Chronic Rhinosinusitis with Nasal Polyps: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Rekha Jhamnani at 301-796-5636 or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the development of drugs or biological products[2] for the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP). The guidance addresses FDA's current recommendations regarding trial population, design, effectiveness, statistical analysis, and safety for drugs being developed for the treatment of CRSwNP.[3]

This guidance does not address the clinical development of drugs for the treatment of chronic rhinosinusitis without nasal polyps or allergic fungal rhinosinusitis.

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[1] This guidance has been prepared by the Division of Pulmonology, Allergy, and Critical Care in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified. For cell and gene therapy products, additional considerations may apply.

[3] Sponsors are encouraged to discuss details of trial design and specific issues relating to individual drugs with review division staff before conducting clinical trials.

II. BACKGROUND

Chronic rhinosinusitis is characterized by inflammation of the nasal mucosa and paranasal sinuses and can be further divided into chronic rhinosinusitis with and without nasal polyps. Nasal polyps are inflammatory hyperplastic growths that protrude into the nasal passages. Symptoms of CRSwNP include nasal congestion, nasal discharge, facial pain or pressure, and loss of smell. The estimated prevalence of CRSwNP in adults is approximately 2.5 percent (Fokkens et al. 2020). In children, the estimated prevalence is difficult to determine. Cases of CRSwNP have, however, been reported in adolescents. Prevalence increases with age and peaks in the sixth decade of life (Stevens et al. 2016). Nasal polyps have associated morbidity that can have substantial effect on day-to-day functioning. Several studies have shown that patients have impaired quality-of-life scores (e.g., decreased general health, emotional function, ability to perform daily activities, sleep quality, and productivity) (Aboud 2014). Mild disease can be treated with intranasal corticosteroids and saline irrigation. Severe disease often requires short-term systemic corticosteroids, a monoclonal antibody, and/or surgery. Treatment goals include reduction of symptoms and systemic corticosteroid use and avoidance of surgery, as well as improved quality of life.

Taking into consideration the anatomic contiguity between the nose and paranasal sinuses, FDA supports the use of the term *chronic rhinosinusitis,* rather than *chronic sinusitis,* as a more accurate description of the underlying pathophysiology. Nasal polyps are considered a subtype of chronic rhinosinusitis. Because of differences in natural history and treatment between chronic rhinosinusitis with and without nasal polyps, this guidance specifically addresses CRSwNP.

III. DEVELOPMENT PROGRAM

A. Trial Population

Sponsors should consider the following general recommendations for clinical trial populations for CRSwNP investigational drug trials intended to provide evidence of safety and effectiveness to support a marketing application.

- The clinical trial population, as defined by the inclusion and exclusion criteria, should reflect the intended use of the drug. In general, a drug intended as an add-on to standard of care therapies would be used in a population with greater disease severity.

- FDA encourages enrollment of pediatric subjects (older than or at least 12 years of age) in clinical trials of adults, depending on the availability of safety data and prospect of benefit.[4]

- Sponsors should enroll subjects who reflect the characteristics of clinically relevant populations, including with regard to race and ethnicity, and should consider clinical trial

[4] See 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations.

sites that include higher proportions of racial and ethnic minorities to recruit a diverse study population.[5]

Below are general recommendations for inclusion and exclusion criteria.

1. Inclusion Criteria

For inclusion in a clinical trial, sponsors should consider subjects with the following:

- Bilateral nasal polyps.[6]
- A prespecified minimum threshold for endoscopic nasal polyp score on each side using a valid scoring system.
- Ongoing symptoms of nasal congestion, with a specified duration. Sponsors can also consider loss of smell and nasal discharge.

2. Exclusion Criteria

Sponsors should consider excluding subjects from trials if they have the following:

- Sinus or intranasal surgery or nasal septal perforation within a specified time period before screening.
- Acute sinusitis or upper respiratory infection within a defined time period before screening.
- A nasal cavity tumor (malignant or benign).
- Evidence of fungal rhinosinusitis.
- Presence of another diagnosis associated with nasal polyps (i.e., eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, Young's syndrome, primary ciliary dyskinesia, cystic fibrosis).
- Rhinitis medicamentosa.
- Nasal septal deviation occluding at least one nostril.

[5] See also the guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[6] If a sponsor chooses to include subjects with unilateral polyps, this should be discussed with the review division in advance.

- Antrochoanal polyps.

B. Trial Design

Sponsors should consider the following general recommendations on clinical trial design for CRSwNP investigational drug trials intended to provide evidence of safety and effectiveness to support a marketing application.

- We recommend randomized, double-blind, placebo-controlled, parallel-group trials, preferably with a 2- to 4-week period before randomization to assess symptom severity or eligibility.

- The sponsor should describe in the protocol the process of ensuring blinding to the investigational drug. If double-blinding is not possible, the sponsor should provide a rationale, along with a discussion of the strategies for reducing or eliminating bias. For topical nasal formulations, a description of the differences between active and placebo treatments in the protocol (e.g., differences in the device, odor, taste, characteristic of the formulation) can help determine the adequacy of the blinding in the trial. For insertable nasal stents or depots, blindfolding the subject and separating assessors and personnel who insert the stents or depots may assist in reduction of bias.

- The trial duration and timing of efficacy assessments should be guided by the goals of therapy, mechanism of action of the drug and its expected onset of action, and the time frame in which a clinical benefit is expected to be observed. Because CRSwNP is a chronic disease, we recommend trials of at least 24 weeks, but ideally 52 weeks, in duration. Sponsors can consider trials of shorter duration for topical corticosteroids; however, this should be discussed with the review division in advance. Sponsors should consider longer trials to determine potential safety concerns and the effect on efficacy outcomes such as reduction in systemic corticosteroid use, surgery, and recurrence of nasal polyps.

- Sponsors should permit subjects to use standard of care therapies, including intranasal corticosteroid sprays and antibiotics, as well as rescue systemic corticosteroids and surgery.

C. Efficacy Considerations

Sponsors should consider the following general recommendations for CRSwNP trials intended to provide substantial evidence of effectiveness to support a marketing application.[7]

[7] For further details, see the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). 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.

1. Efficacy Assessments

Efficacy assessments for CRSwNP should include the effect of treatment on nasal polyps and chronic rhinosinusitis. The preferred coprimary endpoints in CRSwNP investigational drug trials are endoscopic nasal polyp score and symptoms of CRSwNP using a well-defined and reliable clinical outcome assessment (COA) measure (patient-reported nasal symptom score). Demonstrating a treatment effect on both endpoints is necessary to support evidence of effectiveness. FDA recommends a patient-reported outcome (PRO) measure of nasal congestion because it is the most common symptom experienced by patients with CRSwNP (Abdalla et al. 2012).

Details for the assessment of these preferred coprimary endpoints are included below.

- **Nasal polyp score (NPS)**. A common endoscopic nasal polyp rating system that has been used in clinical trials is the following 0 to 4 scale:

  – 0 = no polyps

  – 1 = small polyps in middle meatus not reaching below the inferior border of middle turbinate

  – 2 = polyps reaching below lower border of middle turbinate

  – 3 = large polyps reaching lower border of inferior turbinate or medial to middle turbinate

  – 4 = large polyps completely obstructing the inferior nasal cavity

  The total score is the sum of both sides (for a total score range of 0 to 8).

  We recommend calculating the NPS as the average of scores from two or more trained physician assessors reviewing video recordings of nasal endoscopies where the assessors are blinded to subject treatment assignment. Generally, a prespecified adjudication process should be performed for significant disagreements between two readers.

Nasal congestion score (NCS). For the PRO assessment of nasal congestion, we recommend using response scales that include descriptors because the absence of descriptors may create difficulty in interpretation in this context of use. Each response option should be clearly defined, represent clinically meaningful gradations, and measure a single distinct concept of interest that does not overlap with another concept. Accordingly, using response scales such as visual analogue scales and 0 to10 numeric rating scales may result in interpretation difficulties in this context. The sponsor should discuss with the review division the addition of symptoms other than nasal congestion as a primary endpoint.

- A common rating scale with four levels that has been used in clinical trials is the following (often scored from 0 to 3 where 0 = absent and 3 = severe):

  – absent symptoms
  – mild symptoms
  – moderate symptoms
  – severe symptoms

  PRO measures should be well understood by subjects and include clear instructions for completion and definitions of the different categories in the scale. For a daily diary, we recommend the use of reminders to encourage subject compliance with daily reporting. Using an electronic diary can improve data quality because entries are time-stamped, problems with compliance can be identified early, and reminder functions can be included. The recall period should be appropriate for the concept to measure, for example, reflective of the worst severity over the past 24 hours.[8, 9]

FDA recommends the following secondary endpoints:

- **Smell**. We recommend assessing patient-reported loss of smell using a rating scale of severity (e.g., 0 to 3 scale). We do not recommend use of smell identification tests (e.g., the University of Pennsylvania Smell Identification Test) to assess loss of smell or anosmia because smell identification can be affected by ethnicity/cultural background, gender, age, and olfactory experience (Hsieh et al. 2017).

- **Patient-reported symptom scores**. We recommend analyzing individual symptoms relevant and important to patients with CRSwNP that are not already included in other efficacy assessments (e.g., anterior or posterior nasal discharge (defined using patient-friendly language), facial pain or pressure) on a 0 to 3 scale. We do not recommend use of sino-nasal outcome test (SNOT-22, or other versions of SNOT) to derive key study endpoints to support regulatory decision-making because of interpretability concerns inherent to the design of this PRO instrument (e.g., inclusion of items that either lack relevance or are not well understood by patients with CRSwNP), as well as redundancy

[8] For general recommendations regarding PRO assessments (as well as information relevant for other COAs) and the documents to be provided to FDA for review, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).

[9] For general recommendations regarding PRO assessments (as well as information relevant for other COAs) and the documents to be provided to FDA for review, see the FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making available at https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical. See the guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2020) and the draft guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Methods to Identify What Is Important to Patients* (October 2019). When final, this guidance will represent the FDA's current thinking on this topic.

of some of the SNOT-22 items with the individual symptom items used to derive other study endpoints (e.g., the primary efficacy endpoint).

- **Surgery and oral steroid use**. Clinically meaningful secondary endpoints include reduction in systemic corticosteroid use and surgery. We recommend defining what constitutes surgical treatment (e.g., in-office polypectomy, fenestrated endoscopic sinus surgery). For rescue medications such as systemic corticosteroids, it is important for sponsors to assess total systemic corticosteroid dose, courses of systemic corticosteroid, and days of corticosteroid per course and to define the minimum separation in days between courses to not be considered continuous therapy.

- **Imaging.** Sponsors can consider sinus imaging as a secondary efficacy endpoint with evaluation in subjects with a prespecified minimal threshold score based on baseline imaging. We recommend discussing the choice of imaging score with the review division.

2. Statistical Considerations

Sponsors should consider the following recommendations for statistical analysis:

Estimand

- Sponsors should prespecify a primary estimand of interest (population, treatment, variable of interest, population-level summary, and intercurrent events) for each key endpoint and justify that it is meaningful and can be estimated with minimal and plausible assumptions with the proposed analysis.[10]

- For each key endpoint, the proposed estimands should describe the handling of important intercurrent events including the following:

  – Treatment discontinuation

  – Use of rescue surgical treatment for CRSwNP

  – Use of rescue systemic corticosteroids for CRSwNP or for comorbid conditions

  – Change from study treatment to another drug (e.g., a different intranasal corticosteroid spray (INCS) or biologic therapy) for CRSwNP

- The following are important considerations about different strategies for handling intercurrent events:

[10] For additional recommendations, see the International Council for Harmonisation guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021).

  - We recommend a treatment policy strategy for handling treatment discontinuation.

  - We recommend a composite strategy for handling surgery (i.e., sponsors should incorporate surgery into the endpoint, and sponsors should consider subjects who undergo surgery to have an unfavorable outcome). One reasonable approach is to assign the worst possible score for the coprimary endpoints, NCS and NPS.

  - For systemic corticosteroids, sponsors should consider the following:

    - For trials evaluating intranasal corticosteroids, we recommend a composite strategy for handling rescue systemic corticosteroid use.

    - For trials evaluating therapeutic biological products, we recommend a treatment policy strategy for handling rescue systemic corticosteroid use.

    - We recommend a treatment policy strategy for handling use of systemic corticosteroids for comorbid conditions.

  - We recommend a composite strategy for handling a change from study treatment to another drug (e.g., a different INCS or biologic therapy) for CRSwNP

- To minimize missing data in the evaluation of important estimands, the protocol should distinguish reasons for treatment discontinuation from reasons for trial withdrawal and include plans to follow subjects for collection of relevant data after treatment discontinuation and use of rescue therapies.

- Sponsors can consider evaluating alternative estimands (e.g., with different strategies for handling intercurrent events) in supplementary analyses.

Other statistical considerations

- As patient-reported symptoms can be variable from day to day, we recommend using an average score over several days or weeks to establish a score at baseline and at a landmark time point for each subject.

- For both of the coprimary endpoints, sponsors can consider the change from baseline in the score to a landmark time point or the score at a landmark time point.

- To improve the precision of treatment effect inference, we recommend adjusting for prespecified prognostic baseline covariates (e.g., baseline value of the outcome measure, asthma or nonsteroidal anti-inflammatory drug-exacerbated respiratory disease status, prior surgical history).

- The following are important considerations about the prespecified analyses for efficacy endpoints:

- Sponsors should conduct the analyses in all randomized subjects.

- For intercurrent events handled with a treatment policy strategy, sponsors should continue to collect and analyze outcomes after the intercurrent event.

- We recommend a regression-based approach to compare means between treatment groups.

- Sponsors should prespecify plans for sensitivity analyses (e.g., to explore assumptions about missing data). Sensitivity analyses should systematically and comprehensively explore the effect of potential deviations in assumptions of the analysis on conclusions.

D. Safety Considerations

Sponsors should consider the following recommendations for safety for CRSwNP investigational drug trials intended to support a marketing application:

- CRSwNP is a chronic disease; therefore, sponsors should collect long-term controlled safety data. The extent of the safety database should be consistent with the International Council for Harmonisation (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* C*onditions* (March 1995). We recommend that a sufficient number of subjects receive the highest dose proposed for marketing.[11] Measurements of efficacy endpoints are recommended in long-term safety trials as secondary assessments.

- FDA encourages sponsors to contact the review division regarding appropriate cardiac safety monitoring for their development programs.

- For trials of drugs, such as monoclonal antibodies, that have the potential to induce an immune response, sponsors should see recommendations in the guidances for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014) and *Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection* (January 2019).

- Sponsors should prospectively plan for safety analyses to compare treatment groups with respect to risk (e.g., with a risk difference, relative risk, rate ratio, or hazard ratio) along with a confidence interval for the chosen metric to help quantify the uncertainty in the treatment comparison. Any analyses of integrated data from multiple studies should stratify by trial.

- For topical drugs, given the risk for local toxicity, safety monitoring should include baseline and serial nasal examinations. Prespecified grading criteria to assess for the

[11] See 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* C*onditions*.

presence of nasal irritation (e.g., mucosal edema, erythema, epistaxis), ulceration, and septal perforation can be useful for documenting any changes over the course of the treatment period.

E. Corticosteroid-Specific Issues

Important safety issues for intranasal corticosteroids that sponsors should address in clinical programs include the following:

- Individual drugs may have variations in dose, dosing regimen, and systemic exposure; thus, their indications may need different testing procedures. FDA encourages sponsors to contact the review division before carrying out corticosteroid-induced hypothalamic-pituitary-adrenal axis suppression assessments.

- To assess for the presence of adrenal suppression by exogenously administered corticosteroids, sponsors should use either adrenocorticotropic hormone stimulation testing,[12] 24-hour urinary free cortisol levels, or integrated plasma or serum cortisol concentration pretreatment, at trial endpoint, and approximately 6 weeks poststudy. Other assays such as pharmacokinetic testing for blood levels of the corticosteroid can further evaluate systemic corticosteroid exposure in subjects.

- Sponsors can evaluate enrolled subjects for glaucoma using intraocular pressures monitored pre- and posttreatment. Though corticosteroids are well known to accelerate the development of cataract formation, the effect occurs with chronic use and thus limits the utility of monitoring during a short-term trial. Labeling should carry a warning of the potential to accelerate cataract development similar to other corticosteroid drugs.

F. Drug-Device Considerations

Sponsors should consider the following recommendations for drug-device combination products:

- For drugs that include a device (e.g., nasal spray, nasal sinus stent, prefilled syringe, autoinjector), the whole product, including the dedicated delivery system, is considered a drug-device combination product as defined in 21 CFR 3.2(e). Changes in the formulation, excipients, formulation flow path within the device, or device components (e.g., dimensions, materials of construction, coatings) can alter the delivery characteristics and affect the clinical performance and user interface of the combination product. Therefore, we recommend that sponsors conduct all key trials in the development program, including dose-ranging trials and confirmatory efficacy and safety trials, with the to-be-marketed combination product. Furthermore, the sponsor should provide data on the performance and reliability of the new delivery system over the period of intended use.

[12] Administration of cosyntropin to the same subject repeatedly at intervals of less than 4 weeks may result in higher stimulated cortisol levels after each successive injection, leading to invalid data. Studies using cosyntropin testing should be at least 4 weeks in duration.

- In vitro and clinical bridging data may be needed to support any changes in the formulation and delivery system. Depending on the nature and extent of the changes, the altered combination product may be viewed as a new product, necessitating a separate development program with efficacy and safety trials. We recommend that sponsors discuss any planned changes to a combination product with the review division.

- Bridging studies of nasal drugs for local action, particularly drugs that are in a suspension state, can be a substantial undertaking. Principles that may apply to such a bridging program are outlined in the draft guidance for industry *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (April 2003).[13]

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

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Draft guidance for industry *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (April 2003)[2]

Draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)[3]

Draft guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Methods to Identify What Is Important to Patients* (October 2019)[4]

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Guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020)

Guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2020)

Guidance for industry *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014)

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