul C, Lindwurm A, et al. Impairment in episodic and chronic cluster headache. *Cephalalgia*. 2011;31:671-682.
19. Rozen TD, Fishman RS. Cluster headache in the United States of America: demographics, clinical characteristics, triggers, suicidality, and personal burden. *Headache*. 2012;52:99-113.
20. Sohn JH, Park JW, Lee MJ, et al. Clinical factors influencing the impact of cluster headache from a prospective multicenter study. *Sci Rep*. 2020;10:2428.
21. Torkamani M, Ernst L, Cheung LS, Lambru G, Matharu M, Jahanshahi M. The neuropsychology of cluster headache: cognition, mood, disability, and quality of life of patients with chronic and episodic cluster headache. *Headache*. 2015;55:287-300.
22. Vollesen ALH, Snoer A, Beske RP, et al. Effect of infusion of calcitonin gene-related peptide on cluster headache attacks: a randomized clinical trial. *JAMA Neurol*. 2018;75:1187-1197.
23. Wei DY, Goadsby PJ. Cluster headache pathophysiology—insights from current and emerging treatments. *Nat Rev Neurol*. 2021;17:308-324.
24. Goadsby PJ, Edvinsson L. Human in vivo evidence for trigeminovascular activation in cluster headache. Neuropeptide changes and effects of acute attacks therapies. *Brain*. 1994;117:427-434.
25. Vollesen ALH, Snoer A, Chaudhry B, et al. The effect of pituitary adenylate cyclase-activating peptide-38 and vasoactive intestinal peptide in cluster headache. *Cephalalgia*. 2020;40:1474-1488.
26. Bussone G, Leone M, Peccarisi C, et al. Double blind comparison of lithium and verapamil in cluster headache prophylaxis. *Headache*. 1990;30:411-417.
27. Steiner TJ, Hering R, Couturier EG, Davies PT, Whitmarsh TE. Double-blind placebo-controlled trial of lithium in episodic cluster headache. *Cephalalgia*. 1997;17:673-675.
28. Dodick DW, Goadsby PJ, Lucas C, et al. Phase 3 randomized, placebo-controlled study of galcanezumab in patients with chronic cluster headache: results from 3-month double-blind treatment. *Cephalalgia*. 2020;40:935-948.
29. Goadsby PJ, Dodick DW, Leone M, et al. Trial of galcanezumab in prevention of episodic cluster headache. *N Engl J Med*. 2019;381:132-141.
30. Goadsby PJ, de Coo IF, Silver N, et al. Non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: a randomized, double-blind, sham-controlled ACT2 study. *Cephalalgia*. 2018;38:959-969.
31. Silberstein SD, Mechtler LL, Kudrow DB, et al. Non-invasive vagus nerve stimulation for the acute treatment of cluster headache: findings from the randomized, double-blind, sham-controlled ACT1 study. *Headache*. 2016;56:1317-1332.
32. Pearson SM, Burish MJ, Shapiro RE, Yan Y, Schor LI. Effectiveness of oxygen and other acute treatments for cluster headache: results from the Cluster Headache Questionnaire, an international survey. *Headache*. 2019;59:235-249.
33. Drescher J, Khouri A, Amann TK, et al. Effectiveness of medication in cluster headache. *BMC Neurol*. 2021;21:174.
34. Cohen AS, Burns B, Goadsby PJ. High-flow oxygen for treatment of cluster headache: a randomized trial. *JAMA*. 2009;302:2451-2457.
35. Göbel H, Lindner V, Heinze A, Ribbat M, Deuschl G. Acute therapy for cluster headache with sumatriptan: findings of a one-year long-term study. *Neurology*. 1998;51:908-911.
36. Kudrow L. Response of cluster headache attacks to oxygen inhalation. *Headache*. 1981;21:1-4.
37. May A, Leone M, Áfra J, et al. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. *Eur J Neurol*. 2006;13:1066-1077.
38. Robbins MS, Starling AJ, Pringsheim TM, Becker WJ, Schwedt TJ. Treatment of cluster headache: the American Headache Society evidence-based guidelines. *Headache*. 2016;56:1093-1106.
39. Doesborg P, Haan J. Cluster headache: new targets and options for treatment. *F1000Res*. 2018;7:339.
40. Lipton RB, Micieli G, Russell D, Solomon S, Tfelt-Hansen P, Waldenlind E. Guidelines for controlled trials of drugs in cluster headache. *Cephalalgia*. 1995;15:452-462.
41. *Emgality (galcanezumab-gnlm) Injection for Subcutaneous Use*. Prescribing information. Eli Lilly and Company. Revised March 2021. Accessed September 2, 2021. https://uspl.lilly.com/emgality/emgality.html#pi
42. *EU Clinical Trial Register*. European Medicines Agency. 2021. Accessed September 2, 2021. https://www.clinicaltrialsregister.eu/

43. *ClinicalTrials.gov*. U.S. National Library of Medicine. 2021. Accessed September 2, 2021. https://clinicaltrials.gov/

44. Leone M, D'Amico D, Frediani F, et al. Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. *Neurology*. 2000;54:1382-1385.

45. Obermann M, Nägel S, Ose C, et al. Safety and efficacy of prednisone versus placebo in short-term prevention of episodic cluster headache: a multicentre, double-blind, randomised controlled trial. *Lancet Neurol*. 2021;20:29-37.

46. Pageler L, Katsarava Z, Lampl C, et al. Frovatriptan for prophylactic treatment of cluster headache: lessons for future trial design. *Headache*. 2011;51:129-134.

47. Saper JR, Klapper J, Mathew NT, Rapoport A, Phillips SB, Bernstein JE. Intranasal civamide for the treatment of episodic cluster headaches. *Arch Neurol*. 2002;59:990-994.

48. Tronvik E, Wienecke T, Monstad I, et al. Randomised trial on episodic cluster headache with an angiotensin II receptor blocker. *Cephalalgia*. 2013;33:1026-1034.

49. Evers S, Masur H, Sörös P, Brilla R, Husstedt IW. Prostaglandin analog mechanisms are not effective in refractory chronic cluster headache. *Headache*. 1998;38:618-620.

50. Fontaine D, Lazorthes Y, Mertens P, et al. Safety and efficacy of deep brain stimulation in refractory cluster headache: a randomized placebo-controlled double-blind trial followed by a 1-year open extension. *J Headache Pain*. 2010;11:23-31.

51. Hakim SM. Warfarin for refractory chronic cluster headache: a randomized pilot study. *Headache*. 2011;51:713-725.

52. Ambrosini A, Vandenheede M, Rossi P, et al. Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: a double-blind placebo-controlled study. *Pain*. 2005;118:92-96.

53. El Amrani M, Massiou H, Bousser MG. A negative trial of sodium valproate in cluster headache: methodological issues. *Cephalalgia*. 2002;22:205-208.

54. Leone M, D'Amico D, Moschiano F, Fraschini F, Bussone G. Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups. *Cephalalgia*. 1996;16:494-496.

55. Leroux E, Valade D, Taifas I, et al. Suboccipital steroid injections for transitional treatment of patients with more than two cluster headache attacks per day: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2011;10:891-897.

56. Monstad I, Krabbe A, Micieli G, et al. Preemptive oral treatment with sumatriptan during a cluster period. *Headache*. 1995;35:607-613.

57. Diener HC, Tassorelli C, Dodick DW, et al. Guidelines of the International Headache Society for controlled trials of preventive treatment of migraine attacks in episodic migraine in adults. *Cephalalgia*. 2020;40:1026-1044.

58. Tassorelli C, Diener HC, Dodick DW, et al. Guidelines of the International Headache Society for controlled trials of preventive treatment of chronic migraine in adults. *Cephalalgia*. 2018;38:815-832.

59. Diener HC, Tassorelli C, Dodick DW, et al. Guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults: fourth edition. *Cephalalgia*. 2019;39:687-710.

60. Lipton RB, Diener HC, Barbanti P, et al. Efficacy and safety of fremanezumab for the prevention of episodic cluster headache: results of a randomized, double-blind, placebo-controlled, phase 3 study. *Cephalalgia*. 2019;39(1 Suppl):358-359.

61. Martinez J, Andrews JS, Jackson J, et al. Features of episodic cluster headache in the real world setting: clinical characteristics from a large, multi-national, cross-sectional survey (P5.10-011). *Neurology*. 2019;92(15 Suppl):P5.10-011.

62. Nilsson Remahl AIM, Laudon Meyer E, Cordonnier C, Goadsby PJ. Placebo response in cluster headache trials: a review. *Cephalalgia*. 2003;23:504-510.

63. Russell MB, Andersson PG. Clinical intra- and interfamilial variability of cluster headache. *Eur J Neurol*. 1995;1:253-257.

64. van Vliet JA, Eekers PJE, Haan J, Ferrari MD; for the Dutch RUSSH Study Group. Features involved in the diagnostic delay of cluster headache. *J Neurol Neurosurg Psychiatry*. 2003;74:1123-1125.

65. Vikelis M, Rapoport AM. Cluster headache in Greece: an observational clinical and demographic study of 302 patients. *J Headache Pain*. 2016;17:88.

66. Tfelt-Hansen P. Effective symptomatic medication should be available in prophylactic trials in cluster headache. *Headache*. 2011;51:307.

67. de Coo IF, Naber WC, Wilbrink LA, Haan J, Ferrari MD, Fronczek R. Increased use of illicit drugs in a Dutch cluster headache population. *Cephalalgia*. 2019;39:626-634.

68. Di Lorenzo C, Coppola G, Di Lorenzo G, Bracaglia M, Rossi P, Pierelli F. The use of illicit drugs as self-medication in the treatment of cluster headache: results from an Italian online survey. *Cephalalgia*. 2016;36:194-198.

69. Rozen TD. Cluster headache: diagnosis and treatment. *Curr Pain Headache Rep*. 2005;9:135-140.

70. Mitsikostas DD, Edvinsson L, Jensen RH, et al. Refractory chronic cluster headache: a consensus statement on clinical definition from the European Headache Federation. *J Headache Pain*. 2014;15:79.

71. Farrar JT. What is clinically meaningful: outcome measures in pain clinical trials. *Clin J Pain*. 2000;16:S106-S112.

72. Kudrow D, Andrews JS, Rettiganti M, et al. Treatment outcomes in patients treated with galcanezumab vs placebo: post hoc analyses from a phase 3 randomized study in patients with episodic cluster headache. *Headache*. 2020;60:2254-2264.

73. The Sumatriptan Cluster Headache Study Group. Treatment of acute cluster headache with sumatriptan. *N Engl J Med*. 1991;325:322-326.

74. Abu Bakar N, Torkamani M, Tanprawate S, Lambru G, Matharu M, Jahanshahi M. The development and validation of the Cluster Headache Quality of life scale (CHQ). *J Headache Pain*. 2016;17:79.