

Chapter 17. Headache Disorders

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I. INTRODUCTORY REMARKS

Headache disorders are ubiquitous. Their lifetime prevalence in populations in which it has been measured is over 90%. They are also disabling, and costly.

Migraine manifests in attacks lasting a few hours to three days, with a median frequency of one per month. It has a 1-year prevalence of 12-15% throughout Europe and in North and South America. In other parts of the world there is gathering evidence of similar prevalence. In Japan it is estimated to affect 8.4% of the adult population. Elsewhere in the Far East, surveys of representative samples of the general population are difficult; prevalence and impact, which have been thought to be lower, may be underestimated. In an American survey 80% of people with migraine reported some degree of disability because of it and globally, according to WHO's *World Health Report 2001*, migraine is 19th in the list of all causes of years lived with disability. Because migraine affects people particularly during their productive years, its economic impact is high. Additionally, as well as suffering directly from its symptoms, people with migraine consistently score highly on scales of general physical and mental ill-health.

Tension-type headache is the most common headache disorder. Most is episodic, with occasional attacks lasting hours of what sufferers often describe as "ordinary headache". In its chronic and much more disabling sub-type, on the other hand, it is present on more days than not. **Chronic tension-type headache** overlaps with and is sometimes indistinguishable from other forms of **chronic daily headache**, some of which are unrelentingly present throughout every day. Estimates of the prevalence of this group of conditions in Europe and USA are as high as 1 in 25 of the *entire* adult population. Such frequent headache is associated with long-term morbidity and disability.

Cluster headache has a lower prevalence (lifetime about 0.07%) and at any given time most people with the disorder are not in a cluster period. It is unique amongst the primary headache disorders in affecting men more than women (about 6:1). Typically occurring in bouts of a few weeks each year with periods of full remission between, it is characterised by frequent (daily or more often) short-lasting (15-120 minutes) but excruciating unilateral localised frontal or periorbital pain accompanied by marked but similarly localised autonomic symptoms. In its rarer chronic sub-type there are no periods of remission.

The financial cost of headache arises partly from direct treatment costs but, to a much greater extent, from consequential losses: work time and productivity losses are by far the largest elements. That these costs remain high throughout the world is evidence of treatment failure, a problem attributable in part to the fact that available drugs fall well short of being ideal treatments for any of these headache disorders. In another important part, it is due to the low priority generally given to headache in the queue for health-care resource allocation.

Drugs are therefore required that are not only more effective but also shown to be cost-effective in the relief of headache. Surprisingly, pharmacoeconomic studies in this area are in their infancy. Whilst research is needed to derive simple agreed cost-of-illness measures that adequately capture those aspects of cost that matter to patients, time is an important casualty of headache and time losses (and their reduction by effective treatment) should be relatively easy to measure.

Amongst the primary headaches, only migraine has benefited substantially from recent pharmaceutical investment. The result has been the marketing since 1991 of seven triptans, a class of drug which has unquestionably moved forward the acute treatment of migraine whilst proving to be of some value, albeit limited, in cluster headache also. Yet triptans are far from being 100% efficacious, and they are not universally tolerated. Whilst much current research concentrates on head-to-head comparisons between triptans, invariably showing minor differences, development of new drug classes may have stalled. Meanwhile, symptomatic treatments (analgesics and anti-emetics) remain very useful in acute migraine

therapy. They are still the mainstay of treatment of migraine in children and for many adults, including those for whom triptans are not appropriate, and they are the only option in the large parts of the world that new and relatively expensive drugs do not penetrate. They are, generally, the first-line treatments for tension-type headache.

The triptan successes displaced interest from preventative studies. For all primary headache disorders, prophylactic drugs now available are, at best, of quite limited value.

Clearly there is much unfulfilled therapeutic need in all of these areas requiring further clinical research. For pharmaceutical companies, potential markets are very large indeed although experience shows that the greater part of these is not easily penetrated on the basis of efficacy studies alone.

II. PHASE II STUDIES FOR REGISTRATION OF NEW DRUGS

II.1. Outline of a typical development plan

Whilst the requirements differ for migraine, tension-type headache and cluster headache, and in each of these for acute and preventative therapies, there are general principles applying to all.

During phase II, candidate drugs are assessed for efficacy against placebo. Randomised controlled trials will follow pharmacokinetic studies. For drugs intended for the acute treatment of migraine, pharmacokinetic studies must be conducted during the attack because absorption may be delayed by gastric stasis. For this reason oral administration, though preferred by most patients, is not ideal in acute migraine: early proof-of-concept studies may use parenteral therapy if there is doubt about rapid bioavailability by the oral route and alternative routes may anyway be required in severely nauseated or vomiting patients. Cluster headache attacks typically have duration of 15-120 minutes; rapid bioavailability is needed if treatment is to have worthwhile effect, and this is unlikely to be achieved by the oral route. Phase II must address formulation issues.

Recent experience in migraine has shown that phase II often needs to incorporate dose-finding studies, and the EMEA now require to know both the lower end of the clinically effective dose range and the optimal dose(s) (inter-individual variation may be high enough that a range of doses should be marketed). Typical studies will be double-blind, involving one or up to three or more doses. They may use parallel-groups or (multiple) cross-over designs, with regulators generally favouring the former.

Regulators have not so far distinguished, for drug-development purposes, between episodic tension-type headache and other causes of mild-to-moderate pain.

Acute-treatment trials in phase II usually allow the treatment of a single attack. Attrition rates tend to be high between attacks (one of the arguments against cross-over designs).

Prophylactic trials must allow time for dose-titration (if needed) and then time for effect to develop and be measurable, usually requiring a minimum of three months' treatment for migraine or chronic tension-type headache. The objectives of treatment in these two disorders are not identical: migraine prophylaxis is intended to reduce the frequency of continuing attacks; in chronic tension-type headache the intent is to cause reversion to the episodic subtype. Patients with cluster headache, where use of placebo as a control may be difficult, will expect rapid and obvious efficacy achieving attack suppression or, ideally, attack cessation. Furthermore, in episodic cluster headache, spontaneous remission of the cluster period attenuates a trial's ability to detect true treatment benefits. Any need for a period of dose-titration to balance efficacy and tolerability is a significantly complicating factor in cluster headache trial design. Long-term continuation protocols in cluster headache are not part of phase II.

Most headache disorders are appropriately treated in primary care and arguably that is where studies should be done, but this may not be true of phase II. Nevertheless, at this stage of development patients should be selected who are typical of the disorder, particularly avoiding those with complicated or refractory presentations who tend to accumulate in specialist headache centres. Exclusion criteria commonly markedly constrain recruitment, and in most cases multiple centres are needed to reach recruitment targets within reasonable timeframes.

Pharmacokinetic interactions between the test agent and other drugs likely to be taken in clinical practice should be evaluated early on. The majority of headache patients are women of child-bearing potential so oral contraceptives are important amongst these. Teratogenicity should also be assessed early: not only will teratogenic drugs be of little value in headache but also, with the notable exception of cluster headache, it is extremely difficult to recruit to headache studies if women of child-bearing potential must be excluded.

II.2. Short term studies

II.2.i. Acute treatment of migraine

II.2.i.A. Objectives

To evaluate efficacy in relieving symptoms of the acute attack.

II.2.i.B. Primary end-point

- a. “Pain-free” rate: percentage of patients pain-free at 2 hours after treatment.

II.2.i.C. Secondary endpoints

- a. “Headache-relief” rate: percentage of patients with a decrease in headache intensity from severe or moderate to mild or no pain within 2 hours after treatment (this was widely adopted as the primary end-point in past studies and remains important in phase II for purposes of comparison).
- b. Percentage of patients pain-free at 2 hours and remaining pain-free, without use of further medication, for 48 hours after treatment.
- c. Rate of relapse, defined as the return of headache of any intensity within 48 hours in patients pain-free at 2 hours after treatment.
- d. Headache intensity at various time points after treatment.
- e. Functional disability on a validated scale (usually a 4-point verbal rating scale where 0 = no functional impairment, 1 = “can do everything albeit with difficulty”, 2 = “cannot do some things” and 3 = “cannot do anything and/or bed-bound”) at 2 hours and other time points after treatment.
- f. Effect on associated symptoms such as nausea, vomiting, photophobia and phonophobia.
- g. Rate and timing of use of rescue medication.
- h. Incidence and nature of adverse events.

II.2.i.D. Study design

These are invariably short-term studies. Recommended are randomised, double-blind, placebo-controlled parallel-groups studies treating one attack per patient. Three-arm trials, including placebo, are required for internal validation in active-comparator studies because of the large and highly variable placebo effect in migraine studies. In general, there is no need for stratification. Treatment may, depending on its nature, require the patient to attend a treatment facility such as the doctor’s office or be taken by the patient at home or wherever he or she may be. The former is logistically difficult. In the latter case, outcome variables are usually recorded by the patient in paper or electronic diaries, with prompts at various time points. Rescue medication should be allowed after 2 hours (for this reason, attack duration is not considered a useful secondary endpoint). The observation period after treatment of an attack should be 48 hours. Outpatients should return for final review soon after this.

II.2.i.E. Planned sample

Sample size calculations should be based on demonstrating superiority over placebo in a primary analysis of difference in pain-free rates, with an absolute difference of 20% being clinically significant and allowing for a placebo rate of up to 20%.

II.2.i.F. Study population

Adults with migraine with or without aura.

II.2.i.G. Specific inclusion criteria

- a. Patients with migraine conforming to IHS diagnostic criteria 1.1 or 1.2 for at least 1 year and with at least 3 months' well-documented retrospective history.
- b. Migraine attacks occurring 1-6 times monthly.
- c. Males and females.
- d. Unless otherwise justified, patients should be over 18 years of age.

At the time of treatment:

- a. An acute attack, usually with onset within the previous 12 hours.
- b. At least 48 hours since resolution of the previous attack.
- c. Headache of moderate or severe intensity.
- d. So far untreated.

II.2.i.H. Specific exclusion criteria

- a. Age at onset of migraine of 50 years or over.
- b. Other headaches not well distinguished from migraine or occurring with such frequency as to interfere with assessments (usually taken to mean occurring on >6 days/month).
- c. Other illnesses likely to interfere with assessments.
- d. Use of migraine prophylactic drugs in the previous month.
- e. Use of or requirement for other unacceptable concomitant therapy.
- f. History of drug or alcohol overuse.

II.2.i.I. Tools for assessing endpoints

Paper or electronic diaries, with prompts at various time points.

II.2.i.J. Data analysis method

In early efficacy studies, explanatory (per protocol) analysis may be appropriate. It is unhelpful at this stage to include patients with major protocol violations. Standard statistical methods are appropriate. Adverse events are usually analysed descriptively.

II.2.ii. Acute treatment of episodic tension-type headache

II.2.ii.A. Objectives

To evaluate efficacy in relieving pain and functional impairment attributable to acute episodic tension-type headache.

II.2.ii.B. Primary end-point

- a. "Pain-free" rate: percentage of patients pain-free at 2 hours after treatment.

II.2.ii.C. Secondary endpoints

- a. Headache intensity (scored on either a visual analogue scale or a 4-point verbal rating scale [0 = no pain; 1, 2, 3 = mild, moderate, severe pain]) at 2 hours and other time points after treatment.

- b. Headache intensity difference (the arithmetic change from baseline in headache intensity score) at 2 hours and at other time points after treatment.
- c. Headache relief (on a verbal rating scale from “none” to “complete”, with two or more intermediaries which may include “meaningful relief”; negative scores may be incorporated to indicate worsening) at 2 hours and at other time points after treatment.
- d. Functional disability on a validated scale (*e.g.*, a 4-point verbal rating scale where 0 = no functional impairment, 1 = “can do everything albeit with difficulty”, 2 = “cannot do some things” and 3 = “cannot do anything and/or bed-bound”) at 2 hours and other time points after treatment.
- e. Rate and timing of use of rescue medication.
- f. Incidence and nature of adverse events.

II.2.ii.D. Study design

These are invariably short-term studies. Recommended are randomised, double-blind, placebo-controlled parallel-groups studies treating one attack per patient. Three-arm trials, including placebo, are required for internal validation in active-comparator studies because of the very large placebo effect reported in acute episodic tension-type headache studies. There is no need for stratification. Treatment is taken by the patient at home or wherever he or she may be. Outcome variables are usually recorded by the patient in paper or electronic diaries, with prompts at various time points. Rescue medication should be allowed after 2 hours. The observation period after treatment should be at least 24 hours. Patients should return for final review soon after this.

II.2.ii.E. Planned sample

Sample size calculations should be based on demonstrating superiority over placebo in a primary analysis of difference in pain-free rates, with an absolute difference of 20% being clinically significant and allowing for a placebo rate of up to 50%.

II.2.ii.F. Study population

Adults with episodic tension-type headache drawn (by advertising if necessary) from the general population (this is not a disorder that usually causes medical consultation; if it does, this is probably because of complicating factors or comorbidity).

II.2.ii.G. Specific inclusion criteria

- a. Patients with frequent episodic tension-type headache (occurring on >1 but <15 days per month) conforming to IHS diagnostic criteria 2.2 for at least 1 year and with at least 3 months’ well-documented retrospective history.
- b. Usual headache duration at least 4 hours.
- c. Males and females.
- d. Unless otherwise justified, patients should be over 18 years of age.

At the time of treatment:

- a. An acute episode of tension-type headache, usually with onset within the previous 12 hours.
- b. Headache of at least moderate intensity.
- c. So far untreated.

II.2.ii.H. Specific exclusion criteria

- a. Age at onset of tension-type headache of 50 years or over.
- b. Chronic tension-type headache.
- c. Other headaches, especially migraine and medication-overuse headache.
- d. Other illnesses likely to interfere with assessments.
- e. Use of prophylactic drugs in the previous month.

- f. Use of or requirement for psychotropic medication or other unacceptable concomitant therapy.
- g. History of drug or alcohol overuse.

II.2.ii.I. Tools for assessing endpoints

Paper or electronic diaries, with prompts at various time points.

II.2.ii.J. Data analysis method

In early efficacy studies, explanatory (per protocol) analysis may be appropriate. It is unhelpful at this stage to include patients with major protocol violations. Standard statistical methods are appropriate. Adverse events are usually analysed descriptively.

II.2.iii. Acute treatment of episodic or chronic cluster headache

II.2.iii.A. Objectives

To evaluate efficacy in aborting or suppressing the acute attack.

II.2.iii.B. Primary end-point

- a. “Aborted attack” rate: percentage of patients in whom the attack is effectively stopped (headache intensity reduced to mild or no pain) within a prescribed time interval (which may be as short as 10 minutes).

II.2.iii.C. Secondary endpoints

- a. Time to meaningful relief.
- b. Time to “complete” relief (mild or no pain).
- c. Rate of relapse, defined as the return of headache of moderate or greater intensity within 1 hour in patients reporting an aborted attack.
- d. Rate and timing of use of rescue medication.
- e. Incidence and nature of adverse events.

II.2.iii.D. Study design

The dramatic nature of cluster headache attacks and low placebo-response rates make open and single-blind trials informative as pilot studies. Formal comparisons with placebo must follow. These are invariably short-term randomised, double-blind, placebo-controlled studies with parallel-groups or cross-over design. The latter may be preferable in this disorder since patients are uncommon but attacks occur with high frequency. In phase II, episodic and chronic cluster headache should probably be separated; if they are not, stratification is recommended in parallel-groups studies because responses to treatment may differ. Stratification for gender is also recommended for the same reason. Each patient should treat or be treated for one attack with study medication. Treatment may, depending on its nature, require the patient to be admitted to hospital, or attend a treatment facility such as the doctor’s office at a time when an attack is anticipated, or it may be taken by the patient at home or wherever he or she may be. Outcome variables are usually recorded by the doctor or patient in paper or electronic diaries, with prompts at various time points. Rescue medication should be allowed after the time prescribed for the primary end-point, but options for this are very limited. The observation period after treatment of an attack should be not less than 24 hours unless interrupted by the occurrence of the next attack. Outpatients should return for final review within 2 days.

II.2.iii.E. Planned sample

Sample size calculations should be based on demonstrating superiority over placebo in a primary analysis of difference in aborted-attack rates. Placebo-response rate is low but, because of the short attack-duration, spontaneous remission rates may be high; the two may combine to 50%. An absolute difference of 25% is clinically significant.

II.2.iii.F. Study population

Adults with episodic or chronic cluster headache.

II.2.iii.G. Specific inclusion criteria

- a. Patients with episodic or chronic cluster headache conforming to IHS diagnostic criteria 3.1 or 3.2; patients with episodic cluster headache should be in at least their second cluster period.
- b. Acute attacks occurring between once every 2 days and 5 times per day.
- c. Attack duration of 30-180 minutes.
- d. Males and females.
- e. Unless otherwise justified, patients should be over 18 years of age.

At the time of treatment:

- a. An acute attack, usually with onset within the previous 15 minutes (at least 15 minutes before expected spontaneous resolution).
- b. At least 1 hour since resolution of the previous attack and 24 hours (or 5 half-lives if longer) since the latest previous use of study drug.
- c. Headache of moderate or greater intensity.
- d. So far untreated.

II.2.iii.H. Specific exclusion criteria

- a. Other headaches not well distinguished from cluster headache.
- b. Other illnesses likely to interfere with assessments.
- c. Concurrent use of prophylactic drugs for cluster headache.
- d. Use of or requirement for other unacceptable concomitant therapy.
- e. History of drug or alcohol overuse.

II.2.iii.I. Tools for assessing endpoints

Paper or electronic diaries, with prompts at various time points.

II.2.iii.J. Data analysis method

In early efficacy studies, explanatory (per protocol) analysis may be appropriate. It is unhelpful at this stage to include patients with major protocol violations. Subgroup analyses (for episodic and chronic subtypes and for gender differences) are recommended and should be specified *a priori*. Standard statistical methods are appropriate. Adverse events are usually analysed descriptively.

II.3. Long term studies

II.3.i. Migraine prophylaxis

II.3.i.A. Objectives

To evaluate efficacy in migraine-attack prevention.

II.3.i.B. Primary end-points

- a. Frequency of attacks per specified unit time (usually 4 weeks) measured during treatment after a specified period (usually 8 weeks).
- b. Response rate: percentage of patients with frequency reduction of 50% or more after a specified treatment period.

The number of attacks should be recorded irrespective of their duration, and the following rules distinguish an attack of long duration from two attacks and between attacks and relapses:

- a. A migraine attack which is interrupted by sleep, or which temporarily remits spontaneously and then recurs within 48 hours after its onset, should be recorded as one attack and not two.
- b. An attack treated successfully with medication but with relapse within 48 hours counts as one attack.

II.3.i.C. Secondary endpoints

- a. Frequency of attacks over the entire treatment period.
- b. “Migraine days” (defined as any day on which symptoms of migraine are present) per 4 weeks.
- c. Intensity of migraine headache averaged over attacks within a specified evaluation period.
- d. Drug consumption for symptomatic or acute treatment totalled over an evaluation period.
- e. Incidence and nature of adverse events.

II.3.i.D. Study design

These are invariably medium-term studies (at least 4 months) conducted in outpatients. Recommended are randomised, double-blind, placebo-controlled parallel-groups studies. Three-arm trials, including placebo, are required for internal validation with active comparators because of the large and highly variable placebo effect in prophylactic migraine studies. Randomisation should occur after a run-in (baseline) period of at least one month, when stratification for baseline attack rate (e.g., ≥ 3 or < 3 per 4 weeks) is recommended as the prophylactic effect may depend on this variable. Treatment periods should be at least 3 months. Patients should take their usual acute therapy as required, provided that it can be safely administered with the study drug. Attacks (and, if required, their features), acute medication use and adverse events should be recorded as they occur by patients in paper or electronic diaries. Reviews of patients and their diaries should be undertaken every 4 weeks.

Compliance with medication regimens, and concordance, are known to be highly suspect in migraine prophylaxis. Counts of returned medication are unreliable for detecting poor concordance, which may render an efficacious drug useless. In phase II it is especially important to ascertain that the drug has been taken as prescribed. Consideration should be given to using electronic event monitors.

II.3.i.E. Planned sample

Sample size calculations should be based on demonstrating superiority over placebo in a primary analysis of a) difference in attack frequencies, with a relative difference of 50% or an absolute difference of 1 attack/month being clinically significant and allowing for a reduction on placebo of up to 30% or 1 attack/month; or b) difference in responder rates, with an absolute difference of 20% being clinically significant and allowing for a placebo rate of up to 30%.

II.3.i.F. Study population

Adults with frequent attacks of migraine with or without aura.

II.3.i.G. Specific inclusion criteria

- a. Patients with migraine conforming to IHS diagnostic criteria 1.1 or 1.2 for at least 1 year and with at least 3 months’ well-documented retrospective history.
- b. Migraine attacks occurring 2-6 times monthly.
- c. Males and females.
- d. Unless otherwise justified, patients should be over 18 years of age.

II.3.i.H. Specific exclusion criteria

- a. Age at onset of migraine of 50 years or over.
- b. Other headaches not well distinguished from migraine or occurring with such frequency as to interfere with assessments (usually taken to mean occurring on > 6 days/month).
- c. Other illnesses likely to interfere with assessments.

- d. Use of other migraine prophylactic drugs in the previous month.
- e. Use of or requirement for other unacceptable concomitant therapy.
- f. Risk of pregnancy.
- g. History of drug or alcohol overuse.

II.3.i.I. Tools for assessing endpoints

Paper or electronic diaries.

II.3.i.J. Specific criteria for early withdrawal and discontinuation

- a. Withdrawal of consent (which may be related to lack of efficacy or adverse events).
- b. Medical concerns related to evident lack of efficacy or adverse events.
- c. Other intercurrent illness.
- d. Pregnancy.
- e. Breach of double-blinding.

II.3.i.K. Data analysis method

Even in early efficacy studies of prophylaxis, explanatory (per protocol) analysis may be misleading. Whilst it is unhelpful at this stage to include patients with random major protocol violations, drop-outs may be treatment-related. Analysis should therefore be based on the intention-to-treat (ITT) population. Since time to onset of effect is of interest, analysis of efficacy should be for the entire treatment period as well as for the period specified by the primary endpoint (e.g., the final 4 weeks of treatment). Standard statistical methods are appropriate. Adverse events are usually analysed descriptively.

II.3.ii. Chronic tension-type headache prophylaxis

II.3.ii.A. Objectives

To evaluate efficacy against chronic tension-type headache.

II.3.ii.B. Primary end-points

- a. Number of days with headache per specified unit time (usually 4 weeks) measured during treatment after a specified period (at least 8 weeks).
- b. Response rate: percentage of patients with reduction in headache days per unit time of 50% or more (implying reversion from chronic to episodic tension-type headache) after a specified treatment period.

II.3.ii.C. Secondary endpoints

- a. Number of days with headache over the entire treatment period.
- b. Intensity of headache on a visual analogue scale or 4-point verbal rating scale [0 = no pain; 1, 2, 3 = mild, moderate, severe pain]) averaged over attacks within a specified evaluation period.
- c. Duration of headache each day.
- d. Drug consumption for symptomatic or acute treatment totalled over an evaluation period.
- e. Incidence and nature of adverse events.

II.3.ii.D. Study design

These are invariably medium-term studies (at least 4 months) conducted in outpatients. Recommended are randomised, double-blind, placebo-controlled parallel-groups studies. There are no licensed active comparators. Randomisation should occur after a run-in (baseline) period of at least one month during which the number of days with headache and acute or symptomatic medication consumption are recorded. Stratification is unnecessary. Treatment periods should be at least 3 months. Days with headache, intensity and duration of headache, medication use and adverse events should be recorded as

they occur by patients in paper or electronic diaries. Reviews of patients and their diaries should be undertaken every 4 weeks.

Acute medication is inappropriate treatment for this disorder and should not be encouraged (regular use of acute or symptomatic medication on >2 days per week will put the diagnosis in question as this approaches the threshold for medication-overuse headache).

Compliance with preventative medication has not been evaluated in chronic tension-type headache. It may be better than in migraine because symptoms are present daily or on most days rather than intermittently. Nevertheless, in phase II it is important to ascertain that the drug has been taken as prescribed. Consideration should be given to using electronic event monitors.

II.3.ii.E. Planned sample

Sample size calculations should be based on demonstrating superiority over placebo in a primary analysis of difference in days with headache. A change from baseline of $\geq 50\%$ represents a clinically significant benefit of treatment, but the response to placebo has not been well documented (a reduction of up to 30% should be anticipated). Alternatively the primary analysis may be of difference in response rates. An absolute difference of 20% would be clinically significant. Again the response rate to placebo has not been well documented but up to 30% should be anticipated.

II.3.ii.F. Study population

Adults with chronic tension-type headache drawn from secondary or primary care or from the general population.

II.3.ii.G. Specific inclusion criteria

- a. Patients with chronic tension-type headache conforming to IHS diagnostic criteria 2.3 for at least 3 months and with at least 3 months' well-documented retrospective history.
- b. Males and females.
- c. Unless otherwise justified, patients should be over 18 years of age.

II.3.ii.H. Specific exclusion criteria

- a. Age at onset of chronic tension-type headache of 50 years or over.
- b. Other headaches, especially migraine, not well distinguished from tension-type headache or occurring with such frequency as to interfere with assessments.
- c. Other illnesses, particularly depression, likely to interfere with assessments.
- d. Use of other prophylactic drugs in the previous month.
- e. Use of acute or symptomatic medication for headache on an average of >2 days per week over the previous 2 months.
- f. Other history of drug or alcohol overuse.
- g. Use of or requirement for psychotropic medication or other unacceptable concomitant therapy.
- h. Risk of pregnancy.

II.3.ii.I. Tools for assessing endpoints

Paper or electronic diaries.

II.3.ii.J. Specific criteria for early withdrawal and discontinuation

- a. Withdrawal of consent (which may be related to lack of efficacy or adverse events).
- b. Medical concerns related to evident lack of efficacy or adverse events.
- c. Other intercurrent illness.
- d. Pregnancy.
- e. Breach of double-blinding.

II.3.ii.K. Data analysis method

Even in early efficacy studies of prophylaxis, explanatory (per protocol) analysis may be misleading. Whilst it is unhelpful at this stage to include patients with random major protocol violations, drop-outs may be treatment-related. Analysis should therefore be based on the intention-to-treat (ITT) population. Since time to onset of effect is of interest, analysis of efficacy should be for the entire treatment period as well as for the period specified by the primary endpoint (e.g., the final 4 weeks of treatment). Standard statistical methods are appropriate. Adverse events are usually analysed descriptively.

II.3.iii. Prophylaxis of episodic cluster headache

II.3.iii.A. Objectives

To evaluate efficacy in terminating a cluster period or in reducing frequency, intensity and/or duration of continuing cluster headache attacks.

II.3.iii.B. Primary end-points

- a. Frequency of attacks per specified unit time (usually 1 week) measured during treatment after a specified period (to allow treatment effect to develop) following dosage-stabilisation.
- b. Remission rate: percentage of patients whose attacks have ceased after a specified treatment period.

The number of attacks should be recorded irrespective of their intensity or duration. An attack treated successfully with acute medication but with relapse within 1 hour counts as one attack.

II.3.iii.C. Secondary endpoints

- a. Frequency of attacks over the entire treatment period.
- b. Time to remission.
- c. Intensity of cluster headaches averaged over a specified evaluation period.
- d. Duration of cluster headaches summed or averaged over a specified evaluation period.
- e. Drug consumption for symptomatic or acute treatment totalled over an evaluation period.
- f. Incidence and nature of adverse events.

II.3.iii.D. Study design

In phase II these are short-term randomised, double-blind, placebo-controlled, parallel-groups studies conducted in outpatients. No run-in (baseline) period is needed. Stratification is recommended for time since onset of the cluster period (e.g., ≥ 2 or < 2 weeks, but see below) and gender as each may influence the prophylactic effect or spontaneous remission rate. Treatment periods may be defined by the times prescribed for the primary end-point but should be at least 2 weeks; although they may need to incorporate dose-titration, they should not be substantially longer than this since treatments include placebo. Patients should take their usual acute therapy whenever cluster headache is of at least moderate intensity provided that it can be safely administered with the study drug. Attacks and their intensity and duration (and, if required, their associated features), acute medication use and adverse events should be recorded as they occur by patients in paper or electronic diaries. Reviews of patients and their diaries should be undertaken every week.

Compliance should be monitored. Because of the symptom frequency and severity it may be better in cluster headache than in other headache disorders but consideration should be given to using electronic event monitors.

II.3.iii.E. Planned sample

Sample size calculations should be based on demonstrating superiority over placebo in a primary analysis of a) difference in attack frequencies, with a relative difference of 50% being clinically significant and

allowing for a reduction on placebo of up to 20%; or b) difference in remission rates, with an absolute difference of 20% being clinically significant and allowing for a placebo plus spontaneous resolution rate of up to 20%.

II.3.iii.F. Study population

Adults with episodic cluster headache.

II.3.iii.G. Specific inclusion criteria

- a. Patients with episodic cluster headache conforming to IHS diagnostic criteria 3.1, and in at least their second cluster period.
- b. Expected duration of cluster period, from start of study medication, greater than the treatment period specified by the primary end-point (to limit the spontaneous-resolution rate in phase II, there may be advantage in restricting recruitment to patients within 2 weeks of onset of the cluster period).
- c. Acute attacks occurring between once every 2 days and 5 times per day.
- d. Males and females.
- e. Unless otherwise justified, patients should be over 18 years of age.

II.3.iii.H. Specific exclusion criteria

- a. Other headaches not well distinguished from cluster headache.
- b. Other illnesses likely to interfere with assessments.
- c. Other cluster headache prophylactic therapy in the previous week.
- d. Use of or requirement for other unacceptable concomitant therapy.
- e. Risk of pregnancy.
- f. History of drug or alcohol overuse.

II.3.iii.I. Tools for assessing endpoints

Paper or electronic diaries.

II.3.iii.J. Specific criteria for early withdrawal and discontinuation

- a. Withdrawal of consent (which may be related to lack of efficacy or adverse events).
- b. Medical concerns related to evident lack of efficacy or adverse events.
- c. Other intercurrent illness.
- d. Pregnancy.
- e. Breach of double-blinding.

II.3.iii. K. Data analysis method

Drop-outs may be treatment-related so, even in early efficacy studies of prophylaxis, analysis should be based on the intention-to-treat (ITT) population. Explanatory (per protocol) analysis may be worthwhile and hypothesis-generating as a secondary analysis. Subgroup analysis for gender differences is recommended and should be specified *a priori*. Since time to onset of effect is of interest, analysis of efficacy should be for the entire treatment period as well as for the period specified by the primary endpoint. Standard statistical methods are appropriate. Adverse events are usually analysed descriptively.

II.3.iv. Prophylaxis of chronic cluster headache

The objective in chronic cluster headache prophylaxis is long-term suppression of attacks. No methodology has yet been developed. In view of the difficulties with use of placebo as a comparator it is likely to be similar to that used in epilepsy, with add-on therapy studies preceding monotherapy trials.

III. PHASE III STUDIES FOR REGISTRATION OF NEW DRUGS

III.1. Outline of a typical development plan

During phase III, promising drugs are assessed for effectiveness against placebo in at least two pivotal large multicentre studies. They will be randomised double-blind trials incorporating one or more doses of study drug according to the findings of phase II. They may use parallel-groups or (multiple) cross-over designs, with regulators strongly favouring the former. For acute and prophylactic migraine therapy, and acute treatment of episodic tension-type headache and cluster headache, one or both of these, or additional studies in this phase, should include active comparators.

Acute treatments for cluster headache, which are unlikely to be oral, must be formulated so that patients can self-medicate wherever they may be at time of onset.

Pivotal acute-treatment trials should address not only the treatment of single attacks but also consistency of the therapeutic response across multiple attacks. Additionally in migraine and episodic tension-type headache, long-term continuation protocols are desirable to demonstrate repeatability of effect over time (lack of tachyphylaxis). Such studies contribute helpfully to safety evaluation.

In migraine particularly, the headache is not a stable pain but develops gradually, or sometimes rapidly, to a peak with subsequent spontaneous resolution. This poses challenges regarding timing of intake of medication. Trials in phase III may explore the relationship between timing of acute treatment and effect. Such a study in migraine with aura may incorporate medicating during the aura phase.

Specific trials in migraine and episodic tension-type headache may look at re-medicating, within the same attack, with a second dose of study drug when the first has been inadequately efficacious.

Prophylactic trials require a minimum of three months' treatment for migraine or chronic tension-type headache, but are better designed to reflect treatment periods likely in routine management, which are typically longer (4-6 months or more). Furthermore, continued observation beyond the treatment period, for continuing efficacy or possibly rebound exacerbation, is essential.

Cluster headache to some extent has the status of orphan disease. Long-term prophylaxis may be inappropriate in the episodic subtype, when attacks recur over periods of only a few weeks. Some currently used drugs achieve remission quite quickly, even within a few days, and prolonged treatment may not be necessary. This, and the fact that no treatments currently used for the prevention of cluster headache are licensed for this indication, make active-comparator studies difficult whilst placebo cannot be used long-term. The regulatory requirements for phase III have not been clarified.

In all primary headache disorders, safety of treatment is a major concern since the disorders themselves are self-limiting. On the other hand they are widespread and drugs that treat them, once marketed, are likely to be taken by large numbers of people and not always in strict accordance with instructions. Regulators will look carefully at safety, and may require special studies in diseased populations.

Headache sufferers attending specialist clinics may not be representative of the larger number seen by primary-care physicians. Neither group is likely to match those in the general population who do not seek medical advice. Phase III trials need to recruit widely from the population who will use the agent when marketed, with as few restrictions as possible. Nonetheless, special protocols will be required for children (under the age of 18), whose needs may be different, and may be required for the elderly (over the age of 65), who are less subject to primary headaches and more at risk of symptomatic headache as well as other illness.

III.2. Short term studies

III.2.i. Acute treatment of migraine

III.2.i.A. Objectives

To confirm effectiveness and evaluate comparative efficacy and tolerability in relieving symptoms of the acute attack.

III.2.i.B. Primary end-point

- a. “Pain-free” rate: percentage of patients pain-free at 2 hours after treatment.

III.2.i.C. Secondary endpoints

- a. Percentage of patients pain-free at 2 hours and remaining pain-free, without use of further medication, for 48 hours after treatment.
- b. Rate of relapse, defined as the return of headache of any intensity within 48 hours in patients pain-free at 2 hours after treatment.
- c. Headache intensity at various time points after treatment.
- d. “Headache-relief” rate: percentage of patients with a decrease in headache intensity from severe or moderate to mild or no pain within 2 hours after treatment.
- e. Time to “meaningful” pain relief (usually defined subjectively).
- f. Time to “onset of action” (defined as first noticeable pain relief).
- g. Functional disability on a validated scale (usually a 4-point verbal rating scale where 0 = no functional impairment, 1 = “can do everything albeit with difficulty”, 2 = “cannot do some things” and 3 = “cannot do anything and/or bed-bound”) at 2 hours and other time points after treatment.
- h. Effect on associated symptoms such as nausea, vomiting, photophobia and phonophobia.
- i. Rate and timing of use of rescue medication.
- j. Global evaluation of study medication.
- k. Pharmacoeconomic measures.
- l. Incidence and nature of adverse events.

III.2.i.D. Study design

Short-term studies should be randomised, double-blind, placebo-controlled parallel-groups outpatient trials treating one attack per patient. Three-arm trials, including placebo, are required for internal validation in active-comparator studies because of the large and highly variable placebo effect in migraine studies. In general, there is no need for stratification but phase III studies of acute treatment may opt to include patients with or without specific prophylactic medication(s), in which case stratification is based on this variable. Outcome variables are usually recorded by the patient in paper or electronic diaries, with prompts at various time points. Rescue medication should be allowed after 2 hours. This may be replaced, in patients who first received active drug, by a second dose of study drug or placebo in re-medication trials, with rescue medication deferred to 4 hours. To maintain the double-blind without subjecting patients to placebo only for 4 hours, those who first received placebo are given active drug as the second dose. The observation period after treatment of an attack should be 48 hours. Patients should return for final review soon after this.

III.2.i.E. Planned sample

Sample size calculations should be based on demonstrating superiority over placebo in a primary analysis of difference in pain-free rates, with an absolute difference of 20% being clinically significant and allowing for a placebo rate of up to 20%.

In practice, much greater numbers are required to demonstrate safety. Regulators require data from a large and representative group of patients. Trials including >1,000 patients are not unusual.

III.2.i.F. Study population

- a. Adults with migraine with or without aura.
- b. Adolescents and/or children, if they are to be included in the labelling.

III.2.i.G. Specific inclusion criteria

- a. Patients with migraine conforming to IHS diagnostic criteria 1.1 or 1.2 for at least 1 year and with at least 3 months' well-documented retrospective history.
- b. Migraine attacks occurring 1-6 times monthly.
- c. Males and females.

At the time of treatment:

- a. An acute attack, usually with onset within the previous 12 hours.
- b. At least 48 hours since resolution of the previous attack.
- c. Headache of moderate or severe intensity.
- d. So far untreated.

III.2.i.H. Specific exclusion criteria

- a. Age at onset of migraine of 50 years or over.
- b. Other headaches not well distinguished from migraine or occurring with such frequency as to interfere with assessments (usually taken to mean occurring on >6 days/month).
- c. Other illnesses likely to interfere with assessments.
- d. Use of migraine prophylactic drugs in the previous month or, if the protocol allows inclusion of patients on prophylaxis, any change in nature or dose of prophylactic medication in the previous 3 months.
- e. Use of or requirement for other unacceptable concomitant therapy.
- f. History of drug or alcohol overuse.

III.2.i.I. Tools for assessing endpoints

Paper or electronic diaries, with prompts at various time points.

III.2.i.J. Data analysis method

Analysis should be based on the intention-to-treat (ITT) population, although this may be defined to exclude those known not to have taken treatment. Standard statistical methods are appropriate. Adverse events are usually analysed descriptively.

Cost-effectiveness (or cost-utility) analysis is highly desirable, but the methodology is not yet well developed.

III.2.ii. Acute treatment of episodic tension-type headache

III.2.ii.A. Objectives

To confirm effectiveness, and evaluate comparative efficacy and tolerability, in relieving pain and functional impairment attributable to acute episodic tension-type headache.

III.2.ii.B. Primary end-point

“Pain-free” rate: percentage of patients pain-free at 2 hours after treatment.

III.2.ii.C. Secondary endpoints

- a. Headache intensity (scored on either a visual analogue scale or a 4-point verbal rating scale [0 = no pain; 1, 2, 3 = mild, moderate, severe pain]) at 2 hours and other time points after treatment.

- b. Headache intensity difference (the arithmetic change in headache intensity score) at 2 hours and at other time points after treatment.
- c. Headache relief (on a verbal rating scale from “none” to “complete”, with two or more intermediaries which may include “meaningful relief”; negative scores may be incorporated to indicate worsening) at 2 hours and at other time points after treatment.
- d. Functional disability on a validated scale (e.g., a 4-point verbal rating scale where 0 = no functional impairment, 1 = “can do everything albeit with difficulty”, 2 = “cannot do some things” and 3 = “cannot do anything and/or bed-bound”) at 2 hours and other time points after treatment.
- e. Rate and timing of use of rescue medication.
- f. Global evaluation of study medication.
- g. Incidence and nature of adverse events.

III.2.ii.D. Study design

Short-term studies should be randomised, double-blind, placebo-controlled parallel-groups outpatient trials treating one attack per patient. Three-arm trials, including placebo, are required for internal validation in active-comparator studies because of the very large placebo effect reported in acute episodic tension-type headache studies. There is no need for stratification. Outcome variables are usually recorded by the patient in paper or electronic diaries, with prompts at various time points. Rescue medication should be allowed after 2 hours. This may be replaced, in patients who first received active drug, by a second dose of study drug or placebo in re-medication trials, with rescue medication deferred to 4 hours. To maintain the double-blind without subjecting patients to placebo only for 4 hours, those who first received placebo are given active drug as the second dose. The observation period after treatment should be at least 24 hours. Patients should return for final review soon after this.

III.2.ii.E. Planned sample

Sample size calculations should be based on demonstrating superiority over placebo in a primary analysis of difference in pain-free rates, with an absolute difference of 20% being clinically significant and allowing for a placebo rate of up to 50%.

If the study drug is not already licensed for another indication, much greater numbers may be required to demonstrate safety.

III.2.ii.F. Study population

- a. Adults with episodic tension-type headache drawn from the general population (by advertising if necessary).
- b. Adolescents and/or children, if they are to be included in the labelling.

III.2.ii.G. Specific inclusion criteria

- a. Patients with frequent episodic tension-type headache (occurring on >1 but <15 days per month) conforming to IHS diagnostic criteria 2.2 for at least 1 year and with at least 3 months’ well-documented retrospective history.
- b. Usual headache duration at least 4 hours.
- c. Males and females.

At the time of treatment:

- a. An acute episode of tension-type headache, usually with onset within the previous 12 hours.
- b. Headache of at least moderate intensity.
- c. So far untreated.

III.2.ii.H. Specific exclusion criteria

- a. Age at onset of tension-type headache of 50 years or over.

- b. Chronic tension-type headache.
- c. Migraine if not well distinguished from tension-type headache or occurring in the previous year more frequently than once per month.
- d. Medication-overuse headache.
- e. Other headaches not well distinguished from tension-type headache or occurring with such frequency as to interfere with assessments.
- f. Other illnesses likely to interfere with assessments.
- g. Use of prophylactic drugs in the previous month.
- h. Use of or requirement for psychotropic medication or other unacceptable concomitant therapy.
- i. History of drug or alcohol overuse.

III.2.ii.I. Tools for assessing endpoints

Paper or electronic diaries, with prompts at various time points.

III.2.ii.J. Data analysis method

Analysis should be based on the intention-to-treat (ITT) population, although this may be defined to exclude those known not to have taken treatment. Standard statistical methods are appropriate. Adverse events are usually analysed descriptively.

Longer-term studies should address consistency of the therapeutic response across attacks. These may be double-blind cross-over studies observing treatment of several attacks per patient with the same drug and dose plus, randomly, one or more (e.g., one attack out of five) with placebo. Additionally, long-term continuation protocols are desirable to demonstrate repeatability of effect over time (lack of tachyphylaxis). Such studies contribute helpfully to safety evaluation. They need be neither placebo-controlled nor blinded.

III.2.iii. Acute treatment of episodic or chronic cluster headache

III.2.iii.A. Objectives

To evaluate efficacy and comparative effectiveness and tolerability in aborting or suppressing the acute attack.

III.2.iii.B. Primary end-points

- a. “Aborted attack” rate: percentage of patients in whom the attack is effectively stopped (headache intensity reduced to mild or no pain) within a prescribed time interval (which may be as short as 10 minutes).
- b. Time to meaningful relief.
- c. Time to “complete” relief (mild or no pain).

III.2.iii.C. Secondary endpoints

- a. Rate of relapse, defined as the return of headache of moderate or greater intensity within 1 hour in patients reporting an aborted attack.
- b. Headache intensity (on a 5-point verbal rating scale: 0 = no pain, 1, 2, 3, 4 = mild, moderate, severe, excruciating pain) at 5, 10 and 15 minutes after treatment and every 15 minutes thereafter for up to 3 hours (whilst these repeated assessments are recommended, marked agitation is a feature of acute cluster headache which, combined with severe pain, may make them impractical).
- c. Effect on associated autonomic symptoms.
- d. Functional impairment on a validated scale.
- e. Rate and timing of use of rescue medication.
- f. Global evaluation of study medication.
- g. Patient’s preference (in cross-over studies).
- h. Incidence and nature of adverse events.

III.2.iii.D. Study design

Treatments coming into phase III may be oral but are more likely to be parenteral. There are study-design implications for parenteral therapy, particularly for active-comparator studies and especially because the active comparator may itself be administered parenterally.

Short-term studies should be randomised, double-blind, placebo-controlled parallel-groups or cross-over trials in outpatients treating 1-4 attacks each. The cross-over design has advantages, and may be accepted by regulators, since patients are uncommon whilst attacks occur with high and predictable frequency. Three-arm trials, including placebo, are required for internal validation in active-comparator studies; although placebo effect is relatively slight in cluster headache, trials are easily confounded by high rates of spontaneous resolution of attacks which are short-lasting. Active-comparator studies are likely to require a double-dummy design if one or other treatment, or both, is administered parenterally. At least one large multicentre trial should formally confirm efficacy.

If a parallel-groups trial includes both episodic and chronic cluster headache, stratification is recommended because responses to treatment may differ. Stratification for gender is also recommended for the same reason. Outcome variables are usually recorded by the patient in paper or electronic diaries, with prompts at various time points. Rescue medication should be allowed after the time prescribed for the primary end-point, but options for this are very limited. The observation period after treatment of an attack should be not less than 24 hours unless interrupted by the occurrence of the next attack. Depending on the experience from phase II, reviews may shortly follow each treatment or (in multiple-attack studies) only the last treatment.

Short-term studies in cluster headache can address consistency of the therapeutic response across attacks. These may be double-blind cross-over studies, observing treatment of several attacks per patient with the same drug and dose plus, randomly, one or more (e.g., one attack out of five) with placebo.

III.2.iii.E. Planned sample

Sample size calculations should be based on demonstrating superiority over placebo in a primary analysis of difference in aborted-attack rates. Placebo-response rate is low but, because of the short attack-duration, spontaneous remission rates may be high; the two may combine to 50%. An absolute difference of 25% is clinically significant.

III.2.iii.F. Study population

- a. Adults with episodic or chronic cluster headache.
- b. Adolescents and/or children, if they are to be included in the labelling.

III.2.iii.G. Specific inclusion criteria

- a. Patients with episodic or chronic cluster headache conforming to IHS diagnostic criteria 3.1 or 3.2; patients with episodic cluster headache should be in at least their second cluster period.
- b. Acute attacks occurring between once every 2 days and 5 times per day.
- c. Attack duration of 30-180 minutes.
- d. Males and females.

At the time of treatment:

- a. An acute attack, usually with onset within the previous 15 minutes (at least 15 minutes before expected spontaneous resolution).
- b. At least 1 hour since resolution of the previous attack and 24 hours (or 5 half-lives if longer) since the latest previous use of study drug.
- c. Headache of moderate or greater intensity.
- d. So far untreated.

III.2.iii.H. Specific exclusion criteria

- a. Other headaches not well distinguished from cluster headache.
- b. Other illnesses likely to interfere with assessments.
- c. Use of or requirement for unacceptable concomitant therapy.
- d. History of drug or alcohol overuse.

III.2.iii.I. Tools for assessing endpoints

Paper or electronic diaries, with prompts at various time points.

III.2.iii.J. Data analysis method

Analysis should be based on the intention-to-treat (ITT) population, although this may be defined to exclude those known not to have taken treatment. Subgroup analyses (for episodic and chronic subtypes and for gender differences) are recommended and should be specified *a priori*. Standard statistical methods are appropriate. “Time to” end-points require survival-analysis methods. Adverse events are usually analysed descriptively.

The frequency of medication in cluster headache may lead to high treatment costs; given that, untreated, this disorder is very disabling and ruins quality of life, cost-effectiveness (or cost-utility) analysis is appropriate but the methodology is not yet well developed.

Longer-term studies are desirable, extending throughout a cluster episode or in patients with chronic cluster headache, to demonstrate repeatability of effect over time (lack of tachyphylaxis) and for safety evaluation. These need be neither placebo-controlled nor blinded.

III.3. Long term studies

Longer-term studies should address consistency of the therapeutic response across attacks. These may be double-blind cross-over studies observing treatment of several attacks per patient with the same drug and dose plus, randomly, one or more (e.g., one attack out of five) with placebo. Additionally, long-term continuation protocols are desirable to demonstrate repeatability of effect over time (lack of tachyphylaxis). At least one study of 12 months’ duration is needed for safety evaluation. These need be neither placebo-controlled nor blinded.

One or more of these protocols should accommodate the double-blind investigation, using similar end-points, of re-medication to treat relapse following initial successful treatment with the study drug.

III.3.i. Migraine prophylaxis

III.3.i.A. Objectives

To confirm effectiveness and evaluate comparative efficacy and tolerability in migraine prevention.

III.3.i.B. Primary end-points

- a. Frequency of attacks per specified unit time (usually 4 weeks) measured during treatment after a specified period (usually 8 weeks).
- b. Response rate: percentage of patients with frequency reduction of 50% or more after a specified treatment period.

The number of attacks should be recorded irrespective of their duration, and the following rules distinguish an attack of long duration from two attacks and between attacks and relapses:

- a. A migraine attack which is interrupted by sleep, or which temporarily remits spontaneously and then recurs within 48 hours after its onset, should be recorded as one attack and not two.
- b. An attack treated successfully with medication but with relapse within 48 hours counts as one attack.

III.3.i.C. Secondary endpoints

- a. Frequency of attacks over the entire treatment period.
- b. Frequency of attacks following discontinuation of treatment.
- c. “Migraine days” (defined as any day on which symptoms of migraine are present) per 4 weeks.
- d. Intensity of migraine headache averaged over attacks within a specified evaluation period.
- e. Speed of effect (e.g., response rates in first, second and third months of treatment).
- f. Drug consumption for symptomatic or acute treatment totalled over an evaluation period.
- g. Headache indices multiplying frequency, intensity and/or duration are not recommended: arbitrary weighting in the numerical scores, which may be faulty, is increased by multiplication; and indices cannot meaningfully be compared between patients.
- h. Health-related quality of life measures would be desirable but none are well-established or universally accepted; they should not be used until clinically validated.
- i. Global evaluation of study medication.
- j. Pharmacoeconomic measures.
- k. Incidence and nature of adverse events.

III.3.i.D. Study design

These are medium- or long-term studies (at least 4 months) in outpatients. At least two should be randomised, double-blind, placebo-controlled parallel-groups studies and at least one of these should include an active comparator. Three-arm trials, including placebo, are required for internal validation with active comparators unless the study is designed to show superiority over a well-established comparator (if superiority is not shown, non-inferiority cannot be claimed in the absence of placebo control). Randomisation should occur after a run-in (baseline) period of at least one month, when stratification for baseline attack rate (e.g., ≥ 3 or < 3 per 4 weeks) is recommended as the prophylactic effect may depend on this variable. Treatment periods should be at least 3 months. Patients should take their usual acute therapy as required provided that it can be safely administered with the study drug. Attacks (and, if required, their features), acute medication use and adverse events should be recorded as they occur by patients in paper or electronic diaries. Reviews of patients and their diaries should be undertaken every 4 weeks, and should continue for at least 4 weeks after treatment is discontinued.

Compliance should be monitored.

III.3.i.E. Planned sample

Sample size calculations should be based on demonstrating superiority over placebo in a primary analysis of a) difference in attack frequencies, with a relative difference of 50% or an absolute difference of 1 attack/month being clinically significant and allowing for a reduction on placebo of up to 30% or 1 attack/month; or b) difference in responder rates, with an absolute difference of 20% being clinically significant and allowing for a placebo rate of up to 30%.

Whether or not greater numbers are required for safety evaluation is dependent on whether or not the study drug has been through a development programme, and is licensed already, for another indication.

III.3.i.F. Study population

- a. Adults with frequent attacks of migraine with or without aura.
- b. Adolescents and/or children, if they are to be included in the labelling.

III.3.i.G. Specific inclusion criteria

- a. Patients with migraine conforming to IHS diagnostic criteria 1.1 or 1.2 for at least 1 year and with at least 3 months' well-documented retrospective history.
- b. Migraine attacks occurring 2-6 times monthly.
- c. Males and females.

III.3.i.H. Specific exclusion criteria

- a. Age at onset of migraine of 50 years or over.
- b. Other headaches not well distinguished from migraine or occurring with such frequency as to interfere with assessments (usually taken to mean occurring on >6 days/month).
- c. Other illnesses likely to interfere with assessments.
- d. Use of other migraine prophylactic drugs in the previous month.
- e. Use of or requirement for other unacceptable concomitant therapy.
- f. Risk of pregnancy.
- g. History of drug or alcohol overuse.

III.3.i.I. Tools for assessing endpoints

Paper or electronic diaries.

III.3.i.J. Specific criteria for early withdrawal and discontinuation

- a. Withdrawal of consent (which may be related to lack of efficacy or adverse events).
- b. Medical concerns related to evident lack of efficacy or adverse events.
- c. Other intercurrent illness.
- d. Pregnancy.
- e. Breach of double-blinding.

III.3.i.K. Data analysis method

Analysis should be based on the intention-to-treat (ITT) population. Because time to onset of effect is of interest, analysis of efficacy should be for the entire treatment period as well as for the period specified by the primary endpoint (e.g., the final 4 weeks of treatment). Standard statistical methods are appropriate. Adverse events are usually analysed descriptively.

Cost-effectiveness (or cost-utility) analysis is highly desirable, but the methodology is not yet well developed.

Longer-term studies are desirable to investigate continuing efficacy during and after periods of treatment (up to 6 months or longer) common in routine practice. At least one trial of at least 12 months' duration is required for safety evaluation. These studies can be conducted as continuations of double-blind studies with patients opting, or not, to remain on their treatment (whether active or placebo). In addition, withdrawal of medication at the end of the prescribed period of treatment should be evaluated, ideally by randomised and double blind substitution of placebo in one group of patients and continuation of active therapy in another (with informed consent). Open observational studies, using patients as their own controls, have very limited value and are a poor alternative because of the inherent variability over time of the disease.

III.3.ii. Chronic tension-type headache prophylaxis

III.3.ii.A. Objectives

To confirm efficacy, effectiveness and tolerability in treating chronic tension-type headache.

III.3.ii.B. Primary end-points

- a. Number of days with headache per specified unit time (usually 4 weeks) measured during treatment after a specified period (at least 8 weeks).

- b. Response rate: percentage of patients with reduction in headache days per unit time of 50% or more (implying reversion from chronic to episodic tension-type headache) after a specified treatment period.

III.3.ii.C. Secondary endpoints

- a. Number of days with headache over the entire treatment period.
- b. Intensity of headache on a visual analogue scale or 4-point verbal rating scale [0 = no pain; 1, 2, 3 = mild, moderate, severe pain]) averaged over attacks within a specified evaluation period.
- c. Duration of headache each day.
- d. Headache indices multiplying frequency, intensity and/or duration are not recommended: arbitrary weighting in the numerical scores, which may be faulty, is increased by multiplication; and indices cannot meaningfully be compared between patients.
- e. Functional measures and health-related quality of life measures would be desirable but are not established and should not be used until clinically validated.
- f. Drug consumption for symptomatic or acute treatment totalled over an evaluation period.
- g. Global evaluation of study medication.
- h. Incidence and nature of adverse events.

III.3.ii.D. Study design

These are medium- or long-term studies (at least 4 months) in outpatients. At least two should be randomised, double-blind, placebo-controlled parallel-groups studies. There are no licensed active comparators. Randomisation should occur after a run-in (baseline) period of at least one month during which the number of days with headache and acute or symptomatic medication consumption are recorded. Stratification is unnecessary. Treatment periods should be at least 3 months. Days with headache, intensity and duration of headache, acute medication use and adverse events should be recorded as they occur by patients in paper or electronic diaries. Reviews of patients and their diaries should be undertaken every 4 weeks, and should continue for at least 4 weeks after treatment is discontinued.

Acute medication is inappropriate treatment for this disorder and should not be encouraged (regular use of acute or symptomatic medication on >2 days per week will put the diagnosis in question as this approaches the threshold for medication-overuse headache).

Compliance should be monitored.

III.3.ii.E. Planned sample

Sample size calculations should be based on demonstrating superiority over placebo in a primary analysis of difference in days with headache. A change from baseline of $\geq 50\%$ represents a clinically significant benefit of treatment, but the response to placebo has not been well documented (a reduction of up to 30% should be anticipated). Alternatively the primary analysis may be of difference in response rates. An absolute difference of 20% would be clinically significant. Again the response rate to placebo has not been well documented but up to 30% should be anticipated.

III.3.ii.F. Study population

Adults with chronic tension-type headache drawn from secondary or primary care or from the general population.

III.3.ii.G. Specific inclusion criteria

- a. Patients with chronic tension-type headache conforming to IHS diagnostic criteria 2.3 for at least 3 months and with at least 3 months' well-documented retrospective history.
- b. Males and females.
- c. Unless otherwise justified, patients should be over 18 years of age.

III.3.ii.H. Specific exclusion criteria

- a. Age at onset of chronic tension-type headache of 50 years or over.
- b. Other headaches, especially migraine, not well distinguished from tension-type headache or occurring with such frequency as to interfere with assessments.
- c. Other illnesses, particularly depression, likely to interfere with assessments.
- d. Use of other prophylactic drugs in the previous month.
- e. Use of acute or symptomatic medication for headache on an average of >2 days per week over the previous 2 months.
- f. Other history of drug or alcohol overuse.
- g. Use of or requirement for psychotropic medication or other unacceptable concomitant therapy.
- h. Risk of pregnancy.

III.3.ii.I. Tools for assessing endpoints

Paper or electronic diaries.

III.3.ii.J. Specific criteria for early withdrawal and discontinuation

- a. Withdrawal of consent (which may be related to lack of efficacy or adverse events).
- b. Medical concerns related to evident lack of efficacy or adverse events.
- c. Other intercurrent illness.
- d. Pregnancy.
- e. Breach of double-blinding.

III.3.ii.K. Data analysis method

Analysis should be based on the intention-to-treat (ITT) population. Because time to onset of effect is of interest, analysis of efficacy should be for the entire treatment period as well as for the period specified by the primary endpoint (e.g., the final 4 weeks of treatment). Standard statistical methods are appropriate. Adverse events are usually analysed descriptively.

Longer-term studies are desirable to investigate continuing efficacy over longer periods of treatment that may be necessary in routine management (6 months or longer). At least one trial of at least 12 months' duration is required for safety evaluation. These studies can be conducted as continuations of double-blind studies with patients opting, or not, to remain on their treatment (whether active or placebo). In addition, withdrawal of medication at the end of the prescribed period of treatment should be evaluated, ideally by randomised and double blind substitution of placebo in one group of patients and continuation of active therapy in another (with informed consent). Open observational studies, using patients as their own controls, are of very limited value and a poor alternative because of the inherent variability over time of the disease.

III.3.iii. Prophylaxis of episodic cluster headache

III.3.iii.A. Objectives

To confirm efficacy and evaluate effectiveness and tolerability in terminating a cluster period or in reducing frequency, intensity and/or duration of continuing cluster headache attacks.

III.3.iii.B. Primary end-points

- a. Frequency of attacks per specified unit time (usually 1 week) measured during treatment after a specified period (to allow treatment effect to develop) following dosage-stabilisation.
- b. Remission rate: percentage of patients whose attacks have ceased after a specified treatment period.

The number of attacks should be recorded irrespective of their intensity or duration. An attack treated successfully with acute medication but with relapse within 1 hour counts as one attack.

III.3.iii.C. Secondary endpoints

- a. Frequency of attacks over the entire treatment period.
- b. Time to remission.
- c. Intensity of cluster headaches averaged over a specified evaluation period.
- d. Duration of cluster headaches summed or averaged over a specified evaluation period.
- e. Drug consumption for symptomatic or acute treatment totalled over an evaluation period.
- f. Health-related quality of life measures, and measures of functional disability over the treatment period, would be desirable but are not established and should not be used until clinically validated.
- g. Global evaluation of study medication.
- h. Effects after withdrawal of treatment.
- i. Incidence and nature of adverse events.

III.3.iii.D. Study design

These are short- or medium-term studies depending on the treatment effect observed in phase II. However, studies over >2 weeks cannot be conducted against placebo notwithstanding that high spontaneous remission rates confound trials that are not placebo-controlled. Therefore, superiority over an established comparator must be shown in one or more randomised parallel-groups studies. Whilst a number of reasonably effective potential comparator drugs exist, they are unlicensed for this indication, associated with toxicity and tend to be used in ways that make it very difficult to achieve double-blindness. Open studies are more acceptable with objective end-points (e.g., remission rate).

No run-in (baseline) period is needed. Stratification is recommended for time since onset of the cluster period (e.g., ≥ 2 or < 2 weeks) and gender as each may influence the prophylactic effect or spontaneous remission rate. Treatment periods may need to incorporate dose-titration and, following dosage stabilisation, are defined by the times prescribed for the primary end-point or by the study objective if this calls for longer-term therapy. They are unlikely to exceed 3 months and safety evaluation must be conducted within this period unless safety has been demonstrated already in longer-term use of the drug for other indications.

Patients should take their usual acute therapy whenever cluster headache is of at least moderate intensity provided that it can be safely administered with the study drug. Attacks and their intensity and duration (and, if required, their associated features), acute medication use and adverse events should be recorded as they occur by patients in paper or electronic diaries. Reviews of patients and their diaries should be undertaken every week in short-term studies and at least monthly in medium-term studies.

Compliance should be monitored.

After remission of the cluster period, whether spontaneous or treatment-related, prophylactic medication is withdrawn. At least one trial should observe the consequences of withdrawal over up to several weeks, since these may include relapse.

III.3.iii.E. Planned sample

Sample size calculations should be based on demonstrating superiority over placebo in a primary analysis of a) difference in attack frequencies, with a relative difference of 50% being clinically significant and allowing for a reduction on placebo of up to 20%; or b) difference in remission rates, with an absolute difference of 20% being clinically significant and allowing for a placebo plus spontaneous resolution rate of up to 20%.

III.3.iii.F. Study population

- a. Adults with episodic cluster headache.
- b. Adolescents and/or children, if they are to be included in the labelling.

III.3.iii.G. Specific inclusion criteria

- a. Patients with episodic cluster headache conforming to IHS diagnostic criteria 3.1 and in at least their second cluster period.
- b. Any length of time from onset of the cluster period provided that its expected duration, from start of study medication, is greater than the treatment period specified by the primary end-point.
- c. Acute attacks occurring between once every 2 days and 5 times per day.
- d. Males and females.

III.3.iii.H. Specific exclusion criteria

- a. Other headaches not well distinguished from cluster headache.
- b. Other illnesses likely to interfere with assessments.
- c. Other cluster headache prophylactic therapy in the previous week.
- d. Use of or requirement for other unacceptable concomitant therapy.
- e. Risk of pregnancy.
- f. History of drug or alcohol overuse.

III.3.iii.I. Tools for assessing endpoints

Paper or electronic diaries.

III.3.iii.J. Specific criteria for early withdrawal and discontinuation

- a. Withdrawal of consent (which may be related to lack of efficacy or adverse events).
- b. Medical concerns related to evident lack of efficacy or adverse events.
- c. Other intercurrent illness.
- d. Pregnancy.

III.3.iii.K. Data analysis method

Analysis should be based on the intention-to-treat (ITT) population. Subgroup analysis for gender differences is recommended and should be specified *a priori*. Since time to onset of effect is of interest, analysis of efficacy should be for the entire treatment period as well as for the period specified by the primary endpoint. Standard statistical methods are appropriate. Adverse events are usually analysed descriptively.

IV. OTHER STUDIES (SPECIAL INDICATIONS AND PRAGMATIC STUDIES)

IV.1. Children and adolescents

Development of drugs for headache disorders in these age-groups is clearly required for two indications:

- a. acute treatment of migraine;
- b. prophylaxis of migraine.

Disease characteristics differ in migraine between children/adolescents and adults. The results of acute and prophylactic treatment studies in adults with migraine cannot be extrapolated to younger age-groups. Separate trials in children/adolescents are not required by regulators for initial marketing authorisation, but these age-groups will be excluded from product-labelling if sufficient efficacy and safety data are not included in the regulatory submission. It is not certain whether such differences exist in episodic and chronic tension-type headache, whilst cluster headache is very rare (although not unknown) in children. It is likely, however, that regulators will adopt the same approach in these disorders whilst markets may not be commercially viable.

Further dose-finding studies in these age-groups may be needed. During phase III, drugs with clear efficacy and safety in adults with migraine may be assessed in separate placebo-controlled trials for effectiveness and safety in children and/or adolescents. Pivotal studies will be large multicentre randomised double-blind trials incorporating one or more doses of study drug. They may use parallel-groups or (multiple) cross-over designs, with regulators strongly favouring the former. One or more studies should include an active comparator where licensed comparators exist. Three-arm trials, including placebo, are required for internal validation with active comparators unless the study is designed to show superiority over a well-established comparator (if superiority is not shown, non-inferiority cannot be claimed in the absence of placebo control).

Objectives, end-points, study designs, sample sizes, inclusion/exclusion criteria (other than age), tools for assessing end-points and data analysis methods are all generally similar to those in adult migraine trials. There are a few exceptions:

- a. migraine attacks are usually shorter-lasting, so rapid efficacy is more important;
- b. associated symptoms of nausea and vomiting are commonly more pronounced, and effective treatment of these may be a higher priority;
- c. children with headache are likely to be put to bed to sleep (which is curative), so frequent assessments over several hours is often impractical;
- d. prophylactic medication in children is inappropriate before a review has been conducted of lifestyle and possible triggers, which should be built into the protocol as part of baseline evaluation.

IV.2. The elderly

All primary headache disorders become significantly less prevalent after the age of 60 years. There are no special requirements for trials in the elderly, who should not generally be excluded from adult trials (subject to other inclusion/exclusion criteria). Elderly patients with migraine should have been suffering from this disorder for many years: onset of migraine over the age of 50 years is uncommon and predictive of symptomatic disease, which must be excluded.

IV.3. Menstrual migraine

Migraine in women may be hormonally-triggered and occur solely in close temporal relationship to menstrual periods (menstrual migraine) or it may be more loosely associated with menstruation with a tendency to occur at or around the time of periods (menstrually-associated migraine). It is unlikely that treatment of menstrually-associated migraine should differ from that of migraine generally, whereas other possibilities arise for the treatment of menstrual migraine.

The EMEA advises that studies in menstrual migraine, to be undertaken once efficacy and safety have been demonstrated in non-menstrual migraine, have in principle the same design and end-points as studies in non-menstrual migraine. Subgroups of patients with menstrual migraine included in several studies may be combined in a meta-analysis planned *a priori*. The temporal relationship between menses and migraine attacks should be stringently recorded, and for diagnostic purposes this is necessary for three cycles before trial entry. In acute treatment trials, an important secondary end-point is the percentage of patients pain-free at 2 hours and remaining pain-free, without use of further medication, for 48 hours after treatment. In prophylactic trials there is the option for monthly short-term perimenstrual prophylactic treatment. If this is being evaluated, the trial design should require continuous observation throughout each month since the possibility exists that attacks are merely postponed to later in the menstrual cycle.

IV.4. “Mild” migraine

The previously widely-adopted primary end-point for acute migraine treatment trials (“headache relief”) required that treatment was delayed until pain was moderate or severe. This is counter-intuitive and possibly counter-productive, and many patients will not do it routinely. Although it is in part justified by the argument that earlier treatment results in the inappropriate use of migraine-specific therapy for non-migraine headache, particularly episodic tension-type headache, this argument is not clearly evidence-based. There are good reasons for conducting additional trials of early treatment, whilst pain is still mild. The recommended primary end-point, “pain-free” rate (percentage of patients pain-free at 2 hours after treatment), can and should still be used. Secondary endpoints should include rate of relapse and percentage of patients pain-free at 2 hours and remaining pain-free, without use of further medication, for 48 hours after treatment.

IV.5. Acute treatment of migraine in the aura phase

Patients with migraine with aura have the opportunity to treat during the aura phase, before headache commences. Efficacy of treatment in this phase cannot be assumed from studies of treatment taken later in the attack. Separate studies are required, with similar endpoints.

IV.6. Pragmatic studies

Pragmatic trials attempt to replicate routine practice in the use of a drug rather than the conditions of a controlled experiment. They rarely support marketing authorisation applications but can usefully inform prescribing practitioners.

A major concern in acute migraine trials is that recommended end-points, chosen because they are relatively objectively measurable and have proved statistically robust in differentiating between active treatments and placebo, do not well reflect patients’ views of what they want from a treatment. One suggested design for a preference study dispenses to each patient a quantity of each of two or more comparator drugs (which, if blinded, can include placebo). The patient chooses which to use on the basis of accumulating personal experience of each. The rate of use of each is an index of preference. Other measures of “satisfaction” are needed also since preference for one treatment over another does not indicate that either is adequate.

No studies have yet compared acute migraine therapy alone with acute plus prophylactic therapy, but these are needed. End-points are likely to reflect quality-of-life or pharmacoeconomic measures.

V. STUDIES FOR THE REGISTRATION OF GENERIC DRUGS

Intense discussion is underway that should clarify the regulatory requirements for generic marketing, at least in Europe. The central issue is at what point generic manufacturers are entitled to make reference to an innovator’s clinical trials data to support a marketing authorisation application for a copy product. This issue will soon come to the fore in acute migraine therapy.

VI. EXAMPLES OF LANDMARK WELL-DESIGNED TRIALS

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VII. SUGGESTED READING

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