Nonallergic Rhinitis: Developing Drug Products for Treatment

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Sofia Chaudhry at 301-796-4157.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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I. INTRODUCTION

The purpose of this guidance is to assist applicants of new drug applications and biologics license applications in developing drug products for the treatment of nonallergic rhinitis (NAR) in children and adults.[2] The guidance discusses issues regarding the definition of a clinical phenotype, trial design, efficacy, and safety for new drug products under development. In particular, the guidance addresses development programs for the treatment of vasomotor rhinitis (VMR), which is a subtype of NAR.

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[3]

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.

[1] This guidance has been prepared by the Division of Pulmonary, Allergy, and Rheumatology Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, the term *drug product* is inclusive of the small or large molecule active moiety or moieties in the formulation, along with the delivery device, if applicable.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

II. BACKGROUND

The nomenclature and understanding of the pathophysiology of NAR continue to evolve. The recommendations in this guidance are based on the Agency's current understanding of the definition of NAR and an assessment of important issues raised by the presumed heterogeneity of NAR. In general, rhinitis is regarded as a condition characterized by one or more of the following nasal symptoms: congestion, rhinorrhea, sneezing, and itching. Mucosal inflammation may be present but is not necessarily a requirement for all forms of rhinitis.

Rhinitis can be broadly divided into allergic and nonallergic forms. Allergic rhinitis can be clinically defined as rhinitis characterized by typical history and physical exam findings, associated with positive evidence of Immunoglobin E (IgE) sensitization to relevant environmental allergens. Although specific allergic sensitivities may vary among individuals, the pathophysiology is attributed to the same set of chemical mediators. More information on clinical development programs for allergic rhinitis can be found in the draft guidance for industry *Allergic Rhinitis: Developing Drug Products for Treatment*.[4]

In contrast, NAR is less well-defined. For the purposes of this guidance, NAR refers to the remaining rhinitis patients who do not have positive evidence of IgE sensitization. Both acute and chronic conditions are represented, driven by a wide variety of underlying mechanisms. Two major subtypes of NAR that have been described in the current literature are infectious rhinitis and vasomotor rhinitis (VMR). Infectious rhinitis may range from self-limited rhinitis secondary to common viral upper respiratory infections to more severe disease caused by other pathogens, such as fungal infections in an immunocompromised patient. In contrast, VMR is largely a diagnosis of exclusion. Other causes of rhinitis, including infections, medications, or other inflammatory conditions, must be excluded. VMR patients often cite increased sensitivity to certain stereotypical triggers, such as changes in temperature or humidity, airborne irritants, strong odors, and exercise, but the pathophysiology for these responses has yet to be fully understood.

Less common forms of NAR that have been described include gustatory rhinitis, hormonal rhinitis, drug-induced rhinitis, atrophic rhinitis, nonallergic rhinitis with eosinophilia syndrome, and rhinitis associated with certain inflammatory immunologic disorders. It is worth noting that the nomenclature for NAR subtypes is far from standard, and there may be overlap among the terms. For the most part, there are no diagnostic tests for the multiple forms of NAR, and the diagnosis is usually made by a combination of history, physician and laboratory exam, and the absence of positive evidence for allergic sensitization.

III. GENERAL CONSIDERATIONS FOR DEVELOPMENT

The heterogeneity of NAR poses challenges for drug product development. Designing a development program to address NAR as a single entity may pose issues of feasibility. Therefore, the Agency recommends that applicants focus on a specific NAR subtype. Because

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

VMR is thought to be one of the more common forms of noninfectious NAR, this guidance addresses clinical trial considerations for a VMR development program as an example.

Depending on the NAR subtype of interest, alternative trial designs and other considerations may be relevant. Given the relative lack of consensus at this time on the classification of NAR subtypes, preliminary studies to define and characterize other clinically relevant, reproducible phenotypes may be needed before the initiation of a formal clinical program for drug product development. Observational and population-based studies may play a role in characterizing the natural history and epidemiology of the particular NAR subtype of interest, and mechanistic studies or challenge models may be important for elucidating pathophysiology. These types of investigations, some of which may be beyond the typical scope of a development program for a specific product, might nevertheless be important for guiding patient selection and providing an appropriate context in which to evaluate the risk-benefit of a particular product.

The Agency encourages applicants to consult the review division early in the development program for products intended for other subtypes of NAR.

A. Patient Selection

Patient selection should reflect the NAR subtype of interest, and inclusion and exclusion criteria should be based on clinical meaningful, accessible parameters (i.e., health care providers should be able to identify and diagnose patients with the NAR subtype of interest in a real-world setting).

For VMR trials, it is recommended that patients have a history of VMR for a minimum of 2 years before trial entry. The Agency recommends documentation of a lack of sensitization to environmental allergens relevant to the geographical area of the trial either by negative skin testing (by prick or intradermal methods) or by adequately validated in vitro tests for specific IgE. We suggest that these tests be performed during the 12 months before enrollment.

A positive history of increased sensitivity to certain stereotypical VMR triggers, such as changes in temperature or humidity, airborne irritants, strong odors, and exercise, may be useful for screening patients. However, there is both inter- and intra-patient variability with regard to specific VMR triggers, and many healthy individuals without rhinitis will experience acute rhinitis symptoms when exposed to similar, intense triggers. Therefore, although a positive history can be helpful in corroborating a VMR diagnosis, the diagnosis cannot rely solely upon such history.

If an applicant intends to seek a VMR indication in the context of a specific trigger, it should document sensitivity to that specific trigger for each patient and ensure adequate exposure to that trigger during the course of the trial.

B. Dose

The goal of dose exploration is to identify the optimal dose and dosing frequency, balancing benefit with risk. Dose selection should be based on clinically meaningful endpoints, because

pharmacodynamic markers may not be predictive. Ideally, dose exploration should be conducted in a real-world setting, because other exposure models, such as nasal provocation challenges, may not be predictive of real-world clinical responses. However, the utility of such models may vary depending on the subtype of NAR that is being studied. The Agency encourages applicants to consult the review division to discuss the utility of alternative exposure models for a specific drug product development program.

C. Trial Design

The following are general recommendations for efficacy and safety trials in noninfectious NAR. Other considerations specific to the NAR subtype of interest may be applicable and should be discussed with the review division early in the development program.

- In general, efficacy and safety trials should be conducted under real-life conditions. However, as noted above in the discussion of dose exploration, alternative exposure models may be of use in certain situations, provided that there is evidence to support their relevance to clinical responses in the real world.

- Double-blinded, placebo-controlled, parallel group trials for efficacy and safety are recommended, preferably with a placebo run-in period. The run-in period serves to assess for a minimum level of compliance and symptom severity under *typical* circumstances.

- For VMR, the suggested duration of the treatment period for efficacy assessment is at least 4 weeks. The appropriate trial duration for other NAR subtypes may vary.

- Patients with NAR may have concomitant allergic rhinitis. Therefore, it is helpful for efficacy trials to be conducted during a time when relevant seasonal allergens are less abundant and therefore less likely to influence results of the trial.

D. Formulation Issues

For intranasal products, applicants are encouraged to provide information in the clinical trial protocol on the specific formulations used for both the to-be marketed product and the placebo. We recommend key dose-ranging and efficacy and safety trials use the to-be-marketed formulation. If not, the applicant should address how the safety and effectiveness of the studied formulation will be bridged to the to-be-marketed formulation. If bridging of one formulation to another is proposed, information about the formulation composition and trial lots should be included in the trial reports for the respective products.

One particular consideration for VMR programs is formulation changes that alter the sensorial attributes of the product, because patients with VMR often report sensitivity to scents and irritants. As a result, formulation changes may alter the efficacy and safety of a product. The extent to which previous clinical data obtained with a different formulation can be used in support of a new formulation should be evaluated on a case-by-case basis.

E. Evaluation

1. Assessment of Patient Compliance

The trial protocol or trial report should provide information about how compliance with product use will be determined and documented throughout the trial and how noncompliance and/or missing data will be dealt with, either in the form of patient exclusion or exclusion of data points (e.g., use of last visit data carried forward).

2. Assessment of efficacy

Patient-reported *instantaneous* and *reflective* total nasal symptom scores have been commonly used in clinical trials for various forms of rhinitis. Instantaneous refers to symptoms within a limited time frame before the assessment (e.g., one hour or less) and reflective refers to the interval from the time of last assessment (e.g., 12 hours for morning and evening scoring). These summed scores generally include the following four nasal symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing rated on a 0 to 3 scale of severity. Addition or deletion of symptoms to or from the total score can be appropriate, based on the mechanism of action of the product and the specific form of rhinitis of interest. Such changes should be discussed with the review division. Patient-reported total nasal symptom scores are recommended as the primary measure of efficacy.

A common nasal symptom rating system that has been used in clinical trials is the following 0 to 3 scale:

- 0 = absent symptoms (no sign/symptom evident)
- 1 = mild symptoms (sign/symptom present, but minimal awareness; easily tolerated)
- 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

Regardless of the scoring system chosen, a detailed description of the symptom rating scale should be provided to patients. This should include instructions on proper completion of the symptom diary and definitions of the different categories in the scale.[5]

3. Assessment of Rescue Medication Use

If rescue medications are allowed during the trial, the trial protocol should document how rescue medication use will be analyzed in the different treatment groups. We recommend inclusion of a

[5] See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

section in the clinical trial report that presents rescue medication use in the different treatment groups.

4. Adverse Event Recording

We recommend that adverse events be recorded in a daily patient diary record, in addition to being elicited by trial staff at clinic visits.

IV. CONSIDERATIONS FOR PEDIATRIC DEVELOPMENT

The pediatric age ranges proposed for a product, particularly for young patients, should be justified by the applicant based on the presence of disease and the need for treatment in that age group. The occurrence of different types of noninfectious NAR, including VMR, in younger pediatric patients is uncertain. For topical products, the appropriateness of the delivery system for the proposed age range is an additional consideration. Applicants are encouraged to discuss the specifics of pediatric programs as early as is feasible with the division on a case-by-case basis because applicants are required to submit pediatric study plans under the Pediatric Research Equity Act no later than 60 days after an end-of-phase 2 meeting. We recommend applicants refer to the Pediatric Research Equity Act as amended by the Food and Drug Administration Safety and Innovation Act.[6]

[6] See section 505B(e) of the Federal Food, Drug, and Cosmetic Act, as amended by section 506 of the Food and Drug Administration Safety and Innovation Act, and the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*. When final, this guidance will represent the FDA's current thinking on this topic.