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Guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults: Fourth edition

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Abstract

The quality of clinical trials is an essential part 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*. Scientific and clinical developments in headache medicine led to second and third editions in 2000 and 2012, respectively. The current, fourth edition of the *Guidelines* retains the structure and much content from previous editions. However, it also incorporates evidence from clinical trials published after the third edition as well as feedback from meetings with regulators, pharmaceutical and device manufacturers, and patient associations. Its final form reflects the collective expertise and judgement of the Committee. These updated recommendations and commentary are intended to meet the Society's continuing objective of providing a contemporary, standardized, and evidence-based approach to the conduct and reporting of randomised controlled trials for the acute treatment of migraine attacks.

Keywords

Guidelines, controlled trials, acute treatment of migraine attacks in adults

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Introduction

In 1991, the Clinical Trials Standing Committee of the International Headache Society (IHS) published the first edition of the *Guidelines for controlled trials of drugs in migraine* (1). Its goal was to improve the quality of controlled clinical trials in migraine by encouraging the use of scientifically robust methods in clinical research. To keep pace with developments in the scientific and clinical understanding of acute treatment, the Committee published a second edition of the *Guidelines* in 2000 (2) and a third edition in 2012 (3). The commitment to continuous improvement has been recognized; the *Guidelines* were considered in the 2018 *Guidance for industry* (4) prepared by the Division of Neurology Products in the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA), and they were adopted by the European Medicine Agency (EMA) in a 2016 concept paper that represented an important milestone in its formal revision of the 2007 *Guideline on clinical investigation of medicinal products for the treatment of migraine* (5).

Since the 2012 update, multiple new acute treatments have been developed, including small molecule calcitonin gene-related peptide (CGRP) receptor antagonists, serotonin (5-HT_{1F}) receptor agonists, triptan reformulations, and neuromodulation approaches. Accordingly, the *Guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults: Fourth edition* incorporates data from clinical trials conducted since the third edition of the *Guidelines* was published, as well as feedback from meetings with representatives of the FDA and EMA, pharmaceutical and device manufacturers, and patient associations. Although the Committee considered the comments of pharmaceutical and device manufacturers and members of the IHS on the first draft, the published version is an independent and unbiased reflection of the expertise and consensus judgement of its members.

The present publication retains the structure of the third edition (3), with sub-sections for the selection of subjects, trial design, evaluation of results, statistics, and special issues, as well as a Toolbox, which provides readers with an index to content and summary statements for each section. Several challenges in trial design that were raised in a preliminary statement in the third edition – specifically, the timing of acute treatment, consistency of response, and participants who have migraine with aura – have been addressed in Sections 1.2.9, 1.2.12, and 2.1, respectively. It is therefore hoped that this edition of the *Guidelines* continues the tradition of its predecessors by providing investigators with a contemporary, standardized, and evidence-based approach to the conduct and reporting of clinical trials for the acute treatment of migraine attacks.

1. Clinical trials for the acute treatment of migraine attacks

1.1. Subject selection

1.1.1. Migraine definition

Recommendation:

Eligible subjects should fulfil the diagnostic criteria for migraine according to the most current version of the International Classification of Headache Disorders (ICHD) of the IHS (6).

Comments:

Clinical trials of acute treatments for migraine can include subjects who have migraine without aura, migraine with aura, and both migraine types, but the ICHD diagnostic criteria should be fulfilled to avoid population heterogeneity. In trials focusing on the acute treatment of migraine with aura, subjects with both migraine types can be included, as aura symptoms are recognizable, the attack types are distinguishable, and most people who have migraine with aura also have attacks of migraine without aura (7). (Refer to Section 2.1 for more information about migraine with aura.) In trials enrolling participants with a history of both types of attacks, the type of the treated attack should be classified according to ICHD criteria based on the clinical features captured in a diary. Note that this requirement may be impractical when subjects are instructed to treat early, because early treatment of migraine can modify the clinical features of an attack and thereby prevent analysis by type (refer to Section 2.2 for more information about early intervention trials). In some instances, after efficacy and safety have been demonstrated in subjects with confirmed diagnoses of migraine without aura and migraine with aura, trials targeting subjects with probable migraine – migraine-like attacks missing one of the features required to fulfil all criteria for a type or subtype of migraine (6) – may be appropriate.

1.1.2. Other primary headaches

Recommendations:

1.1.2.1. Individuals satisfying criteria for chronic migraine or with a history of chronic migraine in the last 12 months should be excluded from pivotal efficacy trials for the acute treatment of migraine. In subsequent trials, exploration of the benefits of new acute treatments in subjects with chronic migraine is needed.

1.1.2.2. Subjects with other concomitant primary headache types (e.g. tension-type headache) are allowed if attacks are infrequent (i.e. present on an average of < 1 day/month and < 12 days/year) (6) and can be differentiated from migraine based on the quality of pain and associated symptoms.

Comments:

Individuals with chronic migraine are excluded from the initial clinical trials of acute treatment because they may complicate analyses of efficacy in undifferentiated populations (refer to (8) for guidance about trials evaluating preventive treatments in adults with chronic migraine). Subjects with migraine may have other primary headache types, including tension-type headache (2). Those experiencing primary headaches that cannot be distinguished from ICHD-defined migraine without aura (6) should be excluded.

1.1.3. Secondary headaches

Recommendation:

Individuals with secondary headaches, including medication-overuse headache, should be excluded.

Comments:

Excessive use of acute medications for migraine does not necessarily lead to medication-overuse headache, and some individuals may fulfil IHS criteria for overuse of acute medications without suffering from a chronic pattern of headache. The secondary headache exclusion also applies to these subjects.

1.1.4. Frequency of attacks

Recommendations:

1.1.4.1. Attacks of migraine should occur two to eight times per month.

1.1.4.2. The frequency of other headaches (including non-target) must be no greater than 1 day per month.

1.1.4.3. There should be at least 48 hours of freedom from headache between attacks of migraine under study.

1.1.4.4. Subjects should experience fewer than 15 headache days per month.

Comments:

A minimum of two attacks per month is recommended. The maximum frequency of eight attacks per month reduces the probability that those with incipient medication overuse, medication-overuse headache, or chronic migraine will be included in the trial. Allowing 48 hours of freedom from headache between migraine attacks permits clear identification of individual attacks and distinction from relapse, and it avoids the use of multiple treatments for a single prolonged attack. The evaluation of three to five consecutive attacks provides information on consistency of response and may attenuate the placebo effect on the first attack (refer to Section 1.2.12 for more information about consistency of response).

1.1.5. Duration of migraine

Recommendation:

Migraine should be present for at least 1 year prior to inclusion in a clinical trial.

Comments:

Because there are no objective signs or biomarkers for the diagnosis of migraine, and the 1-year requirement increases the specificity of the diagnostic criteria, a minimum course of 1 year is advised to exclude people with headache types that may mimic migraine. The history may be based on subject recall or physician evaluation of medical records. At least five prior attacks of migraine without aura or two prior attacks of migraine with aura are required for diagnoses using ICHD criteria (6).

1.1.6. Age at onset

Recommendation:

The age at onset of migraine should be less than 50 years.

Comments:

Few adults will be excluded by this criterion, as migraine beginning after the age of 50 years is rare, and the prevalence of secondary headaches or organic diseases mimicking migraine increases after age 50. The inclusion of subjects with onset of migraine after 50 years of age can be considered in phase IV trials, as long as the migraine diagnosis is well established by ICHD criteria, and secondary headaches have been ruled out.

1.1.7. Age at entry

Recommendation:

Adult subjects participating in clinical trials should be between 18 and 65 years of age at entry.

Comments:

Only people who are at least 18 years old can provide informed consent. The inclusion of subjects older than 65 years is encouraged in post-marketing surveillance studies. After age 65, those with migraine are more likely to have (and be taking medications for) coexistent conditions than a younger population, which can confound assessments of safety and drug-drug interactions. Adverse health-related outcomes due to coexistent disease may be difficult to separate from a complication of the treatment under investigation.

1.1.8. Sex

Recommendation:

1.1.8.1. Males and females with migraine are eligible to participate in clinical trials of acute migraine medications.

Comments:

Migraine is at least three times more prevalent in females than in males (9–12). Special caution should

be taken to avoid enrolling women who may be pregnant or lactating, unless they are the target of the trial. Partners of fertile-age women should practice effective contraception (refer to Section 2.3 for information about menstrual migraine).

1.1.9. Concomitant drug use

Recommendations:

1.1.9.1. Therapies not for migraine. Trials allowing participants to treat conditions other than migraine should pre-specify the permitted uses of concomitant therapies (i.e. open or restricted). The use of contraceptive medication should also be pre-specified. In phase II clinical trials, subjects should not be allowed to treat conditions other than migraine unless pharmacokinetic (PK) and pharmacodynamic (PD) analyses have clearly shown a lack of interactions between the intervention being assessed for migraine and the concomitant therapy. In later development trials (i.e. phase III and IV), the treatment of concomitant and comorbid conditions may be specifically permitted with due precautions.

1.1.9.2. Acute migraine treatment. Investigational treatments should not be administered until at least 48 hours after the use of other acute treatments for migraine, including over-the-counter (OTC) drugs, prescription medications, and medical devices.

1.1.9.3. Preventive migraine treatment. If considered exclusionary, the withdrawal of migraine preventive treatment should be completed and the last dose taken at least 1 month before enrolment. For participants taking preventive drugs with a long half-life, at least five half-lives should elapse before enrolment. When the protocol permits migraine preventive drugs, subjects should be on a stable dose of no more than one preventive agent for at least 2 months before enrolment to ensure a stable baseline.

1.1.9.4. Antipsychotics and antidepressants. People who have used antipsychotics on a regular basis during the 3 months prior to consideration for enrolment should be excluded from phase II clinical trials. Individuals co-medicating with antidepressants may be considered for inclusion.

Comments:

Evaluating the potential for interactions is an important aspect of development prior to approval and marketing, especially in the case of small molecules. The absence of a clear understanding of PK and PD profiles and possible drug-drug and drug-device interactions can obscure the interpretation of treatment effects and adverse events (AEs). Persons with a substance use disorder, as defined by the *Diagnostic and statistical manual of mental disorders, fifth edition* (13), should be excluded from clinical trials. Individuals using cannabinoids to treat migraine attacks should also be excluded because the possible effects on pain can confound outcomes. People known to be generally resistant to acute anti-migraine drugs may bias results if they are overrepresented in a trial population. However, because factors such as inadequate dosing, treating late in the course of an attack, inadequate trial, or frequent relapse may be perceived as drug failure or treatment resistance, investigators should establish the true nature of prior treatment failures before excluding those who report them from participation.

1.2. Trial design

1.2.1. Blinding

Recommendation:

Phase II and III efficacy trials of therapies for the acute treatment of migraine should use a double-blind design.

Comments:

Drugs intended for the acute treatment of migraine attacks can only be reliably evaluated in randomized, double-blind, placebo-controlled trials. Blinding may not be required in long-term safety trials and naturalistic trials.

1.2.2. Placebo control

Recommendations:

1.2.2.1. Interventions under evaluation for the acute treatment of migraine should be compared with placebo.

1.2.2.2. When two presumably active treatments are compared, a placebo control should be included for assay sensitivity.

Comments:

The placebo effect is a genuine psychobiological phenomenon that affects the results of clinical trials across different disease states (14). In trials for the acute treatment of migraine placebo response varies widely, from 6% to 56% for headache relief (15) and from 6% to 25% for pain freedom (16,17). This variability makes it difficult to interpret the results of active comparator trials that do not include placebo. Trials using historical controls or active comparators lack assay sensitivity and require large sample sizes to provide the narrow confidence intervals (CIs) needed to ensure that new drugs are not inferior to controls (18).

In the past, modified designs (e.g. exclusion of placebo responders or sequential parallel designs) to reduce placebo response have proved poorly effective. Nonetheless, particular care should be dedicated to identify and mitigate placebo response risks as much as possible.

1.2.3. Design types

Recommendations:

1.2.3.1. Although both parallel-group and crossover designs may be used, parallel-group designs are preferred.

1.2.3.2. Limited to phase II trials, group-sequential, adaptive treatment, and dose-defining designs may be appropriate.

Comments:

The parallel-group design has the advantage of simplicity. Parallel-group trials have successfully demonstrated both superiority and similarity among treatments. Multiple-attack, parallel-group designs can be used to assess intra-individual consistency of response, although carry-over effects and intra-individual correlation must be taken into account (refer to Section 1.2.12 for information about consistency of response). With crossover trial designs, period and carry-over effects may occur, and complexities may be introduced if the tested treatment has notable side effects. Crossover designs can also be used in multiple-attack trials to estimate intra-individual consistency of response with placebo-control groups (19). In addition, crossover designs allow for the assessment of acute treatment preferences. Subjects who have taken more than one treatment can be asked which treatment they would prefer to take again. Reponses to this question reflect subjects' net assessment of benefits and tolerability (20). Given the popularity of social media, participants in crossover trials should be instructed to refrain from posting about the trial.

Non-traditional clinical trial designs include step-wise, adaptive, enriched designs and futility trials. Adaptive designs allow for the modification of aspects of a trial (e.g. dosing) while in progress without undermining its scientific validity or integrity. For phase II evaluations of optimal dosing, randomised group-sequential, adaptive treatment, dose-defining, proof-of-concept (21–23) and two-stage, adaptive, dose-ranging (24) designs are appropriate. The major advantage of these non-traditional designs is that they allow evaluation of the lowest effective dose and highest tolerated dose over a wide dose range in relatively few subjects. The chosen dose(s) can then be confirmed as optimal in phase III clinical trials.

1.2.4. Randomization

Recommendation:

Subjects enrolled in parallel-group and crossover trials should be randomized at entry to the trial, except when considering adaptive randomization.

Comments:

True randomization is crucial to avoid bias and, in large trials, to contribute to group matching. Block randomization using varying block sizes (e.g. blocks sizes of two, four, six, etc.) may be helpful in preventing participants from guessing treatment assignments.

1.2.5. Stratification

Recommendations:

1.2.5.1. There is usually no need for stratification in acute treatment trials.

1.2.5.2. Stratification may be considered when an imbalance between the treatment groups or an important factor may influence the results of a trial.

Comments:

Randomization alone may not ensure full comparability between subjects in different treatment groups, especially in smaller trials, and stratified randomization is sometimes used to circumvent potential imbalances. The EMA recommends that stratification variables usually be included as covariates in primary analyses, regardless of their prognostic value (25). In controlled trials for migraine, the use of stratification by prognostic factors should be limited to a few variables and only to those that have historically demonstrated effects on primary efficacy endpoint(s). Stratification variables that have been used in acute treatment trials include age, body weight, headache intensity at baseline, migraine type (i.e. with or without aura), menstrual versus non-menstrual attacks, and concomitant preventive treatment (26–28). Given the preponderance of females with migraine, sex may also be used as a stratification factor to control for imbalances in treatment groups.

1.2.6. Intention to treat

Recommendations:

1.2.6.1. Randomized controlled trials of acute treatments for migraine should follow the principle of intention to treat (ITT), which implies that analyses should include all randomised subjects in the groups to which they were randomly assigned, regardless of treatment received.

1.2.6.2. The full analysis set may be modified to exclude subjects from the analysis if no treatment was taken or if no data points after treatment were recorded. A plan should be provided prospectively as to how participants missing the 2-hour endpoint or who treat but do not record data will be handled. Those who treat but do not record data should probably be counted as failures, and those who use rescue medication before the 2-hour time assessment should be counted as failures.

Comments:

The ITT principle encourages, where reasonable, the inclusion of subjects who withdrew, were lost to

follow-up, or did not fully adhere to trial protocol (29). The ITT principle should be adhered to when the primary outcome is a variable that measures a change from baseline to any post-dose time point or to the end of the trial. When the primary outcome is defined as a rate of change, and the analysis will therefore imply a slope or rate of calculation, only subjects who have received at least one dose and recorded at least one data point should be included.

1.2.7. Dose-response curves and dosage

Recommendations:

1.2.7.1. Dose-response curves should be defined clearly in early (phase I and II) randomized, clinical trials of new chemical entities for the acute treatment of migraine.

1.2.7.2. Efficacy- and tolerability-based minimum effective and optimal doses should be determined.

1.2.7.3. Effective doses of a well-established or standard drug should be utilized in comparative clinical trials, unless clinically inappropriate, in which case a clear justification for the particular dose selection should be given.

Comments:

New acute treatments for migraine should be tested against a standard comparator with established dose-response curves and optimal efficacy- and tolerability-based doses, such as rizatriptan, sumatriptan, or zolmitriptan (30–34); the CGRP receptor antagonists (i.e. gepants) ubrogepant and rimegepant (23,35); or the 5-HT_{1F} receptor agonist lasmiditan (22).

The accepted optimal therapeutic dose of the comparator should be used.

1.2.8. Route of administration

Recommendations:

1.2.8.1. When pre-clinical and PK data demonstrate an acceptable PK profile in humans (i.e. good oral bioavailability and rapid oral absorption), oral administration of the test treatment is recommended because the oral route is preferred by most people with migraine (36).

1.2.8.2. Alternative routes of administration, including parenteral, inhalational, buccal, intranasal, and rectal, can be utilized as circumstances dictate (e.g. severe nausea, status migrainosus).

Comments:

Gastric absorption of orally-administered medications can be delayed during migraine attacks (37–40). In early phase I or II trials, therefore, it is advisable to establish the intra- and interictal PK profile of oral treatments utilizing a crossover design in order to gauge dose selection in later efficacy trials.

1.2.9. Timing of administration

Recommendations:

1.2.9.1. The timing of acute treatment should be defined in the trial protocol.

1.2.9.2. Usually, participants are instructed to treat when migraine headache pain is of at least moderate intensity, but alternatives include treating as soon as possible after headache onset, treating when pain intensity is mild, and treating when pain intensity is severe.

1.2.9.3. The timing of acute treatment must be consistent with the objectives of the trial.

1.2.9.4. Subjects should record the time and pain intensity at the time of treatment in the trial diary.

Comments:

The head pain of migraine frequently begins with mild intensity, progressively increases with variable speed to a peak, and is followed by resolution; headache pain can also fluctuate spontaneously during a migraine attack (41). These characteristics can pose challenges regarding the timing of treatment (e.g. early or when the attack is fully developed) and the evaluation of trial results. For example, healthcare providers typically recommend treating early in the course of a migraine attack, while pain intensity is mild, because it can enhance efficacy (18,42,43). At the beginning of an attack, however, migraine without aura can be difficult to distinguish from non-migraine headaches. Thus, subjects in migraine clinical trials who are instructed to treat as soon as possible (i.e. at the first sign of migraine) may mistakenly treat other headache types. The potential for confusion is mitigated when attacks are allowed to fully develop. Having subjects wait until pain intensity is moderate or severe before treating increases the specificity of migraine diagnoses. Yet because this strategy conflicts with common clinical advice about early treatment, it is essential that participants in clinical trials receive clear instruction about when to use acute treatment. In later stages of development, depending on the specific objectives of the program, trials evaluating early intervention and treatment when headache pain intensity is severe (e.g. for early morning migraine (44)) are encouraged when investigating the efficacy, safety, and tolerability of new treatments.

1.2.10. Number of attacks treated

Recommendations:

1.2.10.1. Determining the effect of an acute treatment on the first migraine attack should be the primary objective. The attack to be considered should be clearly specified in the protocol.

1.2.10.2. If multiple attacks are treated, the first treated attack or the attack that will be considered for

assessing the primary objective can be randomly selected.

Comments:

In most clinical trials of acute treatment, the first treated attack will be used in the evaluation of efficacy. Refer to Section 1.2.12 for information about multiple-attack trials addressing consistency of response as a primary objective (45–48).

1.2.11. Rescue medication

Recommendations:

1.2.11.1. The use of rescue medication should be allowed at any time after the first primary efficacy time point, typically 2 hours after the initial administration of treatment.

1.2.11.2. Use of rescue medication before the 2-hour endpoint should be considered a treatment failure unless an earlier time point for rescue was pre-specified in the trial protocol.

Comments:

The time interval to using rescue medication can be reduced when the primary efficacy time point is before 2 hours, which is often the case in assessments of parenteral drugs or trials involving paediatric subjects. Little can be learned from delaying rescue medications beyond the primary efficacy time point. Furthermore, delays may unduly discomfort subjects and prolong the attack and associated disability, which are ethically unacceptable. Rescue medication can be taken before the time of the primary endpoint if subjects require it, but such use should be recorded as a treatment failure.

1.2.12. Consistency of response

Recommendations:

1.2.12.1. Intra-individual consistency of response may be evaluated over multiple attacks in double-blind, placebo-controlled trials.

1.2.12.2. Response to at least four attacks should be assessed, and at least one of the four attacks should be treated with placebo in a randomized fashion.

Comments:

Population-level consistency of response refers to the proportion of treated subjects who achieve a trial endpoint for the first, second, third, or n^{th} treated attack. This is best assessed in randomized controlled trials evaluating multiple attacks (≥ 4) using any of the following three designs. In the first design, all subjects use active treatment for at least three attacks, with placebo in one additional attack, in a randomized order. The second design administers the active treatment for all attacks in most subjects, while a subset uses both active treatment and placebo in a randomized manner for at least four attacks. The third design uses a combined approach, with an initial 1-month double-blind phase (subjects use active treatment or placebo for the first attack) followed by a 1- or 2-month open-label phase, during which subjects treat at least three attacks with the active intervention.

Testing the effect of an acute treatment on several migraine attacks may increase the discriminative power for efficacy when outcome measures are averaged across multiple attacks for each subject, provided that all analysed subjects treat the same number of attacks. Using a generalized estimating equation or random-effects modelling, all treated attacks can be used as a basis for comparison (49,50). Generalized estimating equations control for intra-individual correlation, whereas random-effects models treat each individual as a random effect. However, the increase in analytic power can be counterbalanced by a decrease in the number of subjects completing the trial. Relative to single-attack trials, multiple attack trials have higher dropout rates and may introduce an unmanageable bias if dropouts are related to tolerability issues or lack of efficacy (51,52). Furthermore, repeated intake of placebo when a standard treatment is available raises ethical issues.

Assessing intra-individual and population-level consistency of response has been difficult in long-term safety trials because they rarely include a placebo control and often introduce selection bias when responders from an efficacy trial are carried over (53). Long-term trials should be used to evaluate the development of tolerance (tachyphylaxis).

1.3. Evaluation of results

1.3.1. Attack report form (diary)

Recommendation:

An easy-to-use electronic diary that captures predefined endpoints should be used. Investigator-initiated trials may use paper diaries (54).

Comments:

Headache characteristics and response to treatment are best recorded by means of electronic diaries with time-stamp capabilities. Data for the index attack and the 2-hour time point should be entered in real time. Adverse events may be collected in the diary or during follow-up visits. Serious AEs need to be reported within 24 hours. In settings where electronic diaries are not available (e.g. investigator-initiated trials), paper diaries may be used.

With diaries, the quantity and quality of collected data tend to be inversely proportional. Complicated report forms with detailed description of symptoms may be difficult for subjects to fill out during attacks.

Some trials have been successful using algorithms to ensure that the treated attack is a migraine (55,56).

Familiarization with data capture on the trial diary is important. Subjects can complete the diary report for an attack whilst treating with their usual medication prior to entering the trial, and the data are reviewed at the trial site. Subjects can also be asked to complete the diary at the randomization visit by recalling events of their most recent attack. The latter procedure is preferable because it minimizes delays in trial participation.

1.3.2. Primary endpoint: Pain freedom at 2 hours

Recommendation:

1.3.2.1. The percentage of subjects who become pain free at 2 hours after treatment, before the use of any rescue medication, should be the primary measure of efficacy.

Comments:

Freedom from pain before the use of rescue medication is simple, clinically relevant, reflects patients' expectations (57,58), and is independent of the confounding effects of other therapies (e.g. rescue medication). With respect to the 2-hour time point, it may be argued that because some acute treatments have a slow time to maximum or time to effective plasma concentration, an expectation of pain freedom within 2 hours of treatment is unrealistic. This position runs counter to the principles of Good Clinical Practice (59), which give the highest consideration to subject wellbeing; participants in clinical trials should not be subjected to undue harm, and the use of effective rescue therapies should not be delayed beyond 2 hours. Pain freedom at times before 2 hours should be considered as an endpoint in trials of non-oral treatments (e.g. intravenous, intramuscular, subcutaneous, intranasal).

1.3.3. Co-primary endpoint: Absence of the most bothersome symptom

Recommendation:

Absence of the most bothersome migraine-associated symptom at 2 hours after treatment may be used as a co-primary endpoint.

Comments:

In addition to headache pain, migraine attacks are characterized by a number of associated symptoms, including nausea, vomiting, photophobia, and phonophobia (6). To align outcomes in controlled trials with symptom(s) of clinical significance, it is important to measure the effects of an acute treatment on all these features. For regulatory purposes, the FDA recommends that efficacy analyses in acute trials use as co-primary endpoints the proportion of subjects with no headache pain at 2 hours after treatment and the proportion of subjects with absence of the most bothersome associated symptom (MBS) at 2 hours after treatment (4). The use of the MBS as a co-primary endpoint with pain freedom is an alternative to requesting demonstration of a positive treatment effect on all three migraine associated symptoms; it requires larger sample sizes due to the need to consider the frequency of the symptoms. The MBS endpoint should be selected just prior to study drug administration and measured on a binary scale (present or absent) using either of two suggested methods. One method allows subjects to select the MBS prior to randomization and then treat only an attack that occurs with the pre-specified MBS. The other is to use a time-locked recording device (e.g. an electronic diary) and have subjects record their MBS at the onset of the treated attack and then record the effect on the MBS at 2 hours. The trial protocol should specify which of these approaches will be used by all subjects in a clinical trial.

It should be noted that an effect on associated symptoms is very difficult to achieve in trials investigating early treatment, when headache is mild and associated symptoms may not have appeared yet. Moreover, measuring the elimination of an associated symptom that was not present at the time treatment was taken, especially for less common symptoms (e.g. nausea), substantially increases the required sample size and number of subjects that must be exposed. An alternative approach would be to record the elimination of all associated symptoms at 2 hours after treatment.

1.3.4. Secondary endpoints

1.3.4.1. Relapse

Recommendations:

1.3.4.1.1. Relapse is a secondary treatment failure that is defined as the occurrence of headache of any severity within 48 hours of the administration of an investigational treatment among subjects who were pain free 2 hours after the investigational treatment was administered.

1.3.4.1.2. A time interval of 24 hours may be considered if the treatment under investigation has a short half-life.

1.3.4.1.3. Relapse rates should not be compared across trials, and it is recommended that investigators evaluate the differential rates of relapse in comparative trials only when primary efficacy rates are similar (60).

Comments:

Relapse is a major problem with all effective migraine treatments (61,62), and its incidence should be recorded in all trials. Relapse was previously

known as "recurrence" and defined as initially obtaining pain freedom (refer to Section 1.3.2) or headache relief (refer to Section 1.3.4.5) and subsequently experiencing a moderate or severe headache or using rescue medication (even for mild headache pain) from the time point of primary efficacy and up to 48 hours. The reported incidence of relapse under the older definition varied considerably (e.g. from 6% to 50% with oral triptans (63,64)), and it is expected that estimates will stabilize when analyses are based on the new definition.

1.3.4.2. Sustained pain freedom

Recommendations:

1.3.4.2.1. Sustained pain freedom is defined as the percentage of subjects who are pain free at 2 hours with no use of rescue medication or relapse within 24 or 48 hours of the initial treatment.

1.3.4.2.2. Sustained pain free is a recommended secondary endpoint, and it is the primary endpoint in early intervention trials.

Comments:

Sustained pain freedom is an important measure of migraine treatment response. By integrating initial response, use of rescue medication, and relapse (60,61), the sustained pain-free rate is a more scientifically robust outcome measure than the relapse rate alone. It is therefore recommended over relapse as an endpoint in comparative trials (65). Investigators should be aware that the clinical success of acute treatment may be underestimated when using this narrowly-defined efficacy outcome measure, but it has been useful in comparing triptans (66) and can be useful for non-triptan comparisons. Sustained pain freedom can also be helpful in trials evaluating the use of acute treatment in subjects with mild pain (e.g. early intervention trials).

Sustained relief is a composite efficacy outcome measure based on concepts similar to those of sustained pain-free. It is defined as headache relief (not pain freedom) and absence of relapse or use of rescue medication after the initial response (67). Sustained relief is not recommended as a secondary efficacy outcome measure.

1.3.4.3. Total freedom from migraine

Recommendations:

1.3.4.3.1. The absence of pain, nausea, vomiting, photophobia, and phonophobia at the primary efficacy time point (i.e. 2 hours after treatment in most acute trials) is defined as total freedom from migraine. This endpoint can be used as a secondary efficacy measure.

1.3.4.3.2. Freedom from headache and any migraine-associated symptoms may also be considered.

Comments:

Total freedom from migraine is a combined efficacy measure that addresses pain and associated symptoms. Statistically, it is up to four times more powerful than analyses using four separate co-primary endpoints, as the majority of people with migraine do not exhibit all associated symptoms, and because these endpoints are not necessarily independent (68). In a post-hoc analysis based on pooled data from the rizatriptan clinical drug development program, rates of total freedom from migraine were 35% for rizatriptan and 8% for placebo (68). Rates of total freedom from migraine tend to be discouragingly low and often underestimate the benefits of effective acute treatments.

1.3.4.4. Headache intensity

Recommendations:

1.3.4.4.1. Subjects should note the intensity of headache immediately before the first use of the acute treatment being evaluated and at each subsequent prespecified time point.

1.3.4.4.2. Headache intensity should be measured on a 4-point scale where 0 = no headache; 1 = mild headache; 2 = moderate headache; 3 = severe headache. Alternatively, a 100-mm Visual Analogue Scale (VAS) or an 11-point numerical rating scale (NRS) can be used.

1.3.4.4.3. Collecting data about headache intensity at the primary efficacy time point (e.g. 2 hours) and before any rescue medication use is critical for the analysis of the pain-free primary efficacy outcome measure.

1.3.4.4.4. Headache intensity should be measured at the time of treatment, every 30 minutes until 2 hours after treatment; hourly until 4 hours after treatment; at 12, 24, and 48 hours after treatment; and at the time of relapse.

1.3.4.4.5. If the time course of treatment effect on headache intensity has been established in earlier trials, fewer time points can be used (i.e. 1, 2, and 4 hours after treatment).

Comments:

The ordinal 4-point scale is the preferred instrument for measuring headache intensity. It is easy to understand and use, and it can be employed in association with the VAS or 11-point NRS (54). The VAS has shown a very high level of concordance with the categorical scale (69), and the NRS is responsive and easy-to-use in everyday practice; evidence from trials in other painful conditions suggests that the NRS may offer a higher discriminatory capability than a categorical scale for pain exacerbations (70). Trials evaluating the use of acute treatment for mild pain may use sustained pain free as a primary outcome measure, with pain intensity difference (PID) and sum of pain

intensity differences (SPID) considered as secondary endpoints. Used widely in non-headache pain trials (71) and rarely in trials of acute migraine treatment (72,73), PID and SPID have been shown to yield similar results to a 2-hour pain-free analysis (74), the 4-point scale, and the VAS (75–77).)

1.3.4.5. Headache relief

Recommendations:

1.3.4.5.1. Headache relief (45), defined as the decrease in headache pain from moderate or severe at baseline to mild or none at 2 hours after treatment and before taking any rescue medication (refer to Section 1.2.11), should be used as a secondary efficacy measure.

1.3.4.5.2. A time point before 2 hours after treatment can be used when testing parenteral treatments.

Comments:

Headache relief should be used as an outcome measure, but only as a secondary endpoint and mainly to facilitate comparison of the results of new clinical trials with those of previous programmes (30–32,61,74–78). Since headache relief is associated with relief of disability, it can be used in clinical trials as a proxy for pain improvement and restoration of function. Headache relief is also useful for comprehensive cost of treatment analyses.

In older acute migraine clinical trials, headache relief at 2 hours after treatment was used extensively as a primary efficacy outcome (30,31,45,58,79) based on the suggestion that patients may consider an acute treatment effective while residual headache pain persists (45). The validity of this argument has been challenged by evidence showing that patients do not believe a reduction in headache pain from moderate to mild constitutes success (80) and expect acute treatment to provide freedom from pain (57,58). In addition, the headache relief endpoint assumes that the magnitude of change from severe pain to no pain is clinically equivalent to the change from moderate pain to mild pain, which is not the case (81). Finally, the verbal rating of pain intensity as 0 = none, 1 = mild, 2 = moderate, and 3 = severe assumes it is an interval variable in the absence of clinical validation.

1.3.4.6. Time to meaningful relief

Recommendation:

Time to meaningful relief can be used as a secondary efficacy measure.

Comments:

Time to meaningful relief is most often assessed by subjects using electronic diaries with time-stamp capabilities, which have largely replaced the use of stopwatches (73,75). The time-stamped information improves the precision of time estimates relative to the fixed-interval assessments once commonly used in migraine trials by providing data about treatment response over a clinically relevant period of time instead of at pre-specified time points (e.g. 1, 2, or 4 hours after treatment). Time stamping also allows diary entries for time to meaningful relief to be analysed by powerful statistical methods, such as survival analysis (82,83), that are superior to analyses based on fixed intervals.

1.3.4.7. Time to pain freedom

Recommendations:

1.3.4.7.1. Speed of onset of therapeutic effect can be evaluated using a survival analysis of pain freedom at time points earlier than 2 hours after treatment.

1.3.4.7.2. Time to pain freedom is a recommended secondary efficacy outcome measure.

Comments:

Time to pain freedom is a more exact measure than time to meaningful relief. Ratings of headache intensity at pre-defined time points before 2 hours (e.g. at 10- to 15-minute intervals) can be used to analyse the speed of onset of treatment response. Investigators should be aware that additional data recordings can complicate headache diaries and potentially lead to missing data.

Time-to-event analysis is the most appropriate statistical method to assess speed of onset of therapeutic effect, using no headache when pain freedom is the outcome and mild or no headache when headache relief is the outcome. The difference between two treatments should be expressed as a percentage, and because *p*-value calculations alone can be misleading, 95% CIs should be given in order to better inform readers about the significance of the difference. Time-to-headache relief analyses have been used in previous trials (77,78,84), but early response rates were relatively small. Subcutaneous sumatriptan is an exception (85,86).

1.3.4.8. Duration of attacks

Recommendation:

Duration of attacks should not be used as an efficacy measure.

Comments:

The duration of a migraine attack can be influenced by the effect of treatment, as well as by physiological factors (e.g. sleep) and external variables (e.g. use of rescue medication beyond 2 hours). Since these variables cannot be controlled for in a clinical trial, they prevent an accurate and scientifically sound interpretation of the independent effect of an investigational intervention. The robustness of the pain freedom and

sustained pain freedom outcome measures mitigates the need for attack duration as an efficacy measure.

1.3.4.9. Rescue medication

Recommendations:

1.3.4.9.1. The percentage of patients taking rescue medication 2 hours after intake of the test treatment can be used as a secondary efficacy measure.

1.3.4.9.2. The assessment of rescue use medication can be earlier if the primary outcome measure is specified at a time earlier than 2 hours after treatment.

Comments:

Theoretically, use of rescue medication at the primary efficacy time point reflects a judgement of the inefficacy of the test treatment, but subjects in clinical trials may use rescue medication for conditions other than headache (e.g. anxiety, sleep, or associated symptoms). Rates of rescue medication usage have been found to be as sensitive as 2-hour pain-free rates in some trials (86–88), but not in others (89). The use of rescue medication should not be postponed beyond 2 hours after treatment; its use may be permitted at 1 hour after treatment in paediatric trials and in trials where the primary time point for efficacy is at 1 hour after treatment.

1.3.4.10. Global evaluation

Recommendations:

1.3.4.10.1. Subjects' global impression of acute treatment effect can be used as a secondary outcome measure. Efficacy and tolerability should be evaluated separately.

1.3.4.10.2. A simple Likert-type verbal scale is recommended (e.g. very poor, poor, no opinion, good, very good).

1.3.4.10.3. Investigator's impression of treatment effect should not be used.

Comments:

Subject's global impression of change from baseline — the global impression of an investigational treatment's effect — is one of the most clinically relevant outcomes because it is a composite assessment of treatment effects on headache, associated symptoms, and AEs (tolerability). Several scales, including the Patient Global Impression of Change (PGI-C), have been used to assess global impression of change in migraine trials (22,90–92). Global impression of change is recommended for use in phase III and IV trials, as well as for clinical trials comparing two or more active treatments.

1.3.4.11. Global impact (functional disability and quality of life).

Functional disability and health-related quality of life (HRQoL) are important secondary global measures that account for the impact of headache and associated symptoms, as well as any adverse effects of treatment.

Recommendation:

1.3.4.11.1. Subjects should assess functional disability just before and up to 2 hours after the administration of acute treatment, before the use of rescue medication, using a simple verbal, numerical scale. The following question is recommended: "How well can you function right now?" Response options should be: 0 = no disability (i.e. able to function normally); 1 = mild disability (i.e. able to perform all activities of daily living but with some difficulty); 2 = moderate disability (i.e. unable to perform certain activities of daily living); 3 = severe disability (i.e. unable to perform most to all activities of daily living or requiring bed rest).

Comments:

Disability can be defined as a decrement in any of a range of domains (cognition, mobility, self-care, getting along, life activities, or participation) or as the sum of difficulties, impairment, and decreased productivity in daily activities (93,94); HRQoL refers to the overall effect of illness and its therapy on the perception of the ability to live a useful and fulfilling life, including physical and mental components, general health perception, and level of performance/participation in different roles (95,96). Restoring the ability to function and improving quality of life are among the main objectives of acute migraine treatment (97,98), and the global impact of migraine can be measured by considering functional disability and quality of life. However, it is important that the instruments employed are appropriate for assessing the global effect of treatment on subjects' quality of performance in different roles and daily activities and sense of wellbeing.

Based on previous recommendations in IHS *Guidelines* (2,3), an NINDS-CDE recommendation as supplemental evaluation instrument (54), and continuing use in trials of acute treatment of migraine, the Functional Impairment Scale (FIS) and the Migraine Physical Function Impact Diary (MPFID) are recommended instruments for assessing functional disability (54). A simple numerical scale may be used to evaluate HRQoL, and of the global impact assessment tools used in clinical trials of acute treatment (88,99,100), only the 24-hour MSQoL and Minor Symptoms Evaluation Profile (a self-administered, 24-item instrument that uses a VAS to record perceived symptoms of migraine) are well suited for assessing the impact of acute treatment (101,102).

1.3.4.12. Associated symptoms – nausea and vomiting

Recommendation:

The presence or absence of nausea should be recorded at the time trial treatment is administered and

at the time of assessment of the primary efficacy outcome (e.g. 2 hours).

Comments:

Nausea and vomiting are important associated symptoms of migraine, and acute migraine treatments should demonstrate efficacy against these symptoms. Nausea and vomiting can also complicate treatment when they occur as AEs, and therefore these variables should be recorded for at least 24 hours after treatment. When interpreting data about nausea or vomiting, investigators should consider that they can be attributed to (a) treatment efficacy effects; (b) treatment-induced adverse effects (i.e. treatment-emergent nausea or vomiting); and (c) use of rescue medication for nausea or vomiting when applicable. Finally, it is important to rate the severity of nausea in trials that include antiemetics, either alone or in combination with other treatments. A simple 4-point categorical verbal/numerical scale (e.g. 0 = none, 1 = mild, 2 = moderate, or 3 = severe) can and has been used (103–105).

1.3.4.13. Associated symptoms – photophobia

Recommendation:

The presence or absence of photophobia should be recorded before treatment is administered and at the time of assessment of the primary efficacy outcome (2 hours).

Comments:

Photophobia is very commonly associated with migraine attacks and can be disabling. Similar to nausea and phonophobia, the effect of an acute treatment of migraine on photophobia should be evaluated in migraine clinical trials. A simple assessment such as presence or absence of photophobia is practical, although verbal scales of severity can be used (e.g. a 4-point scale where 0 = none, 1 = mild, 2 = moderate, and 3 = severe) (105). The presence or absence of photophobia should also be recorded at 4, 8, 12, 24, and 48 hours post-dose.

1.3.4.14. Associated symptoms – phonophobia

Recommendation:

The presence or absence of phonophobia should be recorded before treatment is administered and at the time of assessment of the primary efficacy outcome (e.g. 2 hours).

Comments:

Migraine-associated phonophobia can be disabling. Similar to nausea and phonophobia, the effect of an acute migraine treatment on photophobia should be evaluated in clinical trials. A simple assessment, such as presence or absence of phonophobia, is practical although verbal rating scales of severity can also be used (e.g. a 4-point scale where 0 = none, 1 = mild, 2 = moderate, and 3 = severe) (105). The presence or absence of phonophobia should also be recorded at 4, 8, 12, 24, and 48 hours after treatment.

1.3.4.15. Time between onset of headache and intake of treatment

Recommendation:

Both timings should be recorded.

Comments:

The time interval between the onset of headache and the use of an acute treatment is important for trials investigating the efficacy of early intervention (refer to Section 2.2 for information about early intervention).

1.3.4.16. Treatment preference

Recommendation:

Subjects' acute treatment preference is a useful exploratory and hypothesis-generating global assessment method (20,106–108) that is best suited for crossover trials.

Comments:

Treatment preference is a subjective assessment that considers treatment benefits and tolerability factors (109). It can be used to compare a new acute treatment with subjects' usual treatment prior to the trial or, in a crossover trial, preference among treatments (20). Past clinical trials have used a questionnaire with preference scores graded from 0 to 5 (110,111). Reported preferences in clinical trials of acute migraine treatments have been difficult to interpret because of the heterogeneity in subjects' assessment of the balance between benefits and tolerability issues; some patients prefer a more effective drug or dose at the expense of more AEs, if they are relatively transient and mild, but others are willing to sacrifice a minimal amount of efficacy for a better tolerability profile.

1.3.4.17. Blinding assessment

Recommendation:

It is important to determine how well a clinical trial is blinded.

Comments:

The quality of blinding can be assessed using questionnaires. Indexes are available for the analysis of results (e.g. James' Index or Bang Index (112,113)), though they are not totally free from bias (114).

1.3.4.18. Treatment of relapse

Recommendation:

The efficacy of treatment for headache relapse should be measured by the percentage of subjects

with pain freedom 2 hours after the administration of treatment for headache relapse.

Comments:

Relapse of headache pain of any intensity can be treated with active treatment or placebo in a randomised, double-blind clinical trial. Participants should be re-randomized to active treatment or placebo for the second dose. Measured by the pain relief endpoint, the efficacy of certain acute medications (e.g. oral triptans) is similar whether the primary or the relapsing headache is treated (34,78).

1.3.5. Adverse events

Recommendations:

1.3.5.1. Adverse events that occur during a clinical trial should be recorded contemporaneously in the trial diary.

1.3.5.2. Spontaneous real-time or synchronous reporting of AEs is recommended and should be supplemented by responses to open questions when appropriate.

1.3.5.3. At a minimum, any subject experiencing an AE in a clinical trial of an acute migraine treatment should record event severity (mild, moderate, severe); event seriousness (serious, non-serious); time of onset; and time of resolution, as recommended by the International Conference on Harmonisation's *Guideline for good clinical practice* (59).

Comments:

Adverse events that occur during a clinical trial are not necessarily related to the acute treatment being evaluated (115), and investigators should determine whether any AEs are believed to be treatment-related. Therefore, AEs should be recorded openly (i.e. spontaneously), without *a priori* biases (to detect any unexpected effects), and within 24 hours of intake of acute treatment (to mitigate problems of recall). The recording of AEs should also adhere to the nomenclature and hierarchy of the *Medical dictionary for regulatory activities*. Reports of AEs should include, at minimum, the following for each treatment arm: Subjects with one or more AE; subjects with any serious AE and details of each serious AE, including causation; subjects who withdrew because of AEs; subjects with individual, pre-specified AEs based on *a priori* knowledge, if any, of treatment or class tolerability profiles; severity of specific AEs; and a detailed table of individual AEs. Detailed tabulation of all AEs by organ system is recommended over a listing of only AEs occurring in a pre-specified percentage of subjects (commonly 3–5% or greater) or with a frequency that significantly differs from another treatment arm. Finally, it is worth noting that many regulatory authorities require additional details of trial-related AEs beyond those aforementioned (59,116,117). Commonly used tools for analysing AEs include the chi-square test and Fisher's exact test.

1.4. Statistics

1.4.1. Hierarchy of endpoints. The following hierarchy of endpoints should be adopted for trials investigating the efficacy, tolerability, and safety of interventions for the acute treatment of migraine.

Co-primary endpoints

- Pain-free after 2 hours
- Freedom from the most bothersome symptom at 2 hours

Secondary endpoints

- Supporting the primary endpoints
  - Headache relief at 2 hours
  - Sustained pain-free to 24 hours
  - Total freedom from migraine
  - Freedom from nausea and vomiting, photophobia, or phonophobia
  - Time to pain freedom
- All other endpoints (i.e. tertiary or exploratory endpoints)
  - Intensity of headache
  - Headache relapse
  - Time to meaningful relief
  - Time to pain freedom
  - Rescue medication
  - Global evaluation
  - Global impact (disability and HRQoL)
  - Time between headache onset and treatment intake
  - Preference to treatment
  - Blinding assessment
  - Treatment of recurrence

The recommended co-primary efficacy measures for single-attack trials are the proportion of subjects who are pain-free within 2 hours of treatment and the proportion of subjects who are free from the MBS within 2 hours of treatment. Inferences regarding differences can be assessed using standard statistical methods, such as the chi-square test or Fisher's exact test, assuming there are no baseline imbalances or known potential confounders to account for by Cochran-Mantel-Haenszel. If a baseline imbalance exists between the two groups on any covariates, then analysis may be performed using logistic regression, with subject status as pain-free within 2 hours as a binary outcome of interest (yes, no) and treatment assignment as a primary predictor with inclusion of other pre-specified covariates identified as imbalanced or confounders at baseline.

To properly calculate a sample size, investigators need to take the following four steps, at a minimum: estimate placebo response rates for the primary outcome measure, based on well-founded assumptions and meta-analyses (118); define a clinically relevant difference between active and placebo response rates for the primary outcome measure; establish the *a priori* statistical errors (α- and ß); and determine an acceptable trial power (1-ß) (119). In addition, the appropriateness of an adjustment for multiple comparisons must be considered in trials with more than one primary endpoint. Investigators do not have to limit these adjustments to Bonferroni corrections, as there are various other alternatives available, notably the hierarchical or gatekeeper approach (120,121). Adjustment for multiple comparisons may not be necessary for secondary and tertiary endpoints. The required sample size may be much larger if the goal of the trial is to establish non-inferiority or equivalence (122). Investigators need to pre-specify acceptable limits for such considerations.

Standard statistical methods can also be used for analysis of assessment measures in crossover and parallel-group trials. In addition to formal hypothesis testing and reporting of *p*-values, CIs for differences between an active treatment and placebo and between two active treatments (123) are strongly recommended to inform readers more fully of the meaning of the results of the trial (124,125). A statement that two drugs are equally effective without giving CIs is unacceptable. Time to event (pain-free) analyses (126) or time to meaningful relief analyses can be performed using Kaplan-Meier survival curves or Cox proportional hazard regression methods to compare the onset of action of two active treatments. Trials that collect data from multiple attacks within a subject or collect data at multiple time points may need to use a repeated measures or generalized estimating equations approach.

The statistical analysis plan needs to specify handling of missing data, with proper justification behind the choice of approach(es) for imputation. Investigators should refer to the guidelines of the agency or agencies funding the trial for information on how to handle missing data.

Trials collecting intra-individual data at multiple time points may benefit from using a slope analysis, which does not require imputation for missing data. With this method, slope for each subject can be estimated using data collected over time by fitting a regression line. The slope estimates then become the outcome of interest and allow the use of available data without the need for any imputation, provided that at least one post-baseline data point is available; they can be summarized as mean (standard deviation), and 95% CIs can be reported. For randomized controlled trials, slope estimates between treatment arms can be compared using a 2-sample t-test or a Wilcoxon rank sum test. If a baseline imbalance exists between treatment groups on any covariates, then a regression analysis may be performed.

2. Special issues

2.1. Migraine with aura

Many people who have migraine without aura also have attacks of migraine with aura (7). Both attack types have, in most cases, similar headache features and associated symptoms, and they may share the same basic pain mechanisms. So far, no treatment has been shown to be effective when administered in the aura phase, either for reducing the duration of the aura or preventing the subsequent headache; in separate assessments of acute treatment given during the aura phase, sumatriptan 6 mg SC and eletriptan 40 mg oral tablets had no effect on the aura or the headache (127,128).

The main challenge in clinical trials focused on subjects who have migraine with aura is diagnostic accuracy. The current ICHD classification (10) recognizes the main type, migraine with typical aura (group 1.2.1), as well as variants for typical aura followed by migraine headache, typical aura followed by non-migraine headache, and aura not followed by headache. Since most acute treatment trials are carried out in mixed populations – subjects who have migraine with aura, subjects who have migraine without aura, and subjects who have attacks of both migraine types – investigators cannot determine whether both types of attacks occurring in the same subject have similar or different responses to treatment unless each attack is separately classified as migraine with aura or migraine without aura. Therefore, a detailed recording of each aura symptom and the total duration of the aura is mandatory, and these should be based on uniform requirements (129). To improve accuracy and ensure that response to migraine-associated aura is being evaluated, diagnostic and treatment diaries capable of recording specific aura symptoms and duration of aura should be used (130). With these specialized instruments, an observation of blurred vision or visual snow (131), which might be mistaken for aura with a standard diary, would not be enough to classify an attack as migraine with aura (132). Note that in trials designed to assess treatment of the aura phase, detailed instruction about the proper use of diaries is mandatory.

Additional challenges hindering clinical trials for the acute treatment of aura include the low incidence and

relatively short duration of aura, together with the high inter-individual variability of aura characteristics (133,134). The adoption of alternative trial designs may help to overcome these challenges and the consequent lack of specific treatments for migraine-associated aura. As a first step, the trial protocol should clearly state if the objective is to abort or reduce the length of the aura or to reduce or eliminate the headache, as these are distinct outcomes that most likely have different neurobiologies. It should also specify that participants have a history of at least one aura or attack of migraine with aura per month. In trials where the expected effect of treatment is to prevent the headache phase, the primary efficacy endpoint should be the number of headaches following the aura, with pain freedom after 2 hours a secondary efficacy measure. When the focus is on headache prevention in migraine with aura, a feasible compromise can be aura followed by headache in at least 80% of the attacks. In trials where aura is the event of interest, the primary efficacy measure should be the duration of the aura.

2.2. Early intervention

To facilitate migraine diagnosis and assess whether acute treatment will be effective when headache intensity is moderate or severe, subjects in clinical trials are often required to wait until headache pain is of at least moderate intensity before they treat an attack (45). This is not how migraine attacks are treated in clinical practice, where early intervention may be the most effective acute treatment strategy. With many oral triptans, for example, early intervention has been shown to lead to a higher percentage of pain-free responses at 2 hours after treatment than traditional administration (i.e. when headache intensity is moderate or severe) (135): 57% versus 43% for zolmitriptan 2.5 mg (136), 68% versus 47% for eletriptan (137), 53% versus 38% for almotriptan 12.5 mg (43), 58% versus 32% for sumatriptan 100 mg (138,139), and 66% versus 44% for rizatriptan 10 mg (140,141)). Early treatment while pain is mild has been associated with higher pain free rates for non-triptan acute treatments as well.

2.2.1. Design. Early intervention trials were once characterized by wide variations in methodology and design and important differences in the definition of an early intervention. As the time of treatment (how soon after onset treatment is taken) and headache intensity (treatment is taken when pain is mild) are not necessarily interchangeable (142), early intervention should be defined as the administration of treatment when pain intensity is mild and within 1 hour of headache onset. By this definition, individuals with headaches predominantly occurring at night or on waking in the morning, as well as those who experience more than one headache type and who are not able to differentiate migraine from other headaches, should be excluded from early intervention trials.

The specifics of an early intervention design depend on the purpose of the trial. If its objective is to show that a drug is more effective than placebo when treating early in the mild phase (138), then a traditional parallel-group comparison or crossover design can be used (refer to Section 1.2.3 for more information about design types). However, if its objective is to show that early treatment (when pain is mild) is more effective than late treatment (when pain is moderate/severe), the theoretically ideal design would be a multiple crossover trial in which the same subject treats four attacks (early intervention with placebo, early intervention with active, late intervention with placebo, and late intervention with active) in randomized order. Because a trial using this design would be complex, an acceptable option would be a design used by Goadsby et al. (43), in which subjects in four parallel arms (early intervention with placebo, early intervention with active, late intervention with placebo, and late intervention with active) treat a single attack. Another suitable alternative would utilize a two-arm parallel design, with treatment arms allocated to early intervention and late intervention, and subjects treating two attacks (one with placebo and one with active) in a randomized order.

2.2.2. Endpoints. The primary efficacy endpoint in early intervention trials should be pain-free at 2 hours after treatment. However, as the aim of early intervention trials is also to evaluate efficacy on pain progression, sustained pain-free to 24 or 48 hours (refer to Section 1.3.4.2) should be used as a co-primary endpoint. The number of protocol violators (subjects assigned to treat mild headache who treat moderate-severe and vice versa) in early intervention trials can be substantial (43). As protocol violators, these subjects can be excluded from the ITT analysis, but there is a risk that analysis of the smaller sample will not be sufficiently powered to detect treatment effects. An acceptable alternative is to reassign these subjects to their actual treatment groups, as long as the re-allocation is done before the blind is broken.

2.3. Menstrual migraine

In menstruating females, the peak incidence of migraine occurs in the interval beginning 2 days before and extending through the first few days of menstruation (143). The Appendix of ICHD-3 provides criteria for

pure menstrual migraine and menstrually-related migraine. For both disorders, attacks occur on days −2 to +3 of menstruation in at least two out of three menstrual cycles (6). For pure menstrual migraine, attacks occur at no other time of the month, while in menstrually-related migraine attacks may occur at other times (6). Pure menstrual migraine is less common than menstrually-related migraine; in one study, only 7% of females had pure menstrual migraine while 34.5% had menstrually-related migraine (144).

Migraine attacks occurring in association with menstruation are generally noted to be severe, of long duration, and associated with higher relapse rates (145,146). Acute treatment trials might therefore investigate the efficacy of a new therapy by comparing its rate of relapse with those of standard treatments in subjects with menstrually-related migraine, pure menstrual migraine, or both conditions. If the effect of an acute treatment on pure menstrual migraine is to be investigated, accurate diagnosis is essential; it is recommended that subjects record migraine attacks and menstrual periods prospectively in a headache dairy for two to three cycles before entering the trial and that investigators apply the strict definition provided above to distinguish them from subjects with menstrually-related migraine. Three months of prospective diary information may be needed to be certain of the diagnosis (147). If the aim is to assess the effect of a treatment on menstrually-related migraine attacks, it is recommended (but not mandatory) that randomized subjects report menstruation in the headache diary, treating at least one menstrually-related attack with the test treatment. In either population, subjects need careful instruction on allowable limits for the temporal relationship between the migraine attack and the first day of menstruation. The primary efficacy measure should be the percentage of subjects who achieve freedom from pain at 2 hours after treatment (refer to Section 1.3.2), but in subjects experiencing these often long-lasting attacks with a high risk of recurrence, sustained pain-free (refer to Section 1.3.4.2.) is also an important measure.

2.4. Children and adolescents

Migraine attacks are usually short-lasting in children and adolescents, and the placebo response tends to be high. The IHS is developing a separate set of recommendations for clinical trials of acute treatment of migraine attacks in children and adolescents.

2.5. Recruitment

Investigators should recruit widely from the population expected to use the acute treatment being evaluated. For example, all individuals being treated for migraine at speciality clinics and primary care facilities should be considered for enrolment in clinical trials, as long as they meet eligibility criteria. Recruitment for phase II clinical trials may be more readily conducted in speciality clinics (where appropriate safety resources exist), whereas trials investigating generic or OTC drugs should try to recruit subjects from pharmacies and primary care facilities, as well as via newspaper advertisements. The inclusion of people who habitually participate in migraine clinical trials is discouraged. It is also recommended that investigators establish a database of the number of migraine trials of any kind in which a particular subject has participated in the 2 years preceding a clinical trial. Subject participation in earlier trials should be recorded and presented in the publication. Recruitment efforts and strategies should also be disclosed in the publication.

2.6. Publication

Publication of trial results is necessary and should include all primary and secondary efficacy endpoints and all safety data, whether positive or negative. Before any trial-related activities are initiated, a Steering Committee (refer to Section 2.9 for details) should agree on timelines for publication and, if possible, include them in the protocol; a Publication Committee may also be formed. At the initiation of the trial or at the end of recruitment, a design paper with baseline data may be published. Authorship of trial-related publications should be based on the criteria of the International Committee of Medical Journal Editors (148).

2.7. Conflicts of interest

To maintain the credibility of a trial, authors must declare their conflicts of interest. A conflict of interest exists whenever professional judgment concerning a primary interest (e.g. subject wellbeing or the validity of research) may be influenced by a secondary interest (e.g. financial relationship to a trial sponsor). Financial relationships that represent potential conflicts of interest include employment, consultancies, research grants, fees and honoraria, patents, royalties, stock or share ownership, and paid expert testimony. Investigators should avoid agreements with sponsors, both for-profit and non-profit, that restrict access to trial data, limit its analysis and interpretation, or interfere with the independent preparation and publication of manuscripts. Note that conflicts of interest extend to an investigator's immediate family (partner and children).

2.8. Independent data safety monitoring board

An independent data safety monitoring board and predefined stopping rules for futility or safety are recommended

for phase III trials. Independent interim analysis by the data safety monitoring board should be considered for assessment of the pre-defined stopping rules.

2.9. Steering committee

For phase III trials sponsored by industry, the formation of a Steering Committee comprised of academics, statisticians, and (if appropriate) company representatives is recommended. For investigator-initiated trials (i.e. developed and sponsored by independent investigators or academia), a Steering Committee is not necessary. Whether or not a committee is formed, investigators and sponsors are responsible for all aspects of a clinical trial, including conception; design; operational execution; data handling; data analysis and interpretation; subsequent reporting and publication; and compliance with all local laws and regulations.

2.10 Trial registration

Prior to the initiation, any trial should be pre-registered in a register acknowledged by regulatory authorities, such as clinicaltrials.gov, clinicaltrialsregister.eu, or a similar regional or national official database.

2.10. Post-approval registries

The IHS recommends post-approval product registries (i.e. prospective open-label observational studies) to evaluate the use of newly approved acute treatments in clinical practice. Registries generate real-world data on long-term efficacy, tolerability, and safety. They also measure compliance and adherence. Registries for acute migraine treatments may also include individuals with relevant coexistent and comorbid diseases (e.g. chronic pain syndromes, cardiovascular disease) who were excluded from clinical trials for acute migraine.

3. Toolbox

Section number	Summary guidance
1.1 Subject selection	
1.1.1 Migraine definition	Use ICHD diagnostic criteria
1.1.2 Other primary headaches	Permitted if infrequent and clearly recognized by the patient
1.1.3 Secondary headaches	Not permitted
1.1.4 Frequency of attacks	2–8 migraine attacks; $\leq$ 1 per month for other headache types (including non-target)
1.1.5 Duration of migraine	$\geq$ 1 year
1.1.6 Age at onset	$<$ 50 years
1.1.7 Age at entry	18–65 years
1.1.8 Sex	Females and males
1.1.9 Concomitant drug use	See text
1.2 Trial design	
1.2.1 Blinding	Use double-blind
1.2.2 Placebo control	Recommended
1.2.3 Design types	Parallel-group and crossover
1.2.4 Randomization	Recommended
1.2.5 Stratification	Generally not necessary
1.2.6 Intention to treat	Should be defined, see text
1.2.8 Route of administration	Oral route is preferable if appropriate for the PK profile
1.2.9 Timing of administration	Should be prospectively defined in the protocol
1.2.10 Number of attacks treated	One, generally the first, see text
1.2.11 Rescue medication	Allowed any time after the first primary efficacy time point
1.2.12 Consistency of response	Evaluate $\geq$ 4 attacks, with $\geq$ 1 treated with placebo
1.3 Evaluation of results	
1.3.1 Attack report form (diary)	An easy-to-use electronic diary that captures predefined endpoints
1.3.2 Primary endpoint	Pain freedom at 2 hours

(continued)

Continued.

Section number	Summary guidance
1.3.3 Co-primary endpoint	Absence of the most bothersome associated symptom at 2 hours
1.3.4 Secondary endpoints	
1.3.4.1 Relapse	Secondary endpoint, see text
1.3.4.2 Sustained pain-free	Secondary endpoint, see text
1.3.4.3 Total freedom from migraine	Secondary endpoint, see text
1.3.4.4 Headache intensity	Secondary endpoint, on a 4-point verbal rating scale
1.3.4.5 Headache relief	Secondary endpoint, see text
1.3.4.6 Time to meaningful relief	Secondary endpoint, see text
1.3.4.7 Time to pain freedom	Secondary endpoint, measured with a survival analysis of pain freedom at time points before 2 hours
1.3.4.8 Duration of attacks	Not recommended
1.3.4.9 Rescue medication	Secondary endpoint, see text
1.3.4.10 Global evaluation	Secondary endpoint, see text
1.3.4.11 Global impact (functional disability and quality of life)	Secondary endpoint, on a 4-point verbal rating scale
1.3.4.12 Associated symptoms — nausea and vomiting	Secondary endpoint, recorded at the time treatment is administered and at the time of assessment of the primary endpoint
1.3.4.13 Associated symptoms — photophobia	Secondary endpoint, recorded at the time treatment is administered and at the time of assessment of the primary endpoint
1.3.4.14 Associated symptoms — phonophobia	Secondary endpoint, recorded at the time treatment is administered and at the time of assessment of the primary endpoint
1.3.4.15 Time between headache onset and treatment intake	Secondary outcome measure
1.3.4.16 Treatment preference	Exploratory and hypothesis-generating global assessment method for crossover trials
1.3.4.17 Blinding assessment	Secondary outcome measure
1.3.4.18 Treatment of relapse	Secondary outcome measure, see text
1.3.4.19 Adverse events	Record and report all events, see text
1.4 Statistics	
1.4.1 Hierarchy of endpoints	Recommended for use in trial design, conduct, and reporting

ICHD, International Classification of Headache Disorders

Clinical implications

- The *Guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults: Fourth edition* provides new information that will affect the design, conduct, and reporting of clinical trials in migraine.
- The current edition supersedes the existing *Guidelines* and should be put to immediate use.

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