Migraine: Developing Drugs for Preventive Treatment

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Migraine: Developing Drugs for Preventive Treatment Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the preventive treatment of migraine.[2] Pharmacological approaches to the treatment of migraine include drugs to abort migraine attacks as they arise (acute treatment of migraine) and drugs to reduce the frequency of migraine attacks (preventive treatment). Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs to support approval of drugs for the preventive treatment of migraine.[3] This guidance does not address the development of drugs indicated for the acute treatment of migraine. Such development has been addressed in the guidance for industry *Migraine: Developing Drugs for Acute Treatment* (February 2018).[4]

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Refer to FDA's ICH guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998), *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021), and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001) for discussion of these topics.

[1] This guidance has been prepared by the Division of Neurology II in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262), unless otherwise specified. Also, see definitions of *drug product* and *biological product* in 21 CFR 314.3 and 600.3, respectively

[3] In addition to consulting guidances, sponsors are encouraged to contact the Division of Neurology II to discuss specific issues that arise during the development of drugs for the preventive treatment of migraine.

[4] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Migraine is a chronic neurovascular disorder characterized by recurrent attacks of often severe headache, typically accompanied by nausea and sensitivity to light and/or sound. In adults, migraine attacks usually last from 4 to 72 hours. Migraine headache is typically throbbing, unilateral, and aggravated by physical activity. Criteria proposed by the International Headache Society are called the International Classification for Headache Disorders (ICHD) and require a combination of some of these characteristics and associated symptoms in at least five attacks to establish a diagnosis of migraine.[5]

Patients may experience migraine with or without aura. Migraine with aura is characterized by focal neurological symptoms (e.g., visual disturbances, abnormal sensations) that typically precede, or sometimes accompany, the headache. These focal neurological symptoms are absent in migraine without aura. Some patients may present with both types of migraine.

III. DEVELOPMENT PROGRAM

A. Efficacy Considerations

Subjects enrolled in clinical trials for the preventive treatment of migraine should have a diagnosis of either chronic migraine or episodic migraine. Chronic migraine is defined by the ICHD as headache occurring on 15 or more days per month for more than 3 months, which, on at least 8 days per month, has the features of migraine headache. Patients with chronic migraine may overuse acute medication and may also fulfill the ICHD criteria for medication overuse headache.[5] Randomization of subjects with chronic migraine into clinical trials should be stratified based on the presence or absence of a concomitant diagnosis of medication overuse headache. Patients with episodic migraine have intermittent, recurrent attacks that meet ICHD criteria[5] for migraine with or without aura, with headache occurring on 14 or fewer days per month. Subjects eligible for enrollment in a chronic or episodic migraine clinical trial should have confirmation of the diagnosis based on their monthly frequency of migraine or headache during a baseline observation period.

Sponsors should consider chronic migraine and episodic migraine separately when developing drugs for the preventive treatment of migraine because the response to treatment may vary in these two patient populations. In addition, episodic migraine patients may be more able to accurately define the beginning and end of a migraine attack, whereas chronic migraine patients

[5] International Classification of Headache Disorders is available at https://ichd-3.org/classification-outline/.

may have difficulty distinguishing individual headache episodes when headache continues over several days.

To support an indication for the preventive treatment of migraine (i.e., an indication comprising both patients with chronic migraine and episodic migraine), efficacy should be demonstrated in a minimum of one adequate and well-controlled trial in each population.

If a drug is already approved for the acute treatment of migraine, a single additional adequate and well-controlled trial evaluating its efficacy for the preventive treatment of migraine could support a preventive treatment indication for the population studied in that trial (i.e., patients with either chronic or episodic migraine).

1. Trial Design

In general, confirmatory trials should use a randomized, double-blind, placebo-controlled parallel group design. There may be circumstances in which randomization to an active control may be appropriate. It is usually preferable to study at least two dose levels in the confirmatory trial (see Section III. A. 3., Dose Selection).

2. Trial Population and Entry Criteria

Subjects enrolled in clinical trials should have a diagnosis of either chronic migraine or episodic migraine, as stated previously. Migraine subjects with and without aura may be enrolled in confirmatory trials. The time since initial diagnosis of migraine should be at least 12 months before enrollment, with eligibility at enrollment based on a minimum 3-month history of migraine frequency, and with confirmation of migraine frequency observed during a minimum 1-month prospective baseline period (although a longer baseline period can provide a more stable estimate of migraine frequency). Although trials should attempt to enroll a broad age range of subjects, the age at the time of initial migraine diagnosis should generally be younger than 50 years old to decrease the chance of enrolling subjects with headaches attributable to another underlying disorder that may mimic migraine (e.g., a brain neoplasm, stroke, temporal arteritis, etc.). If subjects have more than one headache type, they should be able to distinguish their other headache types (e.g., tension-type headaches) from their migraines.

When developing clinical trial protocols, sponsors should ensure that trial sites and outreach efforts are broad enough to allow for a representative sample of the population for which the drug may be indicated. Sponsors should try to include a diverse population, including a sufficient number of racial and ethnic minority subjects, male subjects, and a sufficient number of subjects over 65 years of age to conduct an adequate assessment of safety and efficacy in these subgroups.[6]

[6] See the guidance for industry *Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020).

3. Dose Selection

Early phase trials should explore a range of doses to assess dose-response relationships for safety and efficacy and to inform dose selection for the confirmatory trials. Confirmatory trials should identify the lowest dose that provides a desirable treatment effect. Sponsors should also conduct adequate evaluations of drug interaction potential with combined oral contraceptives.[7]

Sponsors should obtain plasma drug concentration data in subjects. Establishing a plasma concentration (exposure)-response relationship can be useful to support optimal dose selection in the general population. These data can be used to inform dosing recommendations based on specific intrinsic and extrinsic factors (e.g., body weight and hepatic and renal function).

In long-term safety studies, the majority of the safety experience should be in subjects who are on the highest dose planned for marketing.

4. Concomitant Medications

During the conduct of early trials, and until the drug-drug interaction liability of the drug is adequately understood, concomitant medications should be avoided. Assuming no important pharmacokinetic/pharmacodynamic drug-drug interactions are anticipated, sponsors can use concomitant preventive medications for migraine in later stage trials, but only if the dosage of those concomitant medications has been stable for an adequately justified period of time before inclusion into the trial. Subjects should also remain on stable doses of the concomitant drug during the entire duration of the trial. Sponsors should document prior and concomitant use of preventive treatments for migraine during the screening phase of the trials.

Drugs used for the preventive treatment of migraine are also often used for the treatment of nonmigraine indications and/or can be used to treat other comorbid disorders (e.g., epilepsy, depression, hypertension); therefore, sponsors should clearly document the diagnosis associated with each treatment. Because the use of other preventive migraine treatments may influence the interpretation of both safety and efficacy, no more than 30 percent of the study population should be taking a concomitant medication for the preventive treatment of migraine during the trial, and randomization should be stratified by the use of such concomitant medications. Subjects taking more than one such concomitant preventive medication should typically not be enrolled.

If subjects have recently discontinued a drug for the preventive treatment of migraine, withdrawal should be complete for at least 1 month or 5 half-lives, whichever is longer, before entry into the trial. Generally, acute treatments for migraine (triptans, nonsteroidal anti-inflammatories, etc.) should be allowed; however, sponsors should record the use of all such medications. Changes in the frequency of use of medications for the acute treatment of migraine should be evaluated as a secondary efficacy endpoint (see Section III. A. 5).

[7] See also the draft guidance for industry *Clinical Drug Interaction Studies With Combined Oral Contraceptives* (November 2020). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

5. Efficacy Endpoints

In episodic migraine trials, the primary efficacy endpoint should assess the change from baseline in the number of monthly migraine days (see the migraine day example below). For chronic migraine trials, sponsors may use the change from baseline in the number of monthly migraine days or in the number of monthly headache days (of moderate/severe intensity and/or requiring use of an acute migraine medication) as the primary efficacy endpoint. In the latter scenario, the change from baseline in monthly migraine days should be evaluated as a secondary efficacy endpoint instead.

Sponsors should assess the following secondary efficacy endpoints in a manner that controls for type I error:

a. Change from baseline in the number of days per month subjects use an acute/rescue medication to treat an acute migraine

b. Change from baseline in prospectively defined monthly headache days (if monthly migraine days is the primary endpoint) or in monthly migraine days (if monthly headache days is the primary endpoint)

Sponsors may consider evaluating secondary endpoints that assess responder rates for the primary efficacy endpoint (e.g., a reduction in the number of mean monthly migraine days from baseline by at least 50 percent). Sponsors may also consider additional secondary endpoints (see Section III. A. 7., Patient-Reported Outcomes). Ordering of secondary endpoints should be based on the trial objectives and intended claims in labeling. Typically, secondary endpoints to be described in labeling should not be duplicative of the primary endpoint.

A migraine (and/or headache) day should be prospectively defined based on prespecified criteria. For example, a migraine day could be defined as any calendar day during which the subject experienced a qualified migraine headache lasting for at least 30 minutes and having at least two of the following features: unilateral location, throbbing, moderate to severe intensity, exacerbated by exercise/physical activity or at least one of the following symptoms: nausea and/or vomiting, photophobia, or phonophobia. A migraine day should also include any day during which a subject takes acute migraine medications, regardless of the duration of pain.

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.

6. Trial Procedures and Timing of Assessments

The double-blind treatment phase should be at least 3 months in duration. A follow-up visit should occur at least 1 month or 5 half-lives after the last dose, whichever is longer, to adequately capture adverse events that may be related to the drug (including any increase in migraine frequency upon treatment discontinuation).

Data should be collected in a headache diary. We recommend using electronic diaries so that data can be time stamped, tracked, and audited to monitor compliance, ensure data integrity, and reduce recall bias. The headache diary should be shown to be well-defined and reliable for the target population based on the recommendations described in the draft guidance for industry *Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments* (June 2022).[8]

7. Patient-Reported Outcomes

A patient-reported outcome (PRO) is any report of the status of a patient's health condition that comes directly from a patient, without interpretation of the patient's response by a clinician or other person. In clinical studies for migraine, the primary endpoint is typically patient reported. Other PRO instruments can also be used as secondary endpoints to assess treatment benefit. Sponsors that intend to develop and/or include a PRO instrument in their programs should engage early with the review division. In general, instruments should assess concepts or domains that are important to patients, are sensitive to clinically meaningful change, have scoring that can be easily interpreted, and have a recall period that is appropriate for the proposed study design and endpoints. Further information on using a validated PRO may be found in the draft guidances for industry *Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments* and *Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints For Regulatory Decision-Making* (April 2023).[9]

8. Statistical Considerations

The primary efficacy analysis should compare the reduction from baseline in monthly migraine days (or headache days) between treatment groups during a prospectively defined evaluation period. The pharmacodynamic and/or pharmacokinetic (PK) characteristics of a drug may inform the appropriate duration of this period. Sponsors may choose to define this evaluation period as the entire double-blind treatment period (i.e., a minimum of 3 months), or alternatively, over the last month of this period. If the primary efficacy analysis only considers the final month of the double-blind treatment period, then a sensitivity analysis should assess the entire post-randomization period.

To improve the precision of treatment effect estimation and inference, sponsors could consider adjusting for prespecified baseline factors (e.g., baseline use of concomitant medications for preventive treatment of migraine or baseline number of monthly headache/migraine days) that are anticipated to be prognostic of the outcome. If randomization is stratified by baseline covariates, the analysis should account for the stratified randomization.

It is important to prospectively define the secondary endpoints and to include a statistical plan to control the type 1 error rate for multiple comparisons.

[8] When final, this guidance will represent the FDA's current thinking on this topic.

[9] When final, these guidances will represent the FDA's current thinking on these topics.

Study protocols should include provisions to limit missing data through design and monitoring. Sponsors should provide a prospective plan to handle missing diary data. Sensitivity analyses should be conducted to evaluate the impact of missing data on efficacy results.

B. Safety Considerations

Phase 1 trials, during which the investigational drug is administered under close medical supervision, provide the best opportunity to obtain safety data at time points close to administration of the investigational drug. At a minimum, these early study safety assessments should include vital signs; laboratory evaluations including hematology, serum chemistry, and urinalysis; and a 12-lead electrocardiogram, at appropriate intervals pre- and post-dose. Vital signs and electrocardiography should be assessed around the expected maximum concentration for the investigational drug and its major metabolites. Sponsors should include risk assessments for QT prolongation. Sponsors should obtain safety data during long-term phase 3 studies at baseline and at appropriate intervals post treatment. The design of clinical studies should take into consideration the results of the nonclinical studies,[10] prior human experience, and any other specific safety concerns with the investigational drug or with other drugs of the same class.

New molecular entities should follow the safety recommendations in the ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* (March 1995). The safety experience should be at relevant doses and frequency of administration, including substantial experience at the highest dose and highest frequency of administration proposed for marketing. The submission of additional product-specific safety data may also be necessary, including additional nonclinical studies and/or safety studies in populations at risk either before or post approval. Consultation with FDA is advised early in the development program, especially if a safety signal has already been identified.

C. Other Considerations

1. Pediatric Studies

Sponsors are encouraged to begin discussions about their pediatric clinical development plan early in development because, for drug or biological product applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration,[11] pediatric study plans are required to be submitted no later than 60 days (or such other time as agreed upon with FDA) after an end-of-phase 2 meeting.[12] Migraine diagnosis for purposes of pediatric patient enrollment should be based on the most recent ICHD criteria.

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[10] We support the principles of the 3Rs (reduce, refine, replace) for animal use in testing when feasible. We encourage sponsors to consult with us if it they wish to use a nonanimal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

[11] Section 505B(a)(1)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); 21 U.S.C. 355c(a)(1)(A).

[12] See section 505B(e)(2)(A) of the FD&C Act; 21 U.S.C. 355c(e)(2)(A).

Sponsors should refer to section 505B of the FD&C Act[13] to review requirements for submission of an initial pediatric study plan, where appropriate.[14]

Migraine is a relatively common disorder in children. The migraine phenotype is somewhat different between the adult and pediatric populations, and one cannot assume that a drug effective in adults will also be effective in children. Therefore, studies in the pediatric population are needed to determine pediatric efficacy. However, migraine, whether episodic or chronic, is less common in younger children and may be difficult to diagnose in children younger than 6 years old. Of those children diagnosed before 6 years of age, even a smaller proportion of subjects are likely to require preventive therapy; therefore, studies of preventive treatment of either chronic or episodic migraine are considered highly impracticable. For those applications that are subject to section 505B of the FD&C Act (i.e., applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration), and thus required to conduct pediatric studies, partial waivers of the pediatric study requirements are appropriate for studies of episodic migraine in subjects younger than 6 years of age. Chronic migraine typically develops after the onset of episodic migraine and thus is rare in children younger than 12 years old. Therefore, for those applications that are subject to section 505B of the FD&C Act, and thus required to conduct pediatric studies, partial waivers are appropriate for studies of chronic migraine in subjects younger than 12 years old. Disease characteristics often change with puberty, and pediatric studies in episodic migraine should include adequate numbers of subjects to characterize safety and efficacy of the drug across the entire pediatric age range.

Sponsors should assess and compare the PK of the drug in the pediatric population with the PK of the drug in adults to permit proper dose selection for pediatric efficacy and safety studies. PK data could be obtained either by a clinical PK evaluation or by modeling and simulations (currently accepted in adolescents if confirmed by sparse PK in the efficacy study). The development of an age-appropriate formulation may be necessary. Sponsors should consider adequate dose exploration in pediatric populations when feasible. Sponsors may select the dose based on exposure matching to adults or conduct additional dose finding in pediatric populations.[15]

The pediatric studies required under section 505B of the FD&C Act will reflect the approved adult indication (i.e., preventive treatment of episodic migraine, preventive treatment of chronic migraine, or preventive treatment of migraine (which includes episodic and chronic migraine)). For drugs approved for the preventive treatment of migraine in adults (i.e., an indication comprising both episodic and chronic migraine), sponsors should conduct the following pediatric studies:

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[13] Section 505B of the FD&C Act (21 U.S.C 355c) is often referred to as "PREA," the acronym for the Pediatric Research Equity Act of 2003, which originally created it.

[14] See also the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020).

[15] See the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (December 2014). When final, this guidance will represent the FDA's current thinking on this topic.

- Efficacy and safety study of episodic migraine in pediatric patients 6 to 17 years old

  In a study of episodic migraine, a sufficient number of subjects in the 6- to 11-year-old and 12- to 17-year-old subgroups should be included to be able to adequately characterize the efficacy and safety of the drug in each subgroup. At least 25 percent of the subjects should be in the 6- to 11-year-old age group, and at least 25 percent of subjects should be male.

- Efficacy and safety study of chronic migraine in pediatric patients 12 to 17 years old

  In a study of chronic migraine, there should be a similar number of subjects in the 12- to 14-year-old subgroup and in the 15- to 17-year-old subgroup. At least 25 percent of subjects should be male.

The endpoints described above for adult studies should be evaluated in the pediatric safety and efficacy studies, with appropriate control of the type 1 error rate.

A 1-year long-term pediatric safety study should also be conducted. Generally, if the drug is already approved in adults, the pediatric safety database should include data on at least 200 subjects treated for 6 months and 75 subjects treated for 1 year. The long-term safety study should include a sufficient representation of subjects across age subgroups, and at least 25 percent of subjects should be male. The study should evaluate the effects of the treatment on growth, cognition, and pubertal development.