
Guidance for Industry

Allergic Rhinitis: Clinical Development Programs for Drug Products

DRAFT GUIDANCE

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

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(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.

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

42
43 A growing number of chemical mediators are believed to contribute to allergic rhinitis. They
44 include histamine, leukotrienes (LTC₄, LTD₄, and LTE₄), kinins, prostaglandins, chemotactic
45 factors, neuropeptides (e.g., substance P, CGRP, VIP), interleukins -1, -5, -6, -8, and tumor
46 necrosis factor- α . Additional mediators with a potential role in allergic rhinitis will likely be
47 identified in the future. Despite different causes and temporal patterns of disease, the same
48 groups of chemical mediators appear to be regulators of the responses in seasonal and perennial
49 allergic rhinitis. It is for this reason that distinctions between SAR and PAR in terms of clinical
50 trial design will be made only in clinically relevant areas.

III. OVERALL CONSIDERATIONS – ADULT PROGRAM

A. New Molecular Entity

1. Number of Trials

57
58 For approval of a new molecular entity in adult and adolescent patients (age 12
59 years and older), at least two adequate and well-controlled phase 3 clinical trials are
60 recommended to support either the SAR or PAR indication. Alternatively, a
61 sponsor can submit one SAR and one PAR trial in support of both the indications, if
62 both trials are adequate and well-controlled phase 3 trials and both trials
63 demonstrate the safety and effectiveness of the drug for the indications.

2. Dose

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65
66
67 The dose-response relationship for the new drug should be evaluated in these trials.
68 These trials, or other supporting trials, should identify a *lowest effective dose* for
69 the drug (i.e., the lowest dose that demonstrates a statistically significant difference
70 between the to-be-marketed drug and the placebo). This recommendation is
71 particularly important for intranasal corticosteroids.

3. Safety Monitoring

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73
74
75 These trials should also address safety concerns, such as monitoring for adverse
76 events, performing routine laboratory tests (i.e., blood chemistry, liver function tests,
77 complete blood count with differential), urinalyses, and electrocardiograms, as
78 appropriate. For SAR and PAR phase 3 trials, routine laboratory tests should be
79 obtained in study patients at least at the initial screening and at the last visit.

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

- 84 • Screening and end-of-treatment ECGs, including a careful assessment of the
85 QT_c interval and any T wave abnormalities, as read by a ECG reviewer blinded
86 to study treatment.
- 87
- 88 • Human dose escalation studies that evaluate serial ECGs at drug exposures up
89 to dose-limiting toxicity of any organ system.
- 90
- 91 • For drugs metabolized by the cytochrome P450 3A4 system, drug interaction
92 studies performed with both a macrolide and azole antibiotic.
- 93
- 94 • 24-hour Holter monitoring performed before, during, and, as appropriate, on
95 completion of the efficacy trials for allergic rhinitis drugs suspected to have an
96 effect on QT_c intervals from previous studies.
- 97

98
99 In addition to the studies described above, case report forms and study reports
100 should include a detailed description of all serious cardiac adverse events and
101 pertinent ECGs.

102
103 Sponsors are encouraged to contact the review division regarding appropriate
104 cardiac safety monitoring for their respective drug development programs.

105
106 For many allergic rhinitis drugs, some assessment of the degree of sedation
107 compared to the placebo should be provided in the safety database. This should
108 primarily be based on individual patient adverse event reports of sedation and/or
109 drowsiness (or similar terminology, as defined by the sponsor's adverse event
110 dictionary).

111
112 Generally, long-term safety data should include at least 300 patients evaluated for 6
113 months and 100 patients evaluated for 1 year. The overall patient database should
114 include at least 1500 patients. (See the International Conference on Harmonisation
115 guidance on the *Extent of Population Exposure Required to Assess Clinical*
116 *Safety for Drugs Intended for Long-term Treatment of Non-Life Threatening*
117 *Conditions* (March 1995).)

118 119 4. Corticosteroid Issues

120
121 Important safety issues for intranasal corticosteroids that would ordinarily be
122 addressed in the adult clinical program include:

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- 124 • Assessment of adrenal function using either timed urinary free cortisol level
125 measurements (i.e., 12-hour or 24-hour), or 24-hour plasma cortisol AUC
126 levels pretreatment and after at least 6 weeks post-treatment with study
127 medication. A placebo and an active control (e.g., oral prednisone) should be
128 included in these studies.
- 129 • Evaluation for possible cataract formation by slit-lamp examination, pre- and
130 post-treatment.
- 131 • Evaluation for glaucoma, using intra-ocular pressures monitored pre- and post-
132 treatment.
- 133 • Evaluation for glaucoma, using intra-ocular pressures monitored pre- and post-
134 treatment.

B. Change in Formulation and/or Device

1. Oral Formulations

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

2. Topical Nasal Formulations

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

- 159 • Comparability Approach

160 To demonstrate clinical comparability between the new and reference formulations,
161 comparison of the dose-response curves of these two formulations in a single
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167 efficacy and safety trial is recommended. Two doses of each formulation, in
168 addition to placebo, are desirable for dose-ranging determination. The dose-
169 ranging study should be designed to permit determination of how doses of the new
170 formulation compare to the approved doses of the reference formulation with regard
171 to onset of action and effectiveness. Comparative pharmacokinetic (PK)
172 measurements (C_{max} , T_{max} , and AUC) should be included in this trial, as appropriate
173 and technically feasible. If the reference formulation is indicated for both SAR and
174 PAR, the dose-ranging trial can be performed in patients with either SAR or PAR
175 (see section V of this guidance, Protocol Issues and Elements, for recommended
176 trial durations). If the reference formulation is approved for indications in addition
177 to SAR and/or PAR (e.g., nasal polyps or nonallergic rhinitis) no additional studies
178 are needed to support the same indications for the new product, if comparability, as
179 described above, is well established between the new and reference formulation.

- 181 • Stand-Alone Approach

182
183 An alternative approach or *stand-alone approach* for evaluating a topical nasal
184 drug product with a formulation change could be a single, dose-ranging, placebo-
185 controlled efficacy and safety trial of the new formulation in patients with either SAR
186 or PAR. A single dose of the reference formulation as a positive control is
187 recommended. Demonstration of effectiveness for either of these two clinical
188 indications would allow labeling to include efficacy for both, if the reference
189 formulation already had labeling for both. If additional indications (e.g., nasal
190 polyps and nonallergic rhinitis) previously approved for the reference formulation
191 are sought for the new formulation, a single clinical trial for each additional indication
192 is recommended. Furthermore, as with the *comparability approach*,
193 determination of the pharmacokinetics of the drug is recommended during the
194 stand-alone approach and can be performed during the efficacy trial, if feasible.

195 3. *Safety Monitoring*

196
197
198 For both oral and topical nasal formulation programs described above, safety
199 monitoring should be included for the duration of the trials. This would include
200 evaluation of adverse clinical events, routine laboratory tests (i.e., blood chemistry,
201 liver function, complete blood count with differential), urinalysis, and ECGs, as
202 appropriate.

203
204 In either of these formulation programs, demonstration of long-term safety may still
205 be important, if new inactive ingredients have been added that could affect safety, or
206 if the new formulation and/or device results in higher systemic exposure to active
207 ingredients compared to the approved product. In addition, if pharmacokinetic data
208 for the formulations are not feasible, long-term safety data for the new formulation
209 may be recommended. If necessary, long-term safety may be established by

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

221 222 *4. Corticosteroid Issues*

223
224 For corticosteroids, if the new formulation causes higher systemic exposure to the
225 drug substance than other formulations (either intranasally or orally inhaled) already
226 marketed or under development for which an adequate assessment of HPA axis
227 effects has been conducted, or if pharmacokinetic data on these other formulations
228 is unavailable, an evaluation of the effect of the new formulation on the HPA axis is
229 strongly recommended. For HPA axis evaluation, measurement of timed (12- or
230 24-hour) urinary free cortisol levels or serum cortisol AUC before and after 6
231 weeks of treatment are the preferable methods of assessment. If the sponsor plans
232 to claim comparability between the reference and new formulations, and a
233 pharmacokinetic comparison of the two products is not available, comparison with
234 the highest marketed dose of the reference formulation is recommended.

235
236 For a change in a device, data on the performance and reliability of the new device
237 over the period of intended use may need to be provided.

238 239 **IV. OVERALL CONSIDERATIONS – PEDIATRIC PROGRAM**

240 241 **A. New Molecular Entity or New Pediatric Indication**

242
243 The pediatric age ranges proposed for a drug product, particularly for very young
244 patients, should be justified by the sponsor based on the presence of disease and the
245 need for treatment in that age group. Drugs indicated for the treatment of allergic rhinitis
246 are used in children below the age of 2 years; therefore, a complete pediatric program
247 should evaluate the safety of antihistamines in children down to age 6 months. Similarly,
248 based on clinical use experience, the safety of intranasal corticosteroids, cromolyn-like
249 drugs, and anticholinergics should be evaluated in children down to age 2. Sponsors
250 are encouraged to discuss the specifics of pediatric programs with the division on a
251 case-by-case basis.
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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.

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B. Change in Formulation and/or Device

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V. PROTOCOL ISSUES AND ELEMENTS

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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.

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.

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

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

342

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

346

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

349

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

354

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

357

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

363

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

367

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

371

B. Inclusion Criteria

372

373 • For SAR effectiveness trials, patients should have a history of SAR for a minimum
374 of 2 years before study entry. Documentation of sensitivity by positive skin testing
375 (by prick or intradermal methods) or by adequately validated in vitro tests for
376 specific IgE (e.g., RAST, PRIST) to the relevant seasonal allergen for the
377 geographic area of the study within 12 months prior to enrollment is recommended.
378 A positive skin test is generally defined as a wheal ≥ 3 mm larger than the diluent
379 control for prick testing or ≥ 7 mm larger than the diluent control for intradermal
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381 testing. Positive in vitro tests are determined by the standards of the individual
382 reference laboratory.

- 383
- 384 • For PAR effectiveness trials, allergy to perennial allergens (e.g., dust mites,
385 cockroaches, cats, dogs, molds) should be demonstrated in study patients by prick
386 or intradermal skin testing (using the criteria for positivity above) or by adequately
387 validated in vitro tests for specific IgE (e.g., RAST, PRIST). These tests should be
388 done during the 12 months before enrollment. The patient should have a relevant
389 allergy history to the tested allergen.
 - 390
 - 391 • For approximately 1 month preceding enrollment in the study, patients should not
392 start immunotherapy or have a change in dose, and they should maintain the same
393 dose throughout the trial.

394

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

400

401 **C. Exclusion Criteria**

402

403 The following conditions should exclude possible study participants:

404

- 405 • Asthma, with the exception of mild intermittent asthma (see the 1997 NAEPP
406 guideline on asthma severity criteria), to lessen confounding by asthma medications
- 407
- 408 • Chronic or intermittent use of inhaled, oral, intramuscular, intravenous, and/or potent
409 or super-potent topical corticosteroids
- 410
- 411 • Use of long-acting antihistamines
- 412
- 413 • Prohibited medications or inadequate washout periods (for certain classes of
414 medications). The following washout periods are generally sufficient:

415

416 Intranasal or systemic corticosteroids (1 month)

417 Intranasal cromolyn (2 weeks)

418 Intranasal or systemic decongestants (3 days)

419 Intranasal or systemic antihistamines (3 days)

420 Loratadine (10 days).

421

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

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- 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

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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

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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

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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

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467 last visit data carried forward) should be provided in the study protocol and the study
468 report.

469

470 2. *Assessment of Rescue Medication Use*

471

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

476

477 3. *Rating System*

478

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

490

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

493

- 494 • 0 = absent symptoms (no sign/symptom evident)
- 495 • 1 = mild symptoms (sign/symptom clearly present, but minimal awareness;
496 easily tolerated)
- 497 • 2 = moderate symptoms (definite awareness of sign/symptom that is
498 bothersome but tolerable)
- 499 • 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference
500 with activities of daily living and/or sleeping)

501

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

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506 4. *Recording Scores*

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

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

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517 VI. DATA ANALYSIS ISSUES

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A. Collection of Data

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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.

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

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

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B. Time to Maximal Effect

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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.

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

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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.

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D. Onset of Action

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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.

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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.

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- 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

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

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614 **VII. SAR PROPHYLAXIS TRIALS**

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

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- 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

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

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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.