Guidance for Industry

Allergic Rhinitis: Clinical Development Programs for Drug Products

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, (Tel) 301-827-4573, or from the Internet at http://www.fda.gov/cder/guidance/index.htm.

For questions on the content of the draft document contact Martin H. Himmel, 301-827-1050.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
April 2000
Clin.

J:\!GUIDANC\2718dft.doc
06/14/00

Guidance for Industry

Allergic Rhinitis: Clinical Development Programs for Drug Products

Additional copies are available from:

Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
Center for Drug Evaluation and Research (CDER)
5600 Fishers Lane
Rockville, Maryland 20857
(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
April 2000
Clin.

Table of Contents

GUIDANCE FOR INDUSTRY[1]

(Due to the complexity of this draft document, please identify specific comments by line number. Use the pdf version of the document whenever possible.)

Allergic Rhinitis: Clinical Development Programs for Drug Products

I. INTRODUCTION

This guidance is intended to assist sponsors of new drug applications (NDAs) in designing development programs for oral and intranasal drug products for the treatment of allergic rhinitis in children and adults. The guidance addresses issues of study design, effectiveness, and safety for new drugs being developed for the treatment of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR).

II. BACKGROUND

Information about the pathophysiology and treatment of allergic rhinitis and its subtypes, SAR and PAR, has grown markedly in the past decade. The recommendations in this guidance are based on a careful assessment of important issues raised in the review of both adult and pediatric allergic rhinitis clinical trials and the Agency's current understanding of the mechanism of the two related disorders of SAR and PAR. The pathophysiology of SAR and PAR are very similar in terms of the chemical mediators produced and end-organ manifestations, with differences between the two entities primarily based on the causes and duration of disease. The study design issues pertaining to SAR and PAR trials are also very similar. Thus, these two categories are treated collectively in this guidance as *allergic rhinitis,* with differences in recommendations for the design of SAR and PAR trials indicated.

When finalized, this document will replace the previous *Points to Consider: Clinical Development Programs for New Nasal Spray Formulations* (January 1996). Sponsors are encouraged to discuss details of study design and specific issues relating to individual drug products with division review staff prior to conducting clinical trials.

Allergic rhinitis includes both nasal and non-nasal symptoms. The main nasal symptoms of allergic rhinitis are nasal itching (i.e., nasal pruritus), sneezing, rhinorrhea, and nasal congestion. Nasal pruritus and sneezing are induced by sensory nerve stimulation, whereas congestion

[1] This guidance has been prepared by the Division of Pulmonary and Allergy Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on clinical trial design of seasonal and perennial allergic rhinitis studies in adults and children. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

results from vasodilation with resultant engorgement of cavernous sinusoids. Rhinorrhea can be induced by increased vascular permeability as well as direct glandular secretion. Important non-nasal symptoms commonly associated with allergic rhinitis include eye itching, eye tearing, itching of ears and/or palate, and eye redness.

A growing number of chemical mediators are believed to contribute to allergic rhinitis. They include histamine, leukotrienes (LTC_4, LTD_4, and LTE_4), kinins, prostaglandins, chemotactic factors, neuropeptides (e.g., substance P, CGRP, VIP), interleukins -1, -5, -6, -8, and tumor necrosis factor-α. Additional mediators with a potential role in allergic rhinitis will likely be identified in the future. Despite different causes and temporal patterns of disease, the same groups of chemical mediators appear to be regulators of the responses in seasonal and perennial allergic rhinitis. It is for this reason that distinctions between SAR and PAR in terms of clinical trial design will be made only in clinically relevant areas.

III. OVERALL CONSIDERATIONS – ADULT PROGRAM

A. New Molecular Entity

1. Number of Trials

For approval of a new molecular entity in adult and adolescent patients (age 12 years and older), at least two adequate and well-controlled phase 3 clinical trials are recommended to support either the SAR or PAR indication. Alternatively, a sponsor can submit one SAR and one PAR trial in support of both the indications, if both trials are adequate and well-controlled phase 3 trials and both trials demonstrate the safety and effectiveness of the drug for the indications.

2. Dose

The dose-response relationship for the new drug should be evaluated in these trials. These trials, or other supporting trials, should identify a *lowest effective dose* for the drug (i.e., the lowest dose that demonstrates a statistically significant difference between the to-be-marketed drug and the placebo). This recommendation is particularly important for intranasal corticosteroids.

3. Safety Monitoring

These trials should also address safety concerns, such as monitoring for adverse events, performing routine laboratory tests (i.e., blood chemistry, liver function tests, complete blood count with differential), urinalyses, and electrocardiograms, as appropriate. For SAR and PAR phase 3 trials, routine laboratory tests should be obtained in study patients at least at the initial screening and at the last visit.

For some allergic rhinitis drugs (particularly drugs in the antihistamine class), part of the safety program should include a thorough cardiac safety evaluation, with studies performed in both men and women. A suggested approach would include:

- Screening and end-of-treatment ECGs, including a careful assessment of the QT_c interval and any T wave abnormalities, as read by a ECG reviewer blinded to study treatment.

- Human dose escalation studies that evaluate serial ECGs at drug exposures up to dose-limiting toxicity of any organ system.

- For drugs metabolized by the cytochrome P450 3A4 system, drug interaction studies performed with both a macrolide and azole antibiotic.

- 24-hour Holter monitoring performed before, during, and, as appropriate, on completion of the efficacy trials for allergic rhinitis drugs suspected to have an effect on QT_c intervals from previous studies.

In addition to the studies described above, case report forms and study reports should include a detailed description of all serious cardiac adverse events and pertinent ECGs.

Sponsors are encouraged to contact the review division regarding appropriate cardiac safety monitoring for their respective drug development programs.

For many allergic rhinitis drugs, some assessment of the degree of sedation compared to the placebo should be provided in the safety database. This should primarily be based on individual patient adverse event reports of sedation and/or drowsiness (or similar terminology, as defined by the sponsor's adverse event dictionary).

Generally, long-term safety data should include at least 300 patients evaluated for 6 months and 100 patients evaluated for 1 year. The overall patient database should include at least 1500 patients. (See the International Conference on Harmonisation guidance on the *Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life Threatening Conditions* (March 1995).)

4. Corticosteroid Issues

Important safety issues for intranasal corticosteroids that would ordinarily be addressed in the adult clinical program include:

- Assessment of adrenal function using either timed urinary free cortisol level measurements (i.e., 12-hour or 24-hour), or 24-hour plasma cortisol AUC levels pretreatment and after at least 6 weeks post-treatment with study medication. A placebo and an active control (e.g., oral prednisone) should be included in these studies.

- Evaluation for possible cataract formation by slit-lamp examination, pre- and post-treatment.

- Evaluation for glaucoma, using intra-ocular pressures monitored pre- and post-treatment.

B. Change in Formulation and/or Device

1. Oral Formulations

For a change in an oral dosage form from an approved oral formulation to a new oral formulation of the same drug substance, an alternative to conducting the new molecular entity program described above is to demonstrate bioequivalence between the two formulations. This is based on pharmacokinetic comparisons (e.g., AUC, C_{max}, C_{min}) between the approved and to-be-marketed formulations. This equivalence approach allows the indications and patient populations for the new formulation to be the same as those described in the labeling of the approved product. If a significant new excipient, not previously administered at comparable levels to humans, is present in the new formulation, or if the tolerability of the new formulation is otherwise in question, short- and possibly long-term safety data may still be important for patients receiving the new formulation, even if bioequivalence is demonstrated. Additional safety and efficacy trials may be necessary to support a new formulation if bioequivalence is not demonstrated.

2. Topical Nasal Formulations

For changes in formulation and/or device for a topical nasal product (e.g., aqueous pump, spray), one of two approaches can be used to demonstrate the safety and effectiveness of the new drug product: (1) establishment of comparability between the new and previously approved (reference) formulation, or (2) development of the new formulation and/or device by a usual program for a new drug product (i.e., *stand-alone approach*).

- Comparability Approach

To demonstrate clinical comparability between the new and reference formulations, comparison of the dose-response curves of these two formulations in a single

efficacy and safety trial is recommended. Two doses of each formulation, in addition to placebo, are desirable for dose-ranging determination. The dose-ranging study should be designed to permit determination of how doses of the new formulation compare to the approved doses of the reference formulation with regard to onset of action and effectiveness. Comparative pharmacokinetic (PK) measurements (C_{max}, T_{max}, and AUC) should be included in this trial, as appropriate and technically feasible. If the reference formulation is indicated for both SAR and PAR, the dose-ranging trial can be performed in patients with either SAR or PAR (see section V of this guidance, Protocol Issues and Elements, for recommended trial durations). If the reference formulation is approved for indications in addition to SAR and/or PAR (e.g., nasal polyps or nonallergic rhinitis) no additional studies are needed to support the same indications for the new product, if comparability, as described above, is well established between the new and reference formulation.

- Stand-Alone Approach

An alternative approach or *stand-alone approach* for evaluating a topical nasal drug product with a formulation change could be a single, dose-ranging, placebo-controlled efficacy and safety trial of the new formulation in patients with either SAR or PAR. A single dose of the reference formulation as a positive control is recommended. Demonstration of effectiveness for either of these two clinical indications would allow labeling to include efficacy for both, if the reference formulation already had labeling for both. If additional indications (e.g., nasal polyps and nonallergic rhinitis) previously approved for the reference formulation are sought for the new formulation, a single clinical trial for each additional indication is recommended. Furthermore, as with the *comparability approach*, determination of the pharmacokinetics of the drug is recommended during the stand-alone approach and can be performed during the efficacy trial, if feasible.

3. Safety Monitoring

For both oral and topical nasal formulation programs described above, safety monitoring should be included for the duration of the trials. This would include evaluation of adverse clinical events, routine laboratory tests (i.e., blood chemistry, liver function, complete blood count with differential), urinalysis, and ECGs, as appropriate.

In either of these formulation programs, demonstration of long-term safety may still be important, if new inactive ingredients have been added that could affect safety, or if the new formulation and/or device results in higher systemic exposure to active ingredients compared to the approved product. In addition, if pharmacokinetic data for the formulations are not feasible, long-term safety data for the new formulation may be recommended. If necessary, long-term safety may be established by

documenting exposure of at least 200 patients to the new formulation for 6 months at the dosage proposed for marketing. Due to the duration, these studies are generally conducted in patients with PAR. An active control arm, consisting of a single dosage level of the reference formulation, is recommended. Symptom-guided dosage adjustment by study patients during the long-term open label study should be avoided, as this complicates analysis of the safety data. To minimize dropouts and to address ethical considerations, stratification of patients and dosage according to symptom severity is acceptable at the start of the open label study. However, a sufficient number of patients who receive the highest dose proposed for marketing should be included. Rescue medication should not include other intranasal drugs or intranasal products.

4. Corticosteroid Issues

For corticosteroids, if the new formulation causes higher systemic exposure to the drug substance than other formulations (either intranasally or orally inhaled) already marketed or under development for which an adequate assessment of HPA axis effects has been conducted, or if pharmacokinetic data on these other formulations is unavailable, an evaluation of the effect of the new formulation on the HPA axis is strongly recommended. For HPA axis evaluation, measurement of timed (12- or 24-hour) urinary free cortisol levels or serum cortisol AUC before and after 6 weeks of treatment are the preferable methods of assessment. If the sponsor plans to claim comparability between the reference and new formulations, and a pharmacokinetic comparison of the two products is not available, comparison with the highest marketed dose of the reference formulation is recommended.

For a change in a device, data on the performance and reliability of the new device over the period of intended use may need to be provided.

IV. OVERALL CONSIDERATIONS – PEDIATRIC PROGRAM

A. New Molecular Entity or New Pediatric Indication

The pediatric age ranges proposed for a drug product, particularly for very young patients, should be justified by the sponsor based on the presence of disease and the need for treatment in that age group. Drugs indicated for the treatment of allergic rhinitis are used in children below the age of 2 years; therefore, a complete pediatric program should evaluate the safety of antihistamines in children down to age 6 months. Similarly, based on clinical use experience, the safety of intranasal corticosteroids, cromolyn-like drugs, and anticholinergics should be evaluated in children down to age 2. Sponsors are encouraged to discuss the specifics of pediatric programs with the division on a case-by-case basis.

1. Drugs Not Previously Studied in Adults

For approval of a new molecular entity in pediatric patients (patients younger than 12 years), the number of studies recommended depends on whether the drug is already approved in adult patients. For a new molecular entity (NME) not previously approved or adequately studied in adults, the clinical program would be the same as that described for adults. This would include two adequate and well-controlled safety and efficacy trials along with appropriate long- and short-term safety data. For an NME intranasal corticosteroid, the performance of a growth study (possibly postapproval) is recommended in order to assess the potential of the corticosteroid to suppress growth in children.

2. Drugs Already Studied in Adults

For drugs already approved and/or adequately studied in adults but not yet studied in children, an appropriate pediatric dose should be determined. In addition, adequate short- and long-term safety information for the proposed pediatric age group should be provided. For oral formulations where a reasonable pharmacokinetic/pharmacodynamic (PK/PD) link for effectiveness has been established, PK data from children can be used to determine comparable exposure to adult patients, and therefore the appropriate pediatric dose.

For intranasal formulations, the performance of efficacy studies in pediatric patients is recommended, since plasma drug levels are not consistently detectable or reliable as measures of local bioavailability and topical efficacy.

3. Safety Data

Typically, 3 months of additional specific pediatric safety data for intranasal products and 1 month of additional safety data for oral products are recommended. These data should be collected in placebo controlled trials. However, the duration and number of pediatric patients exposed to the study drug for safety monitoring should be determined on an individual basis for each drug, based on anticipated side effects, pediatric PK data, and safety concerns.

4. Corticosteroid Issues

For intranasal corticosteroids, performance of a 6-week HPA axis study is recommended. Because of ethical concerns about the use of oral prednisone as an active comparator in adrenal response studies in children, inclusion of an oral prednisone arm in pediatric adrenal assessment studies is not typically recommended. However, inclusion of an active comparator arm (e.g., an intranasal corticosteroid approved in the pediatric population) is encouraged.

Based on recent information that intranasal corticosteroids have the potential to decrease growth velocity in children, a growth study is recommended for prepubertal children as a phase 4 commitment, if not before. If the studies are to be performed postapproval, it may be useful for a sponsor to include a knemometry study in the NDA submission to provide some PD growth data for consideration during the initial review. Growth studies should evaluate growth before and after treatment with the intranasal corticosteroid, using stadiometry to assess growth. Such a growth study should enroll patients with allergic rhinitis, incorporate a run-in period, and be placebo controlled. Sponsors should ensure that an adequate sample size is studied and that there is a reasonable duration of treatment (ordinarily 1 year). These recommendations allow for a better estimate of the decrease in growth velocity seen in association with intranasal corticosteroid use. Information on a clinically significant change in growth derived from knemometry studies should not be used to determine the expected change in growth velocity for longer-term studies that use stadiometry to measure growth. This is because of the nonlinearity of growth and differences in study durations for these two techniques. Sponsors are encouraged to discuss the details of their pediatric growth study design with the review division.

B. Change in Formulation and/or Device

In situations where a sponsor has conducted a change in the formulation and/or device comparability program in adults, as described above, additional pediatric efficacy studies may not be required if:

- The safety, efficacy, and PK of the new formulation are comparable to that of the reference formulation in adults, and

- The reference formulation has been approved for use in an appropriate pediatric age range.

However, depending on the specific changes that were made in the formulation and/or device, additional safety and/or use studies in children may be needed.

V. PROTOCOL ISSUES AND ELEMENTS

A. Trial Design

In the development programs of allergic rhinitis drugs, otherwise well-designed and well-conducted studies may occasionally fail to show effectiveness. This is due in part to the subjective nature of the assessments and spontaneous variability in the disease. This observation makes the use of a placebo control of paramount importance, since a

positive-control equivalence trial cannot be interpreted in such a situation. If the intent is to show that the new product is significantly more effective than an approved active control, a positive-control study may be sufficient.

The following are general recommendations on trial design for phase 3 allergic rhinitis (SAR and PAR) trials in adults and adolescents (older than 12 years) and children (younger than 12 years).

- These studies should be double-blind, placebo-controlled, and parallel group, preferably with a placebo run-in period.

- Inclusion of an active control arm is recommended for both reformulation programs (as described above) and for new drug development programs. For the new drug development program, the positive-control study is helpful in interpreting trials in which there is not a demonstrable difference between the test drug and the placebo.

- The duration of the double-blind treatment period should be at least 2 weeks for SAR trials and 4 weeks for PAR trials.

- For SAR trials, the study protocol should discuss plans for measuring pollen counts at the different study centers. The study report should document the exposure of patients to the relevant allergens during the study period. It may also be helpful to collect data on the number of rainy days during the trial and the extent of patient exposure to outdoor air.

- For SAR trials, randomization of patients within each center into the double-blind portion over a short time period (e.g., 3-4 days) is encouraged, as this generally reduces variability in allergen exposure.

- Many patients with PAR may have concomitant SAR. Therefore, PAR trials should be conducted during a time when relevant seasonal allergens are less abundant and therefore less likely to influence results of the trial (i.e., late fall and winter).

B. Inclusion Criteria

- For SAR effectiveness trials, patients should have a history of SAR for a minimum of 2 years before study entry. Documentation of sensitivity by positive skin testing (by prick or intradermal methods) or by adequately validated in vitro tests for specific IgE (e.g., RAST, PRIST) to the relevant seasonal allergen for the geographic area of the study within 12 months prior to enrollment is recommended. A positive skin test is generally defined as a wheal ≥ 3 mm larger than the diluent control for prick testing or ≥ 7 mm larger than the diluent control for intradermal

testing. Positive in vitro tests are determined by the standards of the individual reference laboratory.

- For PAR effectiveness trials, allergy to perennial allergens (e.g., dust mites, cockroaches, cats, dogs, molds) should be demonstrated in study patients by prick or intradermal skin testing (using the criteria for positivity above) or by adequately validated in vitro tests for specific IgE (e.g., RAST, PRIST). These tests should be done during the 12 months before enrollment. The patient should have a relevant allergy history to the tested allergen.

- For approximately 1 month preceding enrollment in the study, patients should not start immunotherapy or have a change in dose, and they should maintain the same dose throughout the trial.

Patients enrolled in treatment studies (as opposed to prophylaxis studies) should be experiencing symptoms meeting or exceeding an appropriate minimum level at the time of study enrollment. This could be ensured by assessing the severity of the symptoms for the primary endpoint and requiring at least moderate severity for all or the majority of individual symptoms, as defined by the study's symptom scoring scale.

C. Exclusion Criteria

The following conditions should exclude possible study participants:

- Asthma, with the exception of mild intermittent asthma (see the 1997 NAEPP guideline on asthma severity criteria), to lessen confounding by asthma medications

- Chronic or intermittent use of inhaled, oral, intramuscular, intravenous, and/or potent or super-potent topical corticosteroids

- Use of long-acting antihistamines

- Prohibited medications or inadequate washout periods (for certain classes of medications). The following washout periods are generally sufficient:

  Intranasal or systemic corticosteroids (1 month)
  Intranasal cromolyn (2 weeks)
  Intranasal or systemic decongestants (3 days)
  Intranasal or systemic antihistamines (3 days)
  Loratadine (10 days).

- Documented evidence of acute or significant chronic sinusitis, as determined by the individual investigator

- Chronic use of concomitant medications (e.g., tricyclic antidepressants) that would affect assessment of the effectiveness of the study medication

- A history of hypersensitivity to the study drug or its excipients

- Rhinitis medicamentosa

- Presence of ocular herpes simplex or cataracts (for intranasal corticosteroid trials), or a history of glaucoma (for intranasal corticosteroid or anticholinergic trials)

- Planned travel outside the study area for a substantial portion of the study period by potential participants

D. Blinding

Because allergic rhinitis trials are based on subjective endpoints, blinding is a critical consideration. Blinding to study medication should be carefully described in the study protocol (i.e., description of how the product is masked). If double-blinding is not possible, a rationale for this should be provided, along with a discussion of the means for reducing or eliminating bias. For nasal inhalers or pumps, a description of differences in appearance between active and placebo treatments should be provided in the protocol (e.g., differences in the device or in the odor or characteristic of the formulation) to help determine the adequacy of the study blind.

E. Formulations and Dosage Regimens

For all classes of allergic rhinitis drugs, sponsors are encouraged to provide information in the clinical study protocol on the specific formulations used for both the to-be-marketed drug and the placebo, along with a description of the dosing regimen. The study report should discuss whether the studied formulation was the to-be-marketed product, and if not, 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 study lots should be included in the study reports for the respective products.

F. Evaluation

1. Assessment of Patient Compliance

Information about how compliance with medication 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) should to be provided in the study protocol and the study report.

2. Assessment of Rescue Medication Use

If rescue medications are allowed during the study, documentation should be provided in the study protocol on how rescue medication use will be analyzed in the different treatment groups. In the clinical trial report, a section presenting rescue medication use in the different study medication groups should be provided.

3. Rating System

The preferred measures of effectiveness in allergic rhinitis trials are patient self-rated *instantaneous* and *reflective* composite symptom scores. These summed scores generally include the following four nasal symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing, rated on a 0-3 scale of severity. Addition of non-nasal symptoms to the composite score might be pertinent for certain drug products, such as systemically active antihistamines, and should be discussed with the division on a case-by-case basis. Exclusion of symptoms from the composite score may be allowable, based on the drug's mechanism of action (e.g., exclusion of nasal congestion for antihistamines). While both patient self-rated symptom scores and physician-rated scores can be measured, the patient-rated scores are preferred as the primary measure of effectiveness.

A common allergic rhinitis rating system that has been used in clinical trials is the following 0-3 scale:

- 0 = absent symptoms (no sign/symptom evident)
- 1 = mild symptoms (sign/symptom clearly 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.

4. Recording Scores

Patients should record scores in a diary at least as often as the daily dosing interval. Collection of both *reflective* symptom scores (i.e., an evaluation of symptom severity

after a predefined time period such as 12 hours) and *instantaneous* symptom scores (i.e., an evaluation of symptom severity immediately before the next dose) is recommended. Reflective symptom scores assess the overall degree of effectiveness over a prespecified time interval, whereas instantaneous scores assess effectiveness at the end-of-dosing interval.

VI. DATA ANALYSIS ISSUES

A. Collection of Data

Symptom scores should be collected at baseline and daily over the course of the trial. Collection of baseline symptom scores over several days immediately preceding patient randomization will permit the evaluation of baseline comparability of the various treatment arms, as well as the determination of treatment effects over time.

An appropriate primary efficacy endpoint is the change from baseline in the total nasal symptom score (TNSS) for the *entire* double-blind treatment period (2 weeks for SAR and 4 weeks for PAR). Depending on the drug class being evaluated, the TNSS is defined as a composite score of at least three of the following four nasal symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing. Inclusion of nasal congestion in the TNSS may be appropriate for an intranasal corticosteroid or a decongestant, but may not be for an antihistamine, anticholinergic, or cromolyn-like agent.

When designing allergic rhinitis protocols, sponsors are encouraged to provide the value of a clinically meaningful change in the primary efficacy endpoint and the basis for this value. The statistical section of the protocol should also discuss powering of the trial based on this relevant change.

In addition to evaluating the effectiveness of the drug over the entire double-blind period, additional data presentations are helpful in evaluating the effectiveness of the drug. These include:

- Presenting the a.m. and p.m. symptom scores separately for both the reflective and instantaneous symptom assessments.

- Presenting effectiveness data for the first few days of the trial separately for both the reflective and instantaneous symptom assessments. This data presentation should also separate the a.m. and p.m. scores. This allows some assessment of the onset of action.

- Presenting the efficacy data for each week individually for both the reflective and instantaneous symptom assessments. This allows determination of both the onset of action and the durability of the response over the course of the clinical trial.

Additional secondary efficacy analyses may include the individual patient-rated symptoms that comprise the total symptom complex for the reflective and instantaneous symptom assessments for both a.m. and p.m. In addition, other patient-rated symptoms and all physician-rated symptoms can be included as secondary efficacy endpoints.

B. Time to Maximal Effect

The time to maximal effect for an allergic rhinitis medication is the earliest time (days, weeks) that the primary efficacy endpoint demonstrates the greatest numerical difference from the placebo in change from baseline. Sponsors are encouraged to include frequent symptom measurements to determine when patients may expect to see the greatest benefit from use of the drug.

C. Duration of Effect (End-of-Dosing Interval Analysis)

Evaluation of the duration of effect, as measured by instantaneous symptom scores at the end of the dosing interval, is highly encouraged to assess the appropriateness of the dosing interval. A sponsor should demonstrate, as part of the drug development program, a significant difference between drug and placebo at the end of the dosing interval.

D. Onset of Action

The definition of the onset of action of an allergic rhinitis drug is the point at which patients might reasonably expect to see a meaningful decrease in their allergic rhinitis symptoms. Statistically, it is the first time point after initiation of treatment when the drug demonstrates a change greater than the placebo treatment from baseline in the primary efficacy endpoint. This statistically significant difference between drug and placebo should be maintained for some period from this point onward.

Because onset of action information in labeling may be used as a superiority claim, at least two studies are recommended to support a particular onset of action claim. (It is useful to assess onset of action during development, regardless of any proposed claims). The two trials do not have to be identical in design, nor do they have to evaluate both SAR and PAR. Since onset of action is in large part a pharmacodynamic issue, a number of different study types could be used. Following are three study types that have been used.

- Standard phase 3 allergic rhinitis efficacy trials in which symptom scoring data are collected frequently for the first few days

- A single-dose, parallel group, placebo-controlled study of patients in a *park setting* in which patients are exposed to relevant outdoor seasonal allergens and, following dosing, have nasal symptoms evaluated on an hourly basis

- An inhalation chamber study (also known as environmental exposure unit or EEU) in which previously asymptomatic patients are exposed to a relevant allergen (generally a seasonal allergen, such as ragweed) in a controlled indoor setting and, following dosing, have their nasal symptoms evaluated on an hourly basis

Onset of action data can come from any of these three study types. However, if EEU and/or park studies are used to support an onset of action claim shorter than the onset of action seen in the phase 3 trials, these results should be replicated. This is due to the shorter duration of these trials and the restricted setting and manner in which they are conducted. In any case, information about onset of action derived from the phase 3 trials used to support approval should be included in the proposed package insert along with any data from park or chamber studies, to reflect the real world setting of the treatment trials.

VII. SAR PROPHYLAXIS TRIALS

Many variables should be considered in designing adequate prophylaxis trials for seasonal allergic rhinitis. Some of the issues that should be considered include:

- The recruitment of patients who are asymptomatic or have only mild rhinitis symptoms at baseline

- The optimal duration of pretreatment with study drug

- The difficulty in capturing the peak of the allergy season or a time when pollen counts are at their highest

- The advantages of pretreatment and/or prophylactic therapy versus treatment at the time of symptoms

Sponsors who choose to conduct prophylaxis studies should propose a minimum duration of drug exposure prior to anticipated allergen exposure and should carefully discuss the study design for each drug product with the division before initiating such studies.

634 Performance of an EEU study may address the adequate prophylaxis period for a seasonal
635 allergen. However, a prophylaxis claim should be based in part on standard allergic rhinitis trial
636 settings.