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Guideline on clinical investigation of medicinal products for the treatment of migraine and cluster headache

Draft

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Executive summary

The "Guideline on clinical investigation of medicinal products for the treatment of migraine" came into effect in June 2004 (CPMP/EWP/788/0), with a 1st revision in 2007 adding information on the paediatric population. The first revision focused only on treatment of migraine. This second revision aims to cover recommendations for the clinical development of medicinal products for the treatment of acute migraine attacks and for migraine prophylaxis in episodic and chronic migraine. In addition, recommendations for both acute and prophylactic treatment of episodic and chronic Cluster Headache are provided.

The guideline reflects changes in recommendations for the clinical development of medicinal products for the treatment of episodic and chronic migraine including recommendations for designs of clinical trials, patient selection, primary as well as secondary endpoints and potential use of active comparator in confirmatory studies. The updated revision includes a discussion on the distinction between patients with episodic and chronic migraine and its implications for the clinical trial design for both acute and prophylactic migraine treatment. A different primary endpoint for prophylactic migraine treatment has been recommended in the new edition of the guideline as well. Consequent implications on selection of secondary endpoints are addressed.

Recommendations for Cluster Headache includes advice on study design, patient population and primary and secondary endpoints.

1. Introduction

Migraine is a primary headache disorder defined by the occurrence of recurrent headache attacks, of moderate or severe intensity, usually one sided, pulsating, aggravated by activity and accompanied by nausea, vomiting, photo- and/or phonophobia. In adults, an attack may last for 4-72 hours. The one-year prevalence of migraine is estimated to be around 15.3% globally (1). Women are more frequently affected than men. The prevalence declines in subjects older than 50 years. In children and adolescents, the prevalence is approximately 5% and 13.4%, respectively.

Two main types of migraine are distinguished, migraine with aura and without aura. In migraine with aura the headache is preceded by reversible neurological symptoms. It is believed that regional cerebral blood flow is affected due to cortical spreading depression (CSD), causing aura and activation of the trigeminal nerve afferents which in turn lead to pain and vasodilation. The CSD, is a phenomenon consisting of a self-propagating wave of depolarization across the cerebral cortex associated with cortical cerebral hypoperfusion (2). CSD transiently disrupt ionic gradients causing release of inflammatory mediators resulting in dilation of intracranial arteries. These processes could activate and sensitize trigeminal primary afferents causing pain. Activation of the trigeminovascular pain pathways is believed to mediate release of neuropeptides, such as calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase activating polypeptide (PACAP) (3). In migraine without aura the regional cerebral blood flow remains normal. The pathophysiological mechanisms of migraine pain remain elusive, but the pain is most likely due to activation of the trigeminovascular system.

Migraine can be conceptualized as a spectrum disorder including episodic (EM) and chronic migraine (CM). The latter is evolving from pre-existing EM and is defined as at least 8 migraine days and 15 days of headache per month. Within a single patient, frequency of attacks may vary, and, consequently, periods of episodic and chronic migraine may vary over time.

Migraine is treated with medicine(s) for the acute attack, with prophylactic medicines, or both. Prophylactic treatment is usually considered in patients with a high disease burden, e.g., experiencing at least 4 migraine days per month. Current treatments for acute migraine attacks are either unspecific

or specific for migraine. Unspecific medicines include non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen with or without antiemetics. Standard of care for the specific treatment of acute migraine attacks are triptans (5-HT1B/1D receptor agonist); alternatively, ergotamines, oral CGRP-receptor antagonists (e.g. rimegepant) and an oral serotonin (5-HT) 5-HT1F receptor agonist (lasmiditan). The medicines used for migraine prophylaxis include beta-blockers, calcium blockers, antiepileptics and antidepressants. Botulinum toxin A is approved for prophylaxis of chronic migraine. For most of these medicinal products, the mode of action regarding the preventive effect on migraine is still unknown. With authorization of monoclonal antibodies against the calcitonin-gene related peptide (CGRP) or its receptor as well as oral CGRP receptor antagonists (gepants) treatments with a better-known mode of action have become available.

Cluster headache (CH) is a different, less common primary headache disorder affecting 0.1% of the population with a mean prevalence of 53/100,000 inhabitants (4).

CH presents with attacks of severe, unilateral, periorbital pain associated with accompanying symptoms (e.g. ipsilateral conjunctival injection, lacrimation). Attacks last 15–180 minutes and may occur several times daily. These frequently recurring attacks come in series (so-called cluster periods or bouts) over weeks or months separated by periods of remission (lasting at least 3 months). This typical pattern is called episodic cluster headache (eCH). However, 10–15% of the CH-patients attacks occur for at least one year without remission periods or with remissions lasting less than three months, which is defined as chronic cluster headache (cCH).

Age at onset is usually 20–40 years, men are three times more often affected.

The pathophysiology of CH is believed to be driven by the trigeminovascular system, the trigeminal-autonomic reflex (sphenopalatine ganglion stimulation), and the hypothalamic system. Increases in CGRP levels might lead to vasodilation and hyperactivity of trigeminal nociceptive fibers. Others potential inducers of CH attacks include PACAP38, and vasoactive intestinal peptide (VIP) (4).

Available treatments for acute attacks are triptanes and inhaled oxygen, while corticosteroids and occipital nerve blocks are used as interim treatments to bridge until preventive treatment onset of effect. Verapamil is used as the drug of first choice in the prophylaxis of episodic and chronic cluster headache.

2. Scope

Guidance is provided on the development of medicinal products for the treatment of acute migraine attacks and prevention of migraine in patients with episodic and chronic migraine, including patients with menstrual migraine. In addition, recommendations on clinical development programs for the treatment of cluster headache are given. Additional points to consider in elderly or paediatric patients are provided.

3. Legal Basis and relevant guidelines

This guideline has to be read in conjunction with the introduction and general principles and part I and II of the Annex I to Directive 2001/83 as amended. Further is referred to the EMA and ICH guidelines on pharmaceutical development, PK/PD topics, clinical trial design, special populations including the elderly and paediatric population. These include, but are not limited to:

Clinical Investigation of Medicinal Products in the Paediatric Population (EMA/CPMP/ICH/2711/1999; ICH E11)

Applications with 1.) Meta-analyses and 2.) One Pivotal Study (CPMP/2330/99);

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (EMA/CHMP/ICH/436221/2017).

This guideline is intended to assist applicants during the development of medicinal products for the treatment of migraine. Any deviation from guidelines should be explained and discussed in the Expert reports/ Clinical Overview.

4. General elements on pharmacology and exploratory studies

4.1. Pharmacokinetics and formulations

The general recommendations for pharmacokinetic characterization apply for medicinal products developed for migraine or cluster headache treatment.

In general, pharmacokinetic interaction studies should be mechanistically driven. When the investigational product is being co-administered with other antimigraine medicines used in routine clinical practice, interaction studies are advisable when a pharmacokinetic interaction cannot be excluded due to pharmacokinetic properties of the medicinal product.

For medicinal products intended for oral treatment of an acute migraine attack, it should be taken into consideration that a migraine attack may influence the absorption of oral products due to changes in gastrointestinal motility.

Alternative routes of administration may be explored, especially for patients, who frequently suffer from severe nausea or vomiting.

Furthermore, in paediatric patients, a pharmacokinetic study will be needed to define the dose equivalent to the effective dose in adults (see also section 6.2).

4.2. Pharmacodynamics

There are no established specific pharmacological disease models of migraine or cluster headache, that could be relevant for all medicinal products regardless of the mechanism of action. Depending on the mechanism of action of the study medicine, it is expected that appropriate preclinical and/or clinical studies should be able to support the mechanism of action, identify potentially effective dose and forecast the effects in humans based on accepted theoretical constructs. For example, for CGRP inhibitors, reduction of capsaicin-induced dermal blood flow is accepted as pharmacodynamic model.

Potential pharmacodynamic interaction with other agents (alcohol, vasoconstrictor drugs, oral contraceptives, anti-migraine drugs, and CNS-acting drugs) should be considered, including possible additive adverse effects on e.g., blood pressure.

4.3. Early efficacy and safety studies

While most of the recommendations for the pivotal investigations for migraine and cluster headache apply also to early efficacy and safety studies, only specific considerations are outlined in this section.

Early safety and efficacy studies should preferably exclude patients with other types of headaches. Alternatively, the patients should be able to distinguish between migraine and other types of headaches.

Establishment of exposure-response relation and well-designed dose finding studies are recommended to inform the optimal dose to be used in confirmatory studies.

In particularly, for acute treatment of migraine attacks, the early development programme should aim to answer questions such as the ideal timing of administration within an attack, re-dosing within the same episode, and tachyphylaxis.

5. Methodology of the pivotal investigations for treatments for migraine

5.1. Acute treatment of attacks

The main aim of the acute treatment of migraine attacks is resolution of pain. Furthermore, resolution of the accompanying symptoms should also be part of the objectives of treatment of migraine attacks.

As pain also resolves spontaneously, in response to the use of other medicines, or possibly due to placebo effect, clinical trials aiming at demonstrating an effect on migraine attacks will need to account for these possibilities, through the inclusion of a control arm and randomisation.

Consistently with the re-occurring nature of migraine attacks, it is important to demonstrate that treatments do not only work for the first migraine attacks they are used for, but also for the following ones. Assessing efficacy over multiple migraine attacks is an important goal of these trials. It should be demonstrated that patients who repeat treatment have an acceptable probability to respond to any further migraine attacks after the first one.

5.1.1. Population

When defining the population eligible for clinical trials, the need for external validity should be balanced with the need to have a sensitive population in which treatment effect can be demonstrated.

The diagnostic criteria should conform to those outlined in the most recent version of the International Classification of Headache Disorders (ICHD) [5]. Unless a specific mechanism of action suggests otherwise, patients with migraine with and without aura can be studied together.

Patients included into the clinical trial should have a history of a sufficient frequency of migraine attacks in order to have at least one migraine attack within the duration of the clinical trial to have the possibility to detect a treatment effect. In addition, patients should be able to discriminate between migraine attacks and other headache types. Unless otherwise justified, only adult patients should be included.

Age at onset of migraine is usually less than 50 years. Later-onset migraine-like headache is likely to be secondary to an underlying pathological condition. Therefore, in order to exclude other secondary types of headaches, it is recommended to include only patients with age at onset of less than 50 years in clinical trials.

It is preferable not to include individuals satisfying criteria for chronic migraine or with a history of chronic migraine in the last 12 months; the reason being that it might be difficult for these patients to identify the start of a migraine attack and take the treatment as soon as possible, as usually required in these trials. In addition, patients should have at least 48 hours of freedom from headache between attacks of migraine.

Patients with secondary headache disorders should not be included.

When patients are using prophylactic medications, this should have remained unchanged for 3 months prior to inclusion. If prophylaxis has been withdrawn this should have been at least one month prior to

inclusion or longer for compounds with long half-lives. If the study population includes patients with and without prophylaxis, randomization should be stratified accordingly to ensure balanced distribution between treatment arms and allow an appropriate subgroup analysis. These subgroups with and without the prophylactic treatment should be of sufficient size.

5.1.2. Study design and comparator

Pivotal trials should address both the efficacy in single migraine attacks and the efficacy over multiple migraine attacks.

Two randomised, double-blind, placebo-controlled trials are expected to show superiority over placebo in the treatment of single migraine attacks. When the main objective is demonstration of non-inferiority compared to an active control, a placebo arm is still required to demonstrate study's assay sensitivity.

Efficacy on multiple attacks can be shown in separate clinical trials treating consecutive attacks. Alternatively, investigation of both efficacy on the first migraine attack and efficacy over multiple migraine attacks can be pursued in the same clinical trial (i.e. in at least one of the two clinical trials aiming at demonstrating the effect on a single migraine attack).

The response in the placebo arm in migraine clinical trials usually is large and highly variable. Single migraine attack characteristics and spontaneous resolution may vary, too. It is important to collect baseline information about the headache during migraine attack (i.e., headache intensity, presence or absence of associated symptoms, unilaterality or bilaterality of the headache, aggravation by exercise, throbbing or non-throbbing, duration of migraine attack) to document the characteristics of the acute migraine attack. This information should be collected either within 3 months well-documented retrospective history period or a prospective screening/baseline (run-in period) of at least one month.

It is expected that frequency of migraine attacks determined during screening/baseline period remains similar after randomization. The similar frequency of migraine attacks during both periods would allow better define the expected duration of clinical trial. A certain time from randomization should be considered for treating an attack of migraine, but if no migraine attack has occurred within a pre-specified period the patient may be withdrawn from the trial.

In a migraine attack the headache is evolving gradually, sometimes rapidly, to a peak with subsequent resolution. The timing of intake of test medication may affect efficacy. Therefore, the timing of administration of medicinal product should be defined in the study protocol. Also, the actual time of intake in relation to onset of the migraine attack needs to be reported.

The data collected (e.g. through diaries, see below) should refer to a period after the treatment of a migraine attack of at least 48 hours. Use of rescue medication should be allowed for all patients as part of the protocol. The use of rescue medications should be systematically recorded, especially, since it is considered as an important secondary endpoint (see below).

In migraine with aura, specific studies may be performed to evaluate the action of the medicinal product taken on development of aura symptoms and onset of headache during the aura period. The time from onset of aura symptoms to treatment should be characterised describing development of symptoms, headache intensity and other characteristics of headache (see above).

5.1.3. Endpoints

The primary endpoint is the status of a patient being pain-free 2 hours after administration of test drug without use of rescue medication.

Secondary endpoints typically include:

- The pain-free status without rescue medication at 2 hours and no re-occurrence of pain within 48 hours after use of study medication;
- Return of headache of any severity within 48 hours after the patient has been pain-free at 2 h after use of study medication;
- Re-use of study medication;
- Rescue medication after the patient has been pain-free at 2 h;
- Intensity of headache at various time points;
- The time-to-meaningful relief of pain and other symptoms;
- Use of rescue medication over 48 hours after the first treatment of headache;
- Global evaluation of efficacy by assessing the Patient Global Impression of Change (PGI-C);
- Functional disability at 2 hours and other time points;
- Improvement of most bothering migraine-associated symptoms such as nausea, vomiting, photophobia and/or phonophobia.

Data collection will typically be done through paper or electronic headache diaries. The headache diary might include various variables, at least including headache start and end, headache characteristics (duration, location, pain quality), associated symptoms (nausea, photophobia, phonophobia), intensity of headache, use of medications.

5.1.4. Safety considerations

The medicinal products to treat acute migraine attacks are expected to be used repeatedly, since migraine attacks tend to regularly return. Thus, the use of medicinal products for acute migraine attack treatment is likely to become rather frequent resembling chronic use of medicinal product. Even though treatment of acute migraine attacks is not considered chronic treatment, safety data collection on intermittent use in an open-label long-term extension of the clinical trial lasting 12 months is considered necessary.

The minimum interval for safely re-administering the drug, maximum number of migraine attacks that could be safely treated or maximum dose to be used in a fixed interval (e.g. a week, a month) should be addressed in the protocol.

Specific attention should be given to medication overuse headache, which may occur after frequent use of acute medication for migraine i.e., daily or almost daily usage depending on substance. Drug-drug interactions, potential safety concerns due to combination use on top of potentially used prophylactic treatment and combinations to be avoided should be specified.

Given the demographics of migraine-sufferers, pregnancy-related safety concerns will need to be adequately characterized. Depending on the available data from non-clinical studies, such characterization may need to be completed in the context of post-authorization safety studies.

Special efforts should be made to assess potential adverse effects that are characteristic of the class of medicines being investigated depending on the action on various receptors/pharmacodynamic properties. As many treatments used in acute migraine are vasoactive the safety of such agents in patients with concomitant cardiovascular and/or cerebrovascular disease should be evaluated.

5.1.5. Statistical considerations

5.1.5.1. Target of Estimation

The clinical question of primary interest when treating the single migraine attack relates to the proportion of patients achieving a pain-free and rescue-free status at 2h after their first migraine attack treated with the test treatment (versus control).

A careful specification of the treatment attribute (e.g. ”medicine X taken during a migraine attack”) will allow the exclusion of migraine attacks that were not treated (e.g. because the patient did not carry the medicine while travelling).

In line with the question of interest above, for each patient, the primary estimand should only be related to the first treated migraine attack and the intercurrent event "use of rescue medication” should be handled with a composite strategy.

Emesis is frequent during migraine attacks. For orally administered treatments this intercurrent event can be anticipated and should be accounted for. A treatment-policy strategy is preferred. Patients might also fall asleep between the administration of the medicine and time of assessment. Thus, the time of becoming pain-free cannot be assessed. As the pain-free status still exists in this case, and still holds clinical value, this is not an intercurrent event to consider in the definition of the Estimand, but rather a possible reason for missing data.

To evaluate the efficacy over multiple migraine attacks, it is of interest to both (i) descriptively characterise the probability of responding to active treatment in migraine attacks after the first one and (ii) compare this proportion to the placebo response for the same number of migraine attacks. For the latter, an important caveat is the need to have comparable populations. This could in principle be achieved with trial design or with a principal stratification approach.

5.1.5.2. Methods of estimation

The analysis aligned with the primary estimand is a comparison between proportions, and it should be performed with standard methods.

Analysing treatment effect of a single migraine attack, especially for the primary estimand, as only the first treated migraine attack is targeted, it should be possible to limit the amount of missing data. If patients do not have (treated) migraine attacks in the observation period, they are not included into main analysis. If patients have a treated migraine attack but with non-reported outcome, a missing data problem presents. The primary estimator and the sensitivity analysis should cover a range of possibilities. While the main analysis might make a missing-at-random (MAR) assumption with a reasonable set of covariates to fulfil the MAR definition, it is recommended that analysis under missing-not-at-random (MNAR), treating all missing outcome as non-response, and tipping-point analyses are also presented.

The analysis aligned to the objective of characterising efficacy over multiple migraine attacks presents more difficulties. Different approaches can be pursued. One consists in describing the difference between active treatment and placebo in the proportion of responses in subsequent treatment of migraine attacks in patients who continue treatment. That any difference can be attributed to continued efficacy and not to the different post-randomisation selection of the population should be ensured either through design or through analytical approaches such as principal stratification. In this case the uncertainties inherent to the principal-stratum definition should be discussed and, if necessary, addressed by sensitivity analysis.

5.2. Prophylactic treatment

The main aim of prophylactic treatment is the reduction of frequency of days in which patients have migraine attacks.

The reduction of the intensity of remaining migraine attacks and the reduction of use of medications for the acute treatment of migraine attacks and hence the risk of developing medication-overuse headache are also objectives of prophylactic treatment.

5.2.1. Population

The patient population eligible for prophylactic clinical trials is essentially the same as for trials investigating the treatment acute migraine attacks described in 5.1.1. In addition, patients with chronic migraine are eligible for prophylactic treatment.

Patients should be enrolled in trials for prophylactic treatment of migraine if their disease burden justifies prophylactic treatment. This generally translates into a reported frequency at screening (when not treated or unsuccessfully treated with a prophylactic treatment) of at least 4 migraine days per month. To support an indication for the preventive treatment of migraine (i.e. an indication comprising patients with both episodic and chronic migraine) efficacy should be adequately demonstrated in both populations, EM and CM, as response to treatment may be different.

Patients should generally have had migraine diagnosis for at least 1 year and there should be a 3-months well-documented retrospective history.

The baseline frequency should be prospectively confirmed in a 4-weeks run-in period before starting treatment. Descriptive data on migraine days' frequency should be provided for both treatment arms at the end of the prospectively confirmed 4-week period.

The differential diagnosis between chronic migraine and medication overuse headache and tension headache as defined by ICHD can be difficult. However, subjects with chronic migraine meeting also criteria for medication overuse headache at baseline may be included in chronic migraine trials provided concomitant medication remains stable.

Other medicines used for migraine prophylaxis should be discontinued at least 3 months prior to the trial.

5.2.2. Study design and comparator

Superiority of the investigational product in comparison with placebo should be demonstrated in randomized, 2-arm double-blind controlled parallel group trials. These studies can be two similarly designed studies investigating efficacy and safety of the investigational product, one study in episodic and another in chronic migraine. If subjects with medication overuse headache are included in a trial, it is mandatory to record use of all headache medications during the baseline period and the treatment phase. In this case, medication overuse headache should be one of stratification factors.

Parallel group studies with 3 treatment arms with active comparator and placebo might be sensible to contextualize the observed efficacy of the new treatment, with the superiority to placebo being the primary objective. The choice of an active comparator as well as its dose should be adequately justified. Demonstration of superiority of the active comparator versus placebo could also be useful as a confirmation of the sensitivity of the study in case the study shows superiority of the new medicinal product versus placebo. It is, however, not necessary to formally test for the non-inferiority to the active comparator in the presence of a placebo arm but estimates of treatment effect differences

between the active comparator and new medicinal product should be reported with confidence intervals.

The duration of the placebo-controlled treatment period should be at least 24 weeks after the titration period (if any). Trials of longer duration may be useful for evaluating maintenance of prophylactic effect while also providing additional safety and tolerability data.

Patients should be followed for at least 4 weeks after termination of the treatment period to detect possible rebound phenomena (i.e. frequency of migraine days per month going above its baseline). Depending on the half-life of the investigational product the observational period may need to be longer.

Treatment of an acute migraine attack during the clinical trial is allowed and should follow the usual standard of care. Patients can use their usual symptomatic or migraine specific acute treatment provided, that it can be safely administered with the study medication. Such treatment should preferably not be changed during the trial.

Information for data collection see section 5.1.2.

5.2.3. Endpoints

The primary endpoint in confirmatory trials of preventive treatment for both episodic and chronic migraine should be the change from baseline in the mean number of monthly migraine days (MMDs).

The recommended time-period for analyses of the primary endpoint is the entire treatment period.

A migraine day should be prospectively defined based on prespecified criteria and could be defined as any calendar day with headache lasting at least 30 minutes and meeting ICHD-3 criteria for migraine or probable migraine. A migraine day should also include any day during which a subject takes medications for acute migraine, regardless of the duration of pain.

Based on migraine days, one can derive the frequencies and a binary responder status, where a "responder" should be defined as a patient with a 50% or greater reduction in the primary endpoint (i.e. monthly migraine days during treatment compared to baseline). This might be used as a secondary endpoint to relate an effect observed in the primary endpoint to a clinical relevance of the effect.

Other secondary endpoints might be:

- Number of monthly headache days of moderate to severe intensity. In analogy with migraine days, a headache day could be defined as any calendar day during which the subject experienced a qualified migraine or nonmigraine headache that lasts continuously for greater than or equal to 4 hours or a headache of any duration for which acute treatment is administered.

- Improvement of migraine-associated most bothersome symptoms such as nausea, vomiting, photophobia and/or phonophobia

- Onset of effect

- Acute migraine medication use

- Patient’s Global Impression of Change scale

- Disease-specific Quality of Life (QoL) questionnaires

The validity and the minimal clinically relevant difference for each selected health-related Quality of life (HR-QoL) questionnaires should be specified and justified in the marketing authorization application

(MAA). Examples of acceptable disease-specific QoL measures in migraine are Migraine Disability Assessment Questionnaire (MIDAS), Headache Impact Test (HIT-6) and Migraine-Specific Quality-of-Life Questionnaire (MSQ) v2.1.

Headache indices encompassing frequency, intensity and/or duration into a single composite score are difficult to interpret in terms of clinical relevance of observed changes of the score given that such aggregation can mask the clinical relevance of changes observed in individual domains. Unless specifically validated as an informative endpoint, combined headache indices will only provide exploratory information.

The effects on the primary endpoint may be statistically significant but still difficult to interpret as a clinically relevant effect for the patient. To evaluate the total impact of migraine on the patient, the totality of data from various endpoints measuring different aspects of the impact of headache needs to be weighted together. To this end, the treatment effect on the primary endpoint (number of migraine days) should be supported by secondary endpoints, especially responder rate, patients global impression of improvement (PGI-I) and HR-QOL outcomes.

5.2.4. Safety considerations

Migraine is a chronic condition, and medication for prophylactic treatment is likely to be used over long time periods. Long-term data should be generated by conducting open label extension studies to assess development of tolerance and/or long-term alterations in the therapeutic effect over time and maintenance of safety.

An open-label study of at least 12 months duration in an appropriate number of patients treated at the selected therapeutic dose(s) should be performed to establish the long-term safety and maintenance of prophylactic efficacy. Development of tolerance. possible withdrawal effects, rebound after drug discontinuation should be evaluated. Treatment retention rate may be a global indicator of perceived effectiveness.

The considerations regarding pregnancy (see section 5.1.4.), also apply to prophylactic treatments.

5.2.5. Statistical considerations

5.2.5.1. Target of estimation

The clinical question of primary interest relates to the difference of change from baseline in number of monthly migraine days in the treated period between treatments assignments.

As prophylactic treatment of migraine usually requires chronic treatment, treatment discontinuation is expected to be a relevant intercurrent event, which should be handled in the primary estimand with a treatment policy strategy. A secondary estimand that handles it with a composite strategy (i.e. as a treatment failure) should also be presented.

The subsequent possible switch to another prophylactic treatment should be handled with the hypothetical strategy, whereby the hypothetical effect is in a scenario, where the patient had discontinued treatment instead of switching it, is of interest. The secondary estimand mentioned above will consider these patients as having failed treatment at the moment of discontinuation, before the switch. Changes in concomitant prophylactic treatment, if occurring, should be handled with a treatment policy strategy. The use of medications that only work to treat migraine attacks usually does not pose a problem as the above-mentioned definition of a migraine day already includes the use of medications for migraine attacks. There are, however, medicines that are used to treat migraine attacks, but also have prophylactic activity. For those, a hypothetical strategy might be of interest for

the migraine in the days potentially affected by the intake. This hypothetical strategy can be implemented through the design (i.e. other medications for the acute treatment of migraine attacks can be prioritized when possible) and through adequate estimation methods.

5.2.5.2. Method of estimation

As trials for prophylactic treatment are longer than trials for acute treatment, it is possible that a missing data problem will arise due to missing diary entries or patients discontinuing the study. Minimisation of missing data through study procedures, including continuous follow-up after treatment discontinuation and optimising the diary for this purpose, is encouraged. Importantly, the method of analysis should not assume continued benefit from treatment after discontinuation, or after treatment switch when the hypothetical effect, if the patient had discontinued treatment instead of switching, is of interest. This can be achieved with a treatment indicator in the context of a MAR analysis or with reference-based imputation methods. Sensitivity analysis should be performed, including tipping-point analysis. In addition, estimation problems – different from missingness - arise after intercurrent events that are accounted for by a hypothetical strategy.

6. Special populations and considerations on other headache disorders

6.1. Studies in older patients

For both acute and prophylactic migraine therapy, PK and safety data may be sufficient in elderly patients suffering from migraine for many years, and extrapolation may be done from efficacy results obtained in the adult (18-65 years) population.

However, specific studies may be needed for the population over 65 years because of higher rates of concurrent diseases such as cerebrovascular and cardiovascular diseases in this category of patients.

6.2. Studies in paediatric patients

Migraine is less common in younger children and may be difficult to diagnose in children younger than 6 years old, as compared to adults there are certain differences in disease manifestation (e.g. more predominant gastrointestinal symptoms, tendency to shorter duration of migraine attacks). Moreover, disease characteristics change with age, especially in puberty. On the other hand, the established diagnostic criteria defined by ICHD are similar for adults and paediatric patients. Migraine has a genetic component with environmental influences on attack manifestations, but the pathophysiology is still not fully elucidated.

The extent of possible extrapolation of adult data on paediatric population has not yet been established.

Efficacy in acute treatment of migraine should generally be shown separately for children (6 - < 12 years age) and for adolescents (12-18 years of age). Due to feasibility issues, inclusion of patients under 12 years would not be required in prophylactic studies. Furthermore, the real need for prophylactic treatment even in patients above 12 years old should be justified by demonstrating the debilitating nature of sufficiently frequent migraine attacks.

The diagnostic criteria for migraine should conform to the most recent ICHD criteria [5].

In children, the diagnosis of migraine should be present for at least 6 months prior to trial inclusion.

The development of a child-friendly formulation (e.g. nasal drops, sublingual drops, sprays) is advocated. Pharmacokinetic studies may be needed to define the dose equivalent to the effective dose in adults.

The design and duration of the confirmative clinical trials of acute or prophylactic treatments developed for children and adolescents as well as primary and secondary endpoints are essentially identical to the ones used for adult studies. Assessment of pain and other variables should be based on scales validated for migraine in these age categories. If efficacy over multiple migraine attacks has already been shown in the adult setting a single migraine attack clinical trial in both age categories could be considered sufficient. Cross-over trials might be considered for acute treatments in paediatric patients in order to address the feasibility issue. A single clinical trial including paediatric patients with EM and CM could be considered.

Long-term safety data are required, especially for prophylactic treatment, evaluating the impact of treatment on growth, endocrine function and neurodevelopment of patients. In addition, safety data on cognitive function may be required as a post-authorization measure.

6.3. Menstrual migraine

Pure menstrual migraine is defined as migraine occurring on day 1 ± 2 (i.e., days −2 to +3) of menstruation in at least two out of three menstrual cycles and at no other times of the cycle, while menstrually-related migraine might occur additionally at other times of the cycle [5]. In studies in menstrual migraine the temporal relationship between menses and migraine attacks should be stringently recorded.

Clinical trials in menstrual migraine generally follow the same design and endpoints as those in non-menstrual migraine. Patients with menstrual migraine/menstrually-related migraine might be studied as subgroups in usual clinical trials for acute or prophylactic treatment of migraine if appropriate stratification is applied and a sufficient number of patients enrolled in specific subgroups to allow meaningful comparison. The alternative is to perform separate clinical trials in this specific population. Use of hormonal contraceptives should be considered as stratification factor.

In studies investigating a short-term peri-menstrual prophylactic treatment, correct timing of study drug application relative to the cycle should be ensured. This requires inclusion of women with documented regular menstrual cycles. The design of the prophylactic study should allow evaluating the possibility that attacks are merely postponed to a later time in the menstrual cycle.

Subgroups of patients with menstrual migraine from different studies in the clinical development plan may be combined in a meta-analysis if planned a-priori.

7. Cluster Headache

Pivotal studies should generally be performed separately for episodic CH (eCH) and chronic CH (cCH) or, alternatively, in a single study with stratified randomization in which both subgroups are large enough and the study overall designed to allow evaluation of a consistent treatment effect across subgroups.

The treatment response may be different for acute cluster headache attacks and for prevention of cluster headache attacks. Patients should be diagnosed according to the most recent version of the ICHD diagnostic criteria.

7.1.1. Acute treatment

A parallel group, placebo-controlled, double-blind design is recommended. Cross-over clinical trials may be acceptable, if the investigational medicinal product has a short half-life and no carry-over effect is expected, using a sufficiently long washout period. For cross-over clinical trials, specific considerations should be given to expected adverse drug events in order to preserve blinding.

A prospective baseline period of 1 week is recommended to verify frequency and intensity of attacks.

Treatment should be administered as early as possible in the attack; however, at least moderate intensity of headache should be documented before starting the treatment.

During double blind phase up to 5 attacks should be treated to evaluate consistency of efficacy over multiple attacks, but the primary analysis should be on the treatment results of the first attack.

Primary Endpoint:

The recommended primary endpoint is pain-freedom 15 minutes after study medicinal product administration without recurrence of any level of pain within 3h in the first treated attack.

Secondary Endpoints:

The following secondary endpoints could be recommended:

- pain freedom after 15 min without recurrence in all treated attack
- 50% responder rate (defined as the proportion of participants who are pain-free after 15min in at least 50% of treated attacks)
- Time to meaningful pain relief
- Sustained pain relief response after 15 minutes without worsening or use of rescue medication within 3 hours
- Pain-freedom / pain relief at 5, 10 and 15 min
- Intake of rescue medication and percentage of attacks with need for rescue therapy.
- Number of attacks per day during the study period
- Time to next attack
- Time to normal functioning
- Patient global impression of change

7.1.2. Prevention

A parallel group, placebo-controlled, double-blind, add-on design on top of standard of care (SoC) preventive treatment (e.g. verapamil) is recommended. Patients who are intolerant or resistant to available preventive treatments might be studied in a placebo-controlled study without SoC.

Patients should be diagnosed according to the most recent version of the ICHD diagnostic criteria and should be recruited within the first 2 weeks of the start of a CH period. The period during which the baseline frequency of cluster headache attacks is established should be kept short since it is important

to start treatment as early as possible during a cluster episode and in addition to avoid spontaneous remissions at the time when the data for the primary endpoint are obtained.

The recommended duration of double-blind treatment should be > 3 weeks for eCH, depending also on the expected pharmacology profile of the treatment to be tested. For cCH a longer study duration (1-3 months) is recommended as the weekly attack frequency may fluctuate, and flare ups are described. Open-label extensions should be conducted both to cover the full bout (when not covered in the double-blind phase) and to evaluate the effect on subsequent bouts.

Included eCH-patients should present ≥4 typical attacks per week and cCH-patients with ≥4 weekly typical attacks for ≥4 weeks. Prior history of duration of a cluster period should be considered to ensure that the patient will not enter spontaneous remission of the cluster period during the treatment period.

Patients with concomitant chronic migraine or chronic tension-type headache should not be included in clinical trials. Patients with other concomitant infrequent primary headache types are allowed to participate if they can clearly differentiate them from attacks of CH.

Primary Endpoint

Normally, it may take a few weeks in the beginning of a cluster headache episode before the frequency and pain severity have reached their respective maximum. It is recommended to carefully capture duration of the bout before treatment is administered. The baseline CH attack frequency may be low compared to the maximal weekly CH attack frequency in the untreated patient, which may affect the efficacy size in both treatment groups.

The primary efficacy endpoint could be the change from baseline in number of weekly attacks. The timing of assessment should consider the expected onset/maximum of effect of the drug candidate, and in any case should not be inferior to 3 weeks.

The timing of natural remission should also be taken into consideration.

It should be considered whether bout duration (for the ongoing bout qualifying the subject to be randomised) should be a stratification variable at randomisation, as it could be anticipated that subjects treated at a very early stage may still be in a phase of increasing frequency of cluster headache attacks. Such patients may possibly show a stabilisation of the number of cluster headache attacks rather than a reduction.

Secondary Endpoints

Information should be provided on

- 50% responder rate in the number of weekly cluster headache attacks (single weeks and entire double-blind period)
- Change from baseline in number of weekly attacks (single weeks and entire double-blind period)
- Reduction of pain intensity of attacks over time
- reduced use of abortive medications
- early onset of efficacy: change from baseline in daily attacks
- duration of effect
- disease-specific HR-QoL

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