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Guidelines for controlled trials of preventive treatment of migraine attacks in episodic migraine in adults

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on behalf of the International Headache Society Clinical Trials Committee

Abstract

Clinical trials are a key component of the evidence base for the treatment of headache disorders. In 1991, the International Headache Society Clinical Trials Standing Committee developed and published the first edition of the *Guidelines for Controlled Trials of Drugs in Migraine*. Advances in drugs, devices, and biologicals, as well as novel trial designs, have prompted several updates over the nearly 30 years since, including most recently the *Guidelines for controlled trials of preventive treatment of chronic migraine* (2018), the *Guidelines for controlled trials of acute treatment of migraine attacks in adults* (2019), and *Guidelines for controlled trials of preventive treatment of migraine in children and adolescents* (2019). The present update incorporates findings from new research and is intended to optimize the design of controlled trials of preventive pharmacological treatment of episodic migraine in adults. A guideline for clinical trials with devices will be published separately.

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Contents

Abbreviations

AE: adverse event; BDI: Beck Depression Inventory; C-SSRS: Columbia-Suicide Severity Rating Scale; FIS: Functional Impairment Scale; EQ-5D: EuroQoL-5 Dimension Questionnaire; GAD: generalized anxiety disorder; HADS: Hospital Anxiety and Depression Scale; HIT: Headache Impact Test; HRQOL: health-related quality of life; HTA: Health Technology Assessment; ICHD: International Classification of Headache Disorders; IHS: International Headache Society; MFIQ: Migraine Functional Impact Questionnaire; MIDAS: Migraine Disability Assessment; MPFID: Migraine Physical Function Impact Diary; MOH: medication-overuse headache; MSQ v2.1: Migraine-Specific Quality of Life questionnaire; PGIC: Patient Global Impression of Change; PHQ-9: Patient Health Questionnaire-9; SF-36: Short Form 36-Item Health Survey; STA-I: State-Trait Anxiety Inventory; WPAI: Work Productivity and Activity Impairment.

Introduction

The International Headache Society (IHS) and its Clinical Trials Committee have been active in the development and publication of guidelines for controlled trials of treatments for primary headache disorders for nearly 30 years (1–9). Since the 2012 third edition of the *Guidelines for Controlled Trials of Drugs in Migraine* (6), the IHS has published new guidelines for trials of preventive treatments in adults with chronic migraine (7) and children or adolescents with episodic migraine (9). However, there has been no update addressing trials of preventive treatments for adults with episodic migraine. With the results of many controlled trials of drugs, biologicals, and devices for the prevention of episodic migraine published since the third edition (Supplemental Table), the Committee recognized the need to incorporate this substantial body of work into a revised guideline. The current update, which focuses on the evaluation of drugs and biologicals in adults with episodic migraine, is based on lessons learned from these trials. Forthcoming guidelines will focus on trials of devices for the preventive treatment of migraine, as well on trial designs for data collection required by Health Technology Assessment (HTA) bodies and reimbursement agencies. For more information about issues applying to clinical trials in general, the reader should consult general works on clinical trial methodology (10–12) and previously published discussions (13–15).

The understanding of migraine pathophysiology has vastly improved in the decades since the first trial guideline was issued, and the field of clinical therapeutic research has changed. In particular, the recent introduction of multiple target-specific molecules has increased the need for innovative trial designs that ensure the integrity of trial data while conserving resources and abbreviating the development process (16). To meet this need, trial designers are encouraged to adapt emerging and theoretical approaches from

academia, industry, and regulatory authorities whenever possible, including the use of new designs (Phase 2/3, group-sequential, adaptive dose-finding, multi-arm/multi-stage (17)); novel methods of data collection (automated or semi-automated techniques vs. electronic diaries); personalized endpoints (combining traditional and subject-specific components); and biomarkers (to confirm eligibility and differentiate subpopulations). Using and evaluating these emerging approaches will advance the field of migraine clinical research, inform future updates to the guidelines, and, ultimately, improve the quality of migraine treatment worldwide.

1 Drug trials for the prevention of episodic migraine

Adults with frequent migraine attacks may benefit from preventive treatment, which aims to reduce the (18,19):

- frequency of migraine days
- intensity of headache pain during residual attacks
- use of medication(s) for the acute treatment of migraine attacks

Reducing the use of medication for acute treatment in individuals who experience frequent migraine attacks can decrease the risk of medication-overuse headache (MOH) and progression from episodic migraine to chronic migraine (20,21).

Establishing the efficacy, tolerability, and safety of a preventive treatment for adults with episodic migraine begins with careful subject selection (see Section 1.1). Depending on research needs, the study population can be varied based on history of treatment response to available therapies (e.g. treatment-naïve; current use; failed, could not tolerate, had contraindications). After screening, eligible subjects must be enrolled into double-blind, randomized, controlled trials (see Section 1.2); open-label and single-blind trials should be avoided unless they are for hypothesis-generating purposes. The preventive treatment under evaluation must be compared with an appropriate control, usually placebo (see Section 1.2.2).

Controlled studies must be adequately powered to facilitate detection of clinically-relevant benefit versus placebo (see Section 1.3). Underpowered studies may be hypothesis generating and may provide additional information on dosing and tolerability, but they are inadequate for proving the efficacy or safety of a new drug or biological and insufficient as the basis for treatment decisions. Multicentre studies facilitate efficient enrolment of diverse study samples, which avoids the biases that can compromise single-centre studies and improves the generalizability of results. Pilot studies can provide insights that improve the design of fully-powered studies, including a basis for sample size calculations.

All clinical trials must follow standardized ethical and safety guidelines. Specifically, they must:

- be approved by appropriate institutional review boards or ethics committees
- be conducted in accordance with The Declaration of Helsinki (22) and Good Clinical Practice Guideline (23)
- follow rules in accordance with local regulatory authorities
- be prospectively registered in an acknowledged trial database (see Section 1.5)

In addition, all enrolled subjects must provide informed consent before any study-related activities are undertaken.

The IHS recommends that trial designers consider the use of post-approval prospective registries (see Section 2) and open-label or observational studies to collect long-term data on effectiveness, tolerability, and safety (24).

1.1 Selection of subjects

1.1.1 Definition of episodic migraine

Recommendations.

a. The diagnostic criteria for episodic migraine used in controlled trials should comply with the latest available version of the International Classification of Headache Disorders (ICHD) and satisfy ICHD criteria for migraine with or without aura (25).
b. Subjects with recurrent attacks that do not match ICHD criteria for migraine but successfully respond to migraine-specific medication (e.g. 5-$HT_{1B/1D}$ receptor agonists [triptans], 5-HT_{1F} receptor agonists [ditans], calcitonin gene-related peptide receptor antagonists [gepants], ergotamine) should be considered to have migraine and qualify for enrolment.
c. Once a migraine diagnosis is established, subjects with chronic migraine should be excluded.
d. Some adults with migraine fluctuate around the threshold between episodic migraine and chronic migraine (26), which can complicate enrolment. To avoid excluding them, consider a design that includes subjects with migraine irrespective of the number of headache and migraine days per month and stratify them into subgroups with episodic migraine or chronic migraine at time of randomization (see Section 1.2.5).

Comment. Individuals with episodic migraine should have a history of fewer than 15 monthly attacks

of unilateral, pulsating, moderate or severe headache lasting 4–72 hours that is aggravated by physical activity, associated with nausea and/or photophobia and phonophobia, and, in some cases, preceded by unilateral, fully-reversible central nervous system symptoms (25). People with chronic migraine have at least 15 headache days/month with a minimum of 8 migraine days/month for at least 3 months (25); more frequent attacks should be excluded (guidelines for controlled trials for the preventive treatment of chronic migraine are covered elsewhere (27). Imaging studies have shown that the consensus-developed threshold of 15 headache days/month facilitates accurate classification of subjects with migraine into episodic and chronic subgroups (28). For the analysis of outcome parameters in trials stratifying subjects at time of randomization, subjects should be assigned to the episodic migraine or chronic migraine subgroups based on the number of headache and migraine days they experience in the first 1–3 months of the double-blind phase of a randomized trial. For drugs with a presumed action on the prevention of migraine aura, dedicated trials in subjects who have migraine with aura can be undertaken.

1.1.2 Other headache types

Recommendations.

a. Subjects with other common primary headache types (e.g. tension-type headache) may be enrolled if attacks are infrequent (i.e. present on an average of <1 day/month and <12 days/year) (6) and can be reliably differentiated from migraine attacks by the subject or investigator based on the quality of the pain and associated symptoms.
b. People diagnosed with trigeminal autonomic cephalalgias and neuralgias should be excluded.
c. Subjects with secondary headache conditions should be excluded.

1.1.3 Duration of disease

Recommendations.

a. Episodic migraine should be present for at least 12 months based on monthly average prior to evaluation for study inclusion.
b. The date of onset of episodic migraine should be recorded.

Comments. Considering the spontaneous fluctuations in migraine frequency (21,26), requiring at least 12 months of attacks meeting ICHD criteria for episodic migraine will ensure that subjects enrolled into a clinical trial are less likely to enter a spontaneous remission period.

1.1.4 Duration of screening and baseline phase

Recommendations.

a. The typical phases in a randomized controlled parallel group trial are illustrated in Figure 1.
b. Following a 4-week screening phase, during which preliminary eligibility should be determined, trials should include a prospective baseline phase of 4 weeks before subject enrolment.
c. Subjects should record migraine-related data in an electronic diary (see Section 1.1.12).

Comments. Data collection for the 4 weeks prior to randomization is important for identifying and excluding subjects with chronic migraine and/or MOH. However, subjects with frequent intake of acute medication who do not fulfil the criteria for MOH may be included. Furthermore, a prospective baseline phase of 4 weeks is needed to establish baseline frequency of migraine days and classify each headache day to ensure that the threshold number of headache days meet criteria for migraine, probable migraine, and/or respond to acute treatment with migraine-specific medications. Use of a diary during the baseline phase is also important for assessing headache characteristics (pain quality, intensity, and relationship with routine physical activity); the presence of aura; use of acute headache medication; and subject compliance with the diary.

1.1.5 Age at onset

Recommendation. The age at onset of migraine should be <50 years.

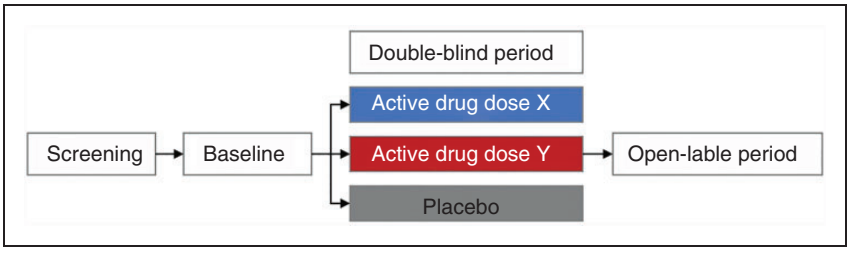

Figure 1. Terminology adopted in these guidelines and representation of the different phases of randomized controlled trials with parallel groups.

Table 1. Patient characteristics regarding inclusion criteria.

Demographics	Headache history	Medication use
Mean age	Age of migraine onset	Concomitant preventive treatment(s)
Sex	Headache days per month	Failure(s) of preventive treatments[a]
Ethnicity	Migraine days per month	Unsuitability to preventive treatment[b]
Race	Presence of aura	Acute medication days per month
Height	Percentage of attacks with aura	Type of acute medications
Weight	Presence of other headache disorders	Number of acute medications
Body mass index	Comorbidities (e.g. depression, anxiety)	

[a]Documented by physician attestation.
[b]Tolerability, sensitivity, and/or contraindication.

Comments. Episodic migraine beginning after 50 years of age is very unusual (29), and the risk of secondary headache increases with age of onset.

1.1.6 Age at entry

Recommendation. The minimum age at entry for trials involving adult subjects is 18 years.

Comments. Regulatory agencies require special protocols and separate trials to show efficacy, tolerability, and safety in children and adolescents (9,30,31); these requirements are addressed in recently published paediatric trial guidelines (9). Some countries require data from subjects older than 65 years of age to be collected, analysed, and presented separately from the larger trial population. Elderly subjects should only be excluded if a potential safety issue is present.

1.1.7 Enrolment

Recommendations.

a. Subjects should meet all predefined protocol inclusion criteria and not meet any of the predefined exclusion criteria. This needs to be documented at the time of the beginning of baseline and again at randomization.
b. According to the Good Clinical Practice Guideline (23), subjects should be given a clear explanation of the purpose of the trial, as well as their role and the possible risks they may face by participating. The explanation must be formulated in a way that does not exaggerate placebo and nocebo responses (32). Subjects should also receive an explanation of how the data will be used, as well as their rights concerning data privacy and exiting the study.
c. Subjects who are allergic or have shown hypersensitivity to compounds similar to the trial drug (including excipients) should be excluded.

Comments. Because adherence to preventive treatment for migraine can be poor (33,34), resulting in decreased efficacy, subjects must be instructed about the importance of taking study medications exactly as directed. Adherence with the protocol should be regularly monitored via medication counts, inspection of injection devices, electronic diary reminders, and smart packaging.

Table 1 shows subject characteristics regarding inclusion criteria that should be collected and reported (Table 1).

1.1.8 Sex

Recommendation. Males and females should be included in clinical trials, ideally in a distribution that reflects the sex ratio of the population with episodic migraine.

Comments. In the general population, the female: male sex ratio in adults with episodic migraine is approximately 3:1 (35), and this preponderance may be exaggerated in controlled trials. To enhance the generalizability of results, the sex ratio in trial populations should approximate the sex ratio reported in epidemiologic studies (35). If assessment of treatment benefits in males is of interest, efforts should be made to ensure that the enrolled sample is of sufficient size to permit analysis.

In adult females, the stages of reproductive life (e.g. fertile, premenopausal, postmenopausal) should be collected. In addition, appropriate precautions should be taken to avoid enrolling those who are or may become pregnant because of inadequate contraception. Pregnant and lactating females should be excluded from trials of treatments with the potential for toxicity to the infant or when the potential for toxicity is unknown. All nonsterile subjects must agree to use appropriate measures of contraception throughout the trial.

1.1.9 Concomitant disorders

Recommendations.

a. Subjects must be screened for concomitant medical conditions (including psychiatric disorders) to

exclude illnesses that may influence the conduct of a trial or the interpretation of its results. Depending on the nature of the migraine research question, the concomitant presence of some medical conditions may justify exclusion based on the potential for exacerbations or because its management may confound results or prevent adherence to and compliance with trial obligations (36).

b. Subjects with conditions that are comorbid with migraine, such as depression, may be included if they are prospectively identified and on a stable ($\geq$3 months) treatment regimen for the comorbid condition, with no anticipated changes during the study.

Comments. Major depression, anxiety, obesity, low back pain, and sleep apnoea are common in patients with episodic migraine (37), and psychiatric comorbidities and allodynia are risk factors for progression from episodic to chronic migraine (38,39). As a result, their presence, characteristics, and treatments need to be assessed before subjects reporting them can be included in a trial. When subjects' treatment for comorbid or concomitant illness may interfere with the preventive treatment of episodic migraine, they should be excluded from participation. Subjects who are overusing alcohol or using illicit drugs, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (40), should also be excluded.

1.1.10 Concomitant drug use

Recommendations.

a. Studies of monotherapy are ideal for establishing the efficacy, safety, and tolerability of novel preventive therapies in Phase 2 clinical trials.
b. In Phase 3 trials, subjects should be permitted to take one concomitant migraine preventive medication during treatment with study drug (i.e. a maximum of two migraine preventive medications). Concomitant preventive medication with a drug from the same class as the drug under investigation should be avoided. The dosage of the non-study medication should be stable ($\geq$3 months) before randomization and should not be changed during the trial (41,42).
c. Subjects taking concomitant preventive medication should undergo stratified randomization to ensure that treatment groups are balanced in terms of concomitant medication use (see Section 1.2.5).
d. In Phase 4 trials, concomitant medications for the same or other indications are allowed as long as subjects are on a stable regimen during the study.

Comments. The trial protocol should specify any concomitant medications that may or may not be used upon enrolment and/or during the trial. We assume that only patients who have a reduction of migraine days with the concomitant medication but do not reach a level of 50% response will be included into trials in which concomitant medication is allowed.

1.1.11 Subjects from previous headache trials

Recommendations.

a. Subjects may not participate in more than one clinical trial at the same time; a trial extension (e.g. open-label phase of long-term safety) should be counted as part of a single trial.
b. Subjects should not participate in more than one trial assessing the same preventive treatment.

Comments. Although concurrent and serial enrolment in preventive trials is not permitted, concurrent participation in prospective registries without treatment regimens is possible.

1.1.12 Data collection and monitoring

Recommendations.

a. An electronic diary capable of time stamps, remote monitoring, and alerts to ensure that trial data are collected in a prospective manner is strongly recommended; paper diaries are less desirable, but they may be used if electronic diaries are not available.
b. Subjects should be instructed to record headache characteristics (pain quality, intensity, and relationship with routine physical activity); the presence of aura; use of acute headache medication; and compliance with treatment.
c. Adverse events (AEs) should be recorded according to regulatory guidance in real time on the diary by the patient. Their characteristics and relation with the treatment under investigation should be ascertained during follow-up visits or phone calls. Data pertaining to AEs should be collected via a list of specific side effects and open-ended questions. Serious AEs need to be reported within 24 hours of their occurrence.
d. Subjects found to have incomplete diaries (e.g. $>$6 non-consecutive days within 28 days) during the baseline or treatment phases should be excluded.

Comment. It is important to minimise the response burden associated with entering information into the diary. In trials for the prevention of episodic migraine, it is not necessary to collect data on autonomic symptoms, photophobia, or phonophobia. For multinational trials, diary design should be standardized, with translations adapted to the linguistic and sociodemographic characteristics of target populations.

1.1.13 Response to previous treatments

Recommendations.

a. Subjects who have previously failed preventive treatments can be included in clinical trials.
b. Treatment failure is defined as any of the following: No meaningful reduction in headache frequency, duration, and/or severity after an adequate trial of medication (usually for 1–3 months for oral drugs and depending on injection intervals for subcutaneously- or intravenously-administered drugs); intolerable AEs (also within 1–3 months); contraindications precluding use or safety concerns.
c. The type(s) of treatment(s) that previously failed or were not well tolerated should be recorded and documented.

Comment. Documentation of previous failure of migraine preventive medication is generally based on the subject's medical record, with the medication name, treatment duration, dose level, and reason for discontinuation. Alternatively, but less desirably, previous preventive medication failure may be documented based on information carefully taken from the subject by the investigator.

1.2 Trial design

1.2.1 Blinding

Recommendation. To establish the efficacy, tolerability, and safety of a preventive treatment for episodic migraine, controlled trials must be double-blinded.

Comments. To limit bias and the effects of placebo, it is necessary that subjects and investigators/site personnel be blinded. Unblinding due to AEs may be a significant factor in placebo-controlled trials of preventive treatments of episodic migraine (see Section 1.2.2). At the end of a trial, subjects and investigators may be asked to predict (best guess) whether subjects were assigned to active treatment or placebo; these data should be recorded to confirm that blinding was successful. The success of blinding can be evaluated by the Bang Index (43).

1.2.2 Placebo control

Recommendations.

a. Treatments used for the prevention of episodic migraine should be compared with placebo.
b. When two presumably active drugs are compared, a placebo control is strongly recommended to provide for a measure of assay sensitivity, if appropriate.

Comments. The placebo effect in the prevention of migraine attacks in episodic migraine studies is variable but can be substantial (44,45). Higher rates are observed when the treatment is parenterally administered than when it is orally administered, and the effect may occur as a result of unbalanced randomization – when more subjects are allocated to active treatment than to placebo (46).

Active treatments must demonstrate superiority to placebo. A trial showing that two presumably active treatments have the same positive effect size does not prove the efficacy of either treatment. If placebo control is not possible because AEs will unblind the treatment to study subjects and/or investigators, the use of an active placebo (minimal AEs and no effect on migraine) should be considered. The use of an active comparator – ideally, an established preventive with evidence of superiority over placebo – should also be considered. An active comparator confirms that the trial design is sensitive to the benefits of established treatment and is a prerequisite for reimbursement in many countries.

1.2.3 Parallel-group and crossover designs

Recommendations.

a. Parallel-group designs should be preferred over crossover designs.
b. For an adequate assessment of the effects in each treatment phase, attack frequency must return to the baseline level before beginning a new treatment phase. This may be particularly difficult to achieve within reasonable timeframes.

Comments. Crossover designs have significant disadvantages. These include fluctuations in treatment effects over time, carry-over effects (which cannot be controlled with certainty, even with washout periods), and the need for a longer study duration, which increases the likelihood of withdrawals and protocol deviations (47), as well as spontaneous changes in migraine attack frequency.

1.2.4 Randomisation

Recommendations.

a. Controlled trials require that subjects be randomized, preferably in relatively small blocks, after the baseline period.
b. The process for randomization should be defined.

Comments. Subjects are often recruited for trials of preventive treatment of episodic migraine over extended periods. Therefore, to ensure balanced randomization across treatment groups, it is preferable to randomize subjects in relatively small blocks of varying size (e.g. 4–8 or 4–10) (48).

1.2.5 Stratified randomisation

Recommendation. Stratification is recommended in parallel-group trials to overcome important potential

confounding factors, such as comorbidity and use of concomitant preventive medications.

Comments. Randomisation alone does not ensure that treatment groups will be balanced for factors that can influence treatment response. This is particularly true when sample sizes are modest or for confounders that are uncommon. As sample size increases, randomization increasingly ensures that that treatment groups will be balanced for a particular confounder.

There are two approaches for addressing unbalanced randomisation: Statistical adjustments in analysis and stratified randomisation. Incorporating potential confounders into planned statistical analyses avoids complications and is more widely used (see Section 1.4). With stratified randomisation, the confounder is used to assign subjects to treatment groups and ensure that the groups are balanced. Stratified randomisation should be considered for known confounders that are readily measured at baseline, such as the number of prior preventive medications. Stratification needs to be limited to a certain number of factors that may be limited by sample size. Stratified randomisation complicates study logistics.

1.2.6 Baseline phase

Recommendations.

a. A prospective baseline phase of 4 to 8 weeks is recommended for ensuring that subjects meet diagnostic criteria for migraine and collecting other important information, including migraine day frequency and duration, the presence or absence of aura, headache characteristics and associated symptoms, impact on functional ability and work, and use of acute medication.
b. Data are optimally captured with electronic diaries that feature time stamps (to reduce recall bias) and allow the option of remotely monitoring data entered by subjects. If this option is not available, paper diaries may be used (see Section 1.1.12).

Comments. The baseline phase should be used to confirm that enrolled subjects are eligible for study, demonstrate that they can adhere to data collection procedures, and provide data for calculation of the primary outcome measures (13,49). Because the change from baseline in migraine days or moderate/severe headache days is usually the primary efficacy endpoint in trials of treatments for the prevention of episodic migraine, the accuracy of measurements during the baseline phase directly influences study results.

Four weeks is the minimum recommended duration of the baseline phase, although 8 weeks may be used, and some studies have used baseline periods of as long as 12 weeks. Since attack frequency can vary weekly and monthly in persons with migraine (26), long baseline periods may provide more accurate assessments of baseline status. At the same time, a long baseline phase can complicate enrolment, increase pre-randomization dropout rates, and delay treatment for patients with unmet treatment needs. Highly variable baseline frequency estimates diminish the statistical power of the primary efficacy analysis. This effect can be minimized by careful consideration of inclusion and exclusion criteria during screening.

1.2.7 Duration of treatment phases

Recommendations.

a. Use a double-blind treatment phase lasting at least 12 weeks.
b. A 24-week double-blind treatment phase may be used in evaluating cumulative benefit and persistence of efficacy and further analyzing safety and tolerability.
c. In Phase 3 trials, after the double-blind treatment phase, a long-term ($\geq$ 3 months) open-label phase is useful for collecting additional information on persistence of treatment effects, tolerability and safety.

Comments. Extending the duration of the double-blind treatment phase may increase the power of the trial by providing adequate time for treatment benefits to develop. Many migraine preventive medications require gradual dose escalation and adjustment before an optimal dose can be established. Thereafter, the effects of treatment may accrue gradually, especially for orally-administered treatments, and some medications may require several weeks or more at an optimal dose before reaching their full preventive potential. After the placebo-controlled phase, a long-term observation phase may help to identify additional AEs or determine time to relapse.

In trials of preventive treatments that have not been approved, the IHS recommends an open-label, long-term extension study to provide subjects who participated in the placebo arm of a controlled trial with access to a novel therapy while collecting useful information about tolerability and safety and adherence to treatment. Re-randomizing subjects to one of two active dose regimens in the open-label phase is a viable approach to assessing dose-dependent AEs (50). An important limitation of a longer randomization phase is that it subjects who remain on placebo for an extended period have an increased risk of discontinuing a trial, often for lack of efficacy.

1.2.8 After a treatment phase

Recommendations.

a. After termination of a randomized treatment or an open-label extension phase, subjects should be followed prospectively for the evaluation of safety; the duration of follow-up depends on the treatment under investigation.
b. Ideally, subjects should continue to complete a daily diary during this period and, if other preventive medications are used, record drug usage.

Comments. Randomized withdrawal trials may be considered when double-blind efficacy trials have been undertaken (51). In withdrawal studies, all subjects initially receive active treatment. After 12 weeks, subjects are randomized in a blinded fashion to continue active treatment or placebo. Trials employing this design may identify withdrawal phenomena, attenuation of response, disease recurrence, and timing of increase in disease activity and persistence of effect that may occur after the termination of active treatment.

1.2.9 Dosage or procedures

Recommendations.

a. In Phase 2 trials, attempts should be made to test as wide a range of dosages as possible (e.g. minimal effective dose and maximum tolerated dose).
b. Phase 3 trials may involve one dose or two doses.
c. Investigating more than two doses increases the number of treatment arms and enhances the placebo effect (see Section 1.2.2).

Comments. If the basis of the efficacy of a preventive treatment is unknown, the choice of dosage and/or the intensity of an intervention is a purely empirical compromise between observed efficacy and tolerability.

1.2.10 Use of acute and preventive treatments

Recommendations.

a. The acute treatment of migraine attacks should be allowed as long as i) the agent and dose remain the same throughout the baseline phase and for the duration of the trial and ii) intake is documented in the diary. Recent evidence suggesting that gepants may have a preventive effect needs to be considered when defining which acute medications are acceptable (52).
b. Concomitant preventive treatments with established efficacy or a probable influence on treatment outcomes should neither be started nor discontinued during the trial (Table 2); if concomitant preventive medication is allowed, the preventive medication and its dose should be stable for at least 3 months.

Table 2. Treatments requiring restricted use during controlled trials for prevention of episodic migraine.

Treatment	Examples[a]
Medications	Topiramate
	Gabapentin
	Beta blockers
	Tricyclic antidepressants
Devices	Non-invasive vagal stimulation
	Transcranial magnetic stimulation
	External trigeminal nerve stimulation
Non-pharmacological	Biofeedback
	Nutraceuticals
Procedures	Occipital nerve blocks
	Other extracranial nerve blocks
Pharmacological	Consecutive day infusion therapy
	Steroid tapers
Physical/manual	Chiropractic
	Acupuncture
	Physical therapy

[a]Selected; not an exhaustive list.

Comments. Subjects must be allowed to use acute headache medication during the trial. During the baseline phase, subjects should be counselled not to change the type, dosage, formulation of acute medication or the manner in which it is taken (during mild pain versus moderate/severe pain). Any instruction on acute medication usage needs to be standardized across treatment centres to avoid confounding the interpretation of study results.

1.2.11 Study visits

Recommendation.

a. Subjects should be followed regularly during the trial, and study visits are usually scheduled at screening, at the beginning and end of the baseline phase, and after randomization/initiation of treatment.
b. During the treatment phase, site visits should occur every 4–8 weeks and may be adjusted to account for the treatment being tested, anticipated AEs, and the duration of the trial.
c. Telephone, messaging (email or text), and video conferencing can be used for interim visits, and remote monitoring methods should be encouraged to improve adherence.

Comments. Regular contact with subjects participating in clinical trials is important for determining eligibility, ensuring adherence, and monitoring for AEs.

1.3 Evaluation of endpoints

Recommendations.

a. All primary and secondary endpoints need to be prospectively defined, with specific comparative groups

defined (e.g. treatment vs. placebo, treatment vs. baseline) and time points identified (e.g. 4-week or 12-week).
b. The selection of endpoints should depend on study objectives.
c. Power calculations for the primary and the most relevant secondary endpoints must be performed prior to study initiation and presented in the trial registration.

Comments. Issues with analysis of multiple comparisons may arise with the use of multiple primary endpoints or three or more treatment groups. In the case of multiple primary endpoints, multiplicity issues can be avoided by using hierarchical testing procedures (53). Should investigators or sponsors decide to use a multiple-comparison adjustment, it needs to be reflected in the calculations of sample size and statistical power.

If composite endpoints are used, each of the components must be clinically relevant and sufficient to establish treatment benefit, as success of the composite may be determined by results of any component. Composite endpoints are problematic when response for a component is inconsistent or when findings for the composite endpoints move in different directions (some positive, others negative).

1.3.1 Primary endpoints

Recommendations.

a. The primary endpoint in controlled trials of preventive treatment of episodic migraine should be the change from baseline in migraine days per unit time.
b. Alternative primary endpoints include change from baseline in moderate/severe headache days or 50% responder rate for the reduction of migraine days.

Comments. For the primary endpoint, the recommended time period for analyses in 12-week trials is the entire treatment phase. Analysis of the last 4 weeks of the treatment phase may be helpful for capturing the effects of treatments with a delayed onset. In 24-week trials, the recommended period for analysis is the last 12 weeks. Alternatively, results over the entire period may be considered in a sensitivity analysis. Evaluations of efficacy should be based on information obtained from electronic diaries (see Section 1.1.12).

1.3.1.1 Definition of migraine day. A migraine day is defined as a day with headache lasting at least 30 minutes without intake of analgesics and meeting ICHD-3 criteria for migraine or probable migraine (25). A migraine day may also be defined as a day with headache that successfully responds to acute treatment with a migraine-specific medication (triptan, ditan, gepant, ergotamine, etc.).

1.3.1.2 Definition of moderate/severe headache day. A moderate/severe headache day is defined as a day with headache pain of moderate or severe intensity that lasts at least 4 hours without medication, or a day with a headache pain of at least moderate intensity that responds to acute treatment with a migraine-specific medication.

1.3.1.3 Definition of responder rate. The responder rate is defined as the percent change from baseline in the number of migraine days or number of moderate/severe headache days in each dosing interval. In episodic migraine trials, subjects achieving at least a 50% reduction from baseline in migraine days or moderate/severe headache days should be considered responders. Other percent changes from baseline (e.g. 30%, 75%, and 100%) are not recommended as the primary endpoint. The responder rate used in controlled trials must be prospectively defined.

Comments. The definitions of migraine day, moderate/severe headache day, and responder rate are designed to facilitate the use of a relatively simple headache diary. Subjects should be instructed to use an electronic diary to record whether an attack was present (yes/no); if yes, they should record its peak severity (mild/moderate/severe), its duration, use/type of acute treatment, and response to treatment.

For the calculation of a migraine day or a moderate to severe headache day, it may be necessary to consider time periods of less than 24 consecutive hours over 1 or more calendar days. Exceptions may apply in specific circumstances, such as when an attack is interrupted by sleep. For example, if a subject goes to bed during an attack and awakens symptom-free, the attack should be considered to have ended at the onset of sleep. If a subject awakens with an attack already in progress, attack onset should be considered to be the time of awakening.

For the responder rate, it is advisable to include individual persistence of 50% response by calculating it for each 4 weeks (28 days) for subjects who had a 50% response in the first 4 weeks and continue to have this response in the subsequent 28-day period.

1.3.2 Secondary outcomes. The secondary outcomes listed below are organized based on the components they explore. The list is not prioritized.

1.3.2.0 Migraine attacks. The secondary outcome with highest priority is the reduction in migraine attacks. A migraine attack is defined as an episode of any qualified migraine headache or migraine-specific medication intake. A migraine attack that is interrupted by sleep, or temporarily remitted, and then recurs within 48 hours is considered as one attack.

Also, an attack treated successfully with medication but with relapse within 48 hours and a migraine attack lasting more than 48 hours is counted as one attack.

1.3.2.1 Headache-related.

1.3.2.1.1 Moderate/severe headache days. Should be used, if not chosen as the primary endpoint.

1.3.2.1.2 Migraine days. Should be used, if not chosen as the primary endpoint.

1.3.2.1.3 50% responder rate. Should be used, if not chosen as the primary endpoint.

1.3.2.1.4 Headache severity. A categorical, four-point scale should be used to rate headache severity during attacks as absent, mild, moderate, or severe. Headache severity alone is not recommended as a primary outcome measure, but it is important that subjects record a decrease in headache severity as an indicator of reduced disability. Depending on the trial design, subjects should be instructed to record the severity of each migraine day. An 11-point numerical rating scale (where 0 = no pain and 10 = worst possible pain) can be used as an alternative to or in association with the four-level categorical rating scale (54).

1.3.2.1.5 Peak headache pain intensity. A categorical, four-level rating scale should be used to rate the intensity of headache pain as absent, mild, moderate, or severe. Although not recommended as a primary outcome measure, headache pain intensity is a component of the primary outcome measure of headache days with moderate or severe intensity. Depending on the trial design, subjects should be instructed to record the maximum intensity for each headache day and any use of medication. An 11-point numerical rating scale can be used as an alternative or together with the four-level categorical rating scale (54).

1.3.2.1.6 Cumulative hours per 28 days of moderate/severe pain. Cumulative hours per 28 days of moderate/severe pain can be calculated with data from electronic diaries, and reductions in this endpoint may be clinically meaningful. If a subject goes to sleep during an attack and awakens with the attack still in progress, the hours during sleep are counted as headache hours. If a subject goes to sleep during an attack and awakens free from headache pain, half the sleeping hours are counted as headache hours.

1.3.2.1.7 Onset of effect. Understanding the onset of action of a preventive treatment may help to refine management strategies. During a trial, the onset of effect can be captured by analysing data from the first 4 weeks of treatment, unless the effects of the treatment being evaluated have a delayed onset (see Section 1.3.1).

1.3.2.1.8 Effect on the most bothersome symptom. Prior to randomization, subjects should be asked to identify the most bothersome symptom other than headache pain during migraine attacks (i.e. nausea, photophobia, or phonophobia). Based on the response, the effect of preventive therapy on the most bothersome symptom can be evaluated.

1.3.2.2 Acute headache treatments.

1.3.2.2.1 Acute treatment utilization. The use of acute migraine medication must be recorded, including the number of days, the specific drug used, and the number and dose of drugs. It is imperative that subjects do not receive any special counsel to change the frequency of use of acute headache medications during the treatment phase so that any change (increase or decrease) is more likely to reflect a change in migraine severity that can be evaluated.

1.3.2.3 Depression and anxiety. Depression and anxiety levels should be recorded at the time of randomization and at the end of the double-blind treatment period.

1.3.2.3.1 Validated scales for depression. Validated scales for depression in migraine include the Patient Health Questionnaire-9 (PHQ-9) (55), Beck Depression Inventory (BDI) (56), and the Hospital Anxiety and Depression Scale (HADS) (57).

1.3.2.3.2 Validated scales for anxiety. For assessment of anxiety, HADS, the State-Trait Anxiety Inventory (STA-I) (58), and the Generalized Anxiety Disorder (GAD-7) (59) can be used.

1.3.2.3.3 Scales for suicidal ideation. In trials investigating centrally-acting drugs, suicidal ideation should be monitored. Many migraine clinical trials have employed the Columbia-Suicide Severity Rating Scale (C-SSRS) (60).

1.3.2.4 Patient-reported outcome measures.

1.3.2.4.1 Patient Global Impression of Change. The Patient Global Impression of Change scale (PGIC) (61) can be used to evaluate subjects' impression of their clinical status. This scale asks subjects how they are doing overall at specified post-baseline time points (e.g. 4, 8, or 12 weeks) relative to their pre-treatment baseline.

1.3.2.4.2 Functional Impairment Scale. The Functional Impairment Scale (FIS) is a four-point scale that

assesses functional status and the intensity of impairment during daily activities (4,62). It can be used in conjunction with the four-point pain intensity scale and is usually completed daily and summarized over 4-week intervals.

1.3.2.4.3 Migraine Functional Impact Questionnaire. The Migraine Functional Impact Questionnaire (MFIQ) is a 26-item self-administered instrument for the assessment of the impact of migraine on physical functioning, usual activities, social functioning, and emotional functioning over the past 7 days (63). Although this measure has been accepted by the FDA, it is proprietary (Amgen, Inc., Thousand Oaks, CA, USA) and not widely available.

1.3.2.4.4 Migraine Physical Function Impact Diary. The Migraine Physical Function Impact Diary (MPFID) measures the impact of migraine on everyday acts and tasks experienced on days with migraine as well as days between attacks (64).

1.3.2.4.5 Other. Other patient-reported outcome instruments may be adopted as soon as they are validated and approved by regulatory agencies.

Comments. The use of subjects' preferences is not recommended as a primary efficacy measure. However, it is important to evaluate subjects' well-being throughout a clinical trial, and it is useful to define clinically meaningful changes in whichever outcome measures are selected. Note that comparisons of subject preferences for treatments can only be adequately assessed in clinical trials that use a crossover design.

1.3.2.5 Exploratory outcome measures. Exploratory outcome measures can be used to capture outcomes that may be clinically meaningful and correlate with primary/other secondary endpoints.

1.3.2.5.1 Symptom-free days. Symptom-free days are defined as the days free of premonitory, aura, headache, and postdromal symptoms. They may be quantified using data from subject diaries.

1.3.2.5.2 Headache and symptom-free days. Headache and symptom-free days are defined as days with no headache or associated symptoms (including disability and cognitive/emotional impairment) that are directly attributable to migraine.

1.3.2.5.3 Other. Other interictal burden outcome instruments may be used as they are validated.

1.3.2.6 Healthcare outcomes/quality of life. Validated, disease-specific health-related quality of life (HRQOL) and disability instruments are recommended as secondary endpoints. For some of the instruments listed in this section, the between-group minimal important difference has already been defined and used in trials involving subjects with episodic migraine (65,66).

1.3.2.6.1 Migraine-Specific Quality of Life questionnaire. The Migraine-Specific Quality of Life questionnaire (MSQ v2.1) is recommended for evaluating the change in quality of life related to episodic migraine (67). This 14-item instrument includes a global scale and three subscales. The Role Function Physical subscale has been accepted by the US Food and Drug Administration and is included in product labelling.

1.3.2.6.2 Headache Impact Test. The Headache Impact Test (HIT-6) (65) is recommended for evaluating migraine-related disability with a 1-month recall period. Note that HIT-6 needs to be licensed.

1.3.2.6.3 Migraine Disability Assessment questionnaire. Migraine-related disability can also be measured with the Migraine Disability Assessment (MIDAS) questionnaire (68), which was originally validated using a 3-month recall period. Forms using 4-week recall have been developed and used in clinical trials (69).

1.3.2.6.4 EuroQoL-5 Dimension Questionnaire. The EuroQoL-5 Dimension Questionnaire (EQ-5D) is a self-administered standardized measure of health status (70,71). Registration is needed to use this instrument.

1.3.2.6.5 Short Form 36-Item Health Survey. The Short Form 36-Item Health Survey (SF-36) is a well-known generic instrument for the evaluation of quality of life (72).

Comments. Health-related quality of life, which represents the net effect of an illness and the impact of therapy on subjects' perception of their ability to live a useful and fulfilling life (73,74), can be measured with generic and/or specific questionnaires. Generic questionnaires are usually chosen to compare study populations with different diseases, whereas disease-specific questionnaires are designed to assess problems associated with a single disease or treatment. Disease-specific instruments are more likely to be sensitive to changes in a treatment trial. Instruments for measuring HRQOL in episodic migraine must be scientifically developed and standardized. No single instrument is currently recognized as the gold standard in migraine HRQOL assessment.

For HRQOL endpoints to be valid, it is also important that instructions and education on lifestyle factors

(e.g. sleep hygiene, diet, caffeine use, exercise, etc.) are consistent across study centres and treatment groups. The same applies to behavioural treatments (e.g. cognitive therapy, biofeedback). If these methods are included in the study design, they should be prospectively defined and standardized to avoid confounding study outcomes.

1.3.3 Pharmacoeconomic endpoints

Recommendations.

a. The economic value of preventive treatment for episodic migraine should be assessed in studies that capture both the costs of medical treatment (direct costs) and lost productivity (indirect costs).
b. Reduction in work productivity and activity represent important components of disability and episodic migraine-associated costs.
c. The mean change from baseline can be measured by the Work Productivity and Activity Impairment (WPAI) instrument (75), which exists in a migraine-specific version (76).

Comments. The high cost of episodic migraine to individual sufferers and society may be offset or reduced by effective preventive treatment (77,78). The costs of medical treatment can be estimated using diaries or electronic data before and after treatment. Lost productivity (e.g. work, household work, and other activities) can be measured with self-reported diaries, through experience-based sampling, using employer work records. It is important to assess both presenteeism and absenteeism using reliable and valid measures, such as the WPAI-migraine (76) and the MIDAS questionnaire (68). Demonstrating that treatments for episodic migraine are effective and cost-effective will support the development and implementation of health policies that prioritize episodic migraine.

1.3.4 Adverse events

Recommendations.

a. Documentation of AEs and serious AEs during treatment should follow local institutional review board requirements and the guidelines of regulatory authorities and Good Clinical Practice.
b. Acceptable methods of documentation include lists of AEs, spontaneous reports, recordings, open-ended questions (if the event is not covered by the AE listing), and direct questioning.
c. Report AEs separately for active treatment and placebo.

Comments. Adverse events often occur before maximum efficacy is reached. In clinical practice, AEs are a major problem in preventive migraine treatment, and they often lead to discontinuation of treatment. The incidence of AEs, especially those leading subjects to discontinue a trial, should be regarded as a major measure of the tolerability of treatments for the prevention of episodic migraine.

Adverse events are not necessarily related to treatment. During the development of a new treatment, AEs must be recorded to detect any unexpected and unwanted effects, and investigators must try to determine whether AEs were treatment-related. Note that regulatory authorities require detailed reporting of AEs using the Medical Dictionary for Regulatory Activities system.

1.4 Statistics

Recommendations. Issues that need to be prospectively defined in preplanning the analysis of data for episodic migraine studies are shown in Table 3.

Comments. Statistical analyses are based on certain assumptions, and statistical analysis plans need to employ methods and tests designed to evaluate them. Investigators need to be prepared to propose an alternative analysis plan if assumptions are not met.

Table 3. Analytic issues to be prospectively defined during preplanning.

Endpoints/outcomes	Statistics	
Primary efficacy variable	Statistical analysis plan	Analysis populations
Secondary efficacy variables	Multiple-testing procedure	Rules for imputation of missing data[a]
Modalities of data collection to evaluate efficacy[b]	Sample size needed for statistical significance	Methods for comparing: • The baseline and treatment phases • Treatment groups

[a]For example, if the stop-time of an attack is unknown, it might be assumed that it stopped at the end of the last day (e.g. 23 hours and 59 minutes) it was reported as ongoing. Missing data for a total day may be imputed based on the rest of the 4-week diary.

[b]For example, if moderate/severe headache days are being evaluated, the record of occurrence, start and stop time, duration of headache, and minimum duration required for counting a headache day (i.e. $\geq$ 4 hours) are all individual outcomes that should be defined and captured.

For efficacy endpoints, subjects should be analysed according to the randomization assignment, regardless of actual treatment received. Specifically, the full analysis set should be derived using the intent-to-treat principle, clearly defined, and analysed as randomized (23). For safety variables, it may be reasonable to analyse subjects according to the treatment(s) actually received, regardless of the treatment assigned. To have data for all subjects in the full analysis set, it is possible to impute missing data for at least the primary variable of interest, either as a primary analysis or as a sensitivity analysis. Alternate statistical methods may be used if verified by a statistician.

Summary tables for each treatment and for each measurement time should include the number of subjects and descriptive statistics (mean, standard deviation, median, minimum, and maximum) and/or response frequencies.

Randomization does not always guarantee that treatment groups will be balanced on all baseline characteristics. If such imbalances are observed for key variables of interest, then analysis needs to be performed using regression methods. To improve evaluations of the efficacy of different interventions, the effect size for the primary outcome measure(s) should be calculated with available statistical methods. This approach will also facilitate comparisons of findings from different studies (79,80).

1.5 Trial registration

Prior to initiation of a trial, registration is necessary at clinicaltrials.gov, clinicaltrialsregister.eu, anzctr.org.au/or a similar regional or national official database.

1.6 Publication of results

Recommendations.

a. A publication committee should be formed prior to the start of the trial.
b. Before a trial is initiated, investigators and sponsors (if applicable) should agree upon timelines for publication; ideally, they should form part of the protocol.
c. All research results – primary and secondary endpoints and all safety data, either positive or negative – must be published in manuscript form; at the time of trial initiation or at the end of recruitment, a design paper with baseline data may be published.
d. Authorship should be based on the recommendations of the International Committee of Medical Journal Editors (81).
e. For sake of transparency, all authors must declare their conflicts of interest.
f. Investigators should avoid entering into agreements with sponsors, both for-profit and non-profit, that restrict access to study data, limit its analysis and interpretation, or interfere with the independent preparation and publication of manuscripts.

Comments. When applicable, controlled trials should be published on behalf of a study group that includes the investigators who enrolled subjects into the trial. A conflict of interest exists whenever professional judgment concerning a primary interest (such as subjects' welfare or the validity of research) may be influenced by a secondary interest (such as a financial tie to the sponsor). Financial ties that represent potential conflicts of interest include employment, consultancies, grants, fees and honoraria, patents, royalties, stock or share ownership, and paid expert testimony. Potential conflicts of interest usually extend to an investigator's spouse and children. Their presence may undermine the credibility of the study.

1.7 Independent data safety monitoring board

An independent data safety monitoring board and predefined stopping rules for futility or safety are recommended for Phase 3 trials initiated after the publication of these guidelines.

1.8 Steering committee

Recommendations.

a. For Phase 3 trials sponsored by industry, a steering committee comprised of academics, statisticians, and company representatives (where appropriate) is recommended.
b. For investigator-initiated trials (i.e. studies developed and sponsored by independent investigators or academia), a steering committee is not necessary.

Comments. Whether or not a committee is used, investigators and sponsors are responsible for study conception, design, operational execution, investigator training, data handling, data analysis and interpretation, subsequent reporting and publication, and compliance with all local laws and regulations.

2 Post-approval registries

Recommendations.

a. Prospective post-approval registries, open-label or observational studies should be used to evaluate newly approved drugs and biologics in clinical practice.
b. Registries/studies may include subjects following the double-blind treatment phase of randomized trials and subjects excluded from randomized trials, including individuals with comorbid and concomitant conditions (e.g. episodic pain syndromes,

cardiovascular disease) and those using concomitant drugs and treatments.

Comments. Registries generate data on long-term efficacy, tolerability, and safety. They also measure compliance and adherence and may provide information about withdrawal symptoms. As migraine is most often a disorder of women of childbearing potential, pregnancy registries are also recommended (82).

3 Health technology assessment (HTA)

In some countries, HTA bodies require dedicated studies for cost-effectiveness and calculation of a cost-benefit ratio as a precondition to granting reimbursement; they may require a comparison with an approved drug treatment. For the purpose of these studies, healthcare costs associated with office and emergency department visits, diagnostic tests, hospital admission and medication must be collected; working days lost (i.e. the total number of days off work due to illness or injury) may also be measured.

4 Methodology used for the development of these guidelines

The IHS Clinical Trials Standing Committee developed the present edition of the *Guidelines for controlled trials of preventive treatment of episodic migraine in adults* as a modification of the *Guidelines for controlled trials of preventive treatment of chronic migraine in adults* (7).

The Committee's work was independent and unbiased, and the process of developing this edition of the guideline involved two phases. The initial draft of the guideline was reviewed by the Clinical Guidelines Committee of the IHS, and multiple changes were proposed. This version of the guideline was shared with representatives of the European Medicines Agency, the US Food and Drug Administration, pharmaceutical manufacturers, and patient associations. These bodies reviewed the proposed changes, and their suggestions were discussed in a series of face-to-face meetings with members of the Committee. After incorporating the views of these stakeholders, the Committee posted a pre-final version on the IHS website (http://www.ihs-headache.org/ichd-guidelines) in March 2020, calling for comments from IHS members. The Committee incorporated member comments to finalize this edition.

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CT has participated in advisory boards for Allergan, ElectroCore, Eli Lilly, Novartis and Teva; she has lectured at symposia sponsored by Allergan, Eli Lilly, Novartis and TEVA; she is principal investigator or collaborator in clinical trials sponsored by Alder, Eli-Lilly and Teva. She has received research grants from the European Commission, the Italian Ministry of Health and the Italian Ministry of University.

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