

Draft Guidance on Azelastine Hydrochloride and Fluticasone Propionate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient: Azelastine hydrochloride and Fluticasone propionate

Dosage Form; Route: Spray, metered; nasal

Recommended Studies: In vitro and in vivo studies

FDA recommends the following in vitro and in vivo studies to establish bioequivalence (BE) of the test (T) to the reference (R) nasal sprays containing azelastine hydrochloride and fluticasone propionate.

In Vitro Studies

In vitro BE studies should be performed on samples from each of three or more batches of the T product and three or more batches of the R product, with no fewer than 10 units from each batch. Whenever possible, T product samples should be from the primary stability batches used to establish the expiration date period. When three batches are studied, we recommend the T product be manufactured, preferably from three different batches of the drug substance, different batches of critical excipients, and different batches of the same device (pump and actuator) components. The BE batches to be studied should be at least one-third of the to-be-marketed production batch size. The manufacturing process of these batches should simulate that of large-scale production batches for marketing.

For comparative in vitro studies, T and R should be studied under the same instrumental conditions. Actuation should be conducted in a manner that removes potential operator bias, either by employing automatic actuation or by employing blinded procedures when manual actuation is used, where feasible. The analyst performing the post-actuation evaluations of the collected data should be blinded to the identity of the samples. Method validation should be performed using R product, and the lot number(s) for the R bottles used for the validation should be provided.

FDA recommends the following in vitro studies to establish in vitro BE of the test and reference nasal sprays containing azelastine hydrochloride and fluticasone propionate.

1. **Type of study:** Single Actuation Content (SAC)

Design: The SAC test should be performed at the beginning (B) and end (E) lifestages of the product.¹ An appropriate apparatus may be used to determine the SAC using a validated assay. The number of actuations per determination should be one.

Equivalence based on: The SAC comparison of the T and R products is based on the population bioequivalence (PBE). Refer to the product-specific recommendation for budesonide inhalation suspension for additional information regarding PBE analysis procedures

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf>)

2. **Type of study:** Droplet Size Distribution by Laser Diffraction

Design: Droplet size distribution should be determined using laser diffraction or an appropriately validated alternate methodology. Droplet size distribution should be measured for fully developed phase only at B and E lifestages. It is recommended that the studies be performed within a range of 2 to 7 cm from the actuator orifice, with the two distances separated by 3 cm or more.

Additional comments: Single spray droplet size distribution and span should be reported based on volume (mass). Mean D_{10} , D_{50} , D_{90} values for a given unit should be computed from the mean of up to three consecutive sprays from that unit at each lifestage. Span can be computed as $((D_{90} - D_{10})/D_{50})$. To assess precision, the data of each spray should also be reported.

Equivalence based on: PBE analysis of D_{50} and span at two selected distances.

3. **Type of study:** Drug in Small Particles/Droplets

Design: Determination of drug in small particles/droplets is recommended to be performed at the B lifestage of the product using the U.S. Pharmacopeia (USP) <601> Apparatus 1 (flow rate of 28.3 L/min), Apparatus 6 (flow rate of 15 L/min), or another appropriate method using a validated, highly sensitive assay. Drug in small particles/droplets should be determined using fewest numbers of actuations (generally not exceeding 10 actuations) justified by the sensitivity of the assay, to be more reflective of individual doses.

Additional comments: Drug deposition should be reported in mass units. Mass balance should be based on drug deposition on each of valve stem, actuator, adapters, induction port, any other accessories, the top stage, and all lower stages to the filter. Mass balance accountability should be reported based on the sum of all deposition sites. The total mass of drug collected on all stages and accessories is recommended to be between 85 and 115% of the amount labeled on a per actuation basis.

Equivalence based on: PBE modified to be one-sided for mean comparison of drug mass in the small particles/droplets less than 9.0 μm . Refer to the product-specific

¹ Based on the labeled number of actuations, the terms B lifestage, M lifestage, and E lifestage represent the first actuation(s) following the labeled number of priming actuations, the actuation(s) corresponding to 50 percent of the labeled number of actuations, and the actuation(s) corresponding to the labeled number of actuations, respectively.

recommendation for fluticasone propionate nasal spray metered for the step-wise procedure for PBE modified to be one-sided for mean comparison analysis.

4. Type of study: Spray Pattern

Design: The spray pattern test should be performed at the B lifestage of the product and at two different distances from the actuator orifice. The selected distances should be at least 3 cm apart and based on the range of 3 to 7 cm from the R actuator tip. Impaction (thin-layer chromatography plate impaction), non-impaction (laser light sheet and high-speed digital camera), or other suitable method may be used to determine the spray pattern.

Additional comments: Spray pattern should be measured quantitatively in terms of ovality ratio and area within the perimeter (to include a high proportion, e.g., 95% of the total pattern) of the true shape for the automated analysis, or ovality ratio, and D_{\max} for the manual analysis. Ovality ratio is defined as the ratio of D_{\max} to D_{\min} . D_{\max} and D_{\min} are the longest and shortest diameters, respectively, that pass through the center of mass or the center of gravity, as appropriate. The number of sprays per spray pattern should preferably be one.

Equivalence based on: At two selected distances, (i) qualitative comparison of spray shape, and (ii) PBE analysis of ovality ratio and area for automated analysis, or ovality ratio and D_{\max} for manual analysis.

5. Type of study: Plume Geometry

Design: The plume geometry test should be performed at B lifestage of the product. The time sequence sound-triggered flash photography method, laser light sheet technology, and high speed digital camera, or other suitable method may be used to determine the plume geometry at the appropriate post-actuation delay time.

Additional comments: Plume geometry measurements should be reported at a single delay time while the fully developed plume is still in contact with the actuator tip. Plume geometry should be measured quantitatively in terms of plume angle and width of one side view. The plume angle is based on the conical region of the plume extending from a vertex that occurs at or near the actuator tip. The plume width is measured at a distance equal to the greater of the two distances selected for characterization of the spray pattern.

Equivalence based on: Ratio of the geometric mean of the three batches of T to that of the three batches of R (based on log-transformed data) for both plume angle and width, which should fall within 90-111% of plume angle and plume width.

6. Type of study: Priming and Repriming

Design: Priming and repriming tests should be based on the emitted dose (ex-actuator) of a single actuation immediately following the specified number of priming or repriming actuations specified in the R product labeling. The repriming test should be performed following storage for the specified period of non-use after initial use and/or other conditions (e.g., dropping), if the R product labeling provides such repriming information.

Additional comments: For BE evaluation, the priming and repriming tests should be based on products stored in the valve-upright position, with the exception of a nasal spray for which the R labeling recommends storage in the valve-down position. The priming data can be based on the SAC data at the B lifestage. Repriming would be similarly established based on a single actuation following the specified number of repriming actuations in the R product labeling.

Equivalence based on: PBE analysis of the emitted dose of a single actuation immediately following the specified number of priming or repriming actuations specified in the R product labeling.

In vitro BE data submission recommendations

- For data summary tables and SAS data tables for the in vitro data recommended for nasal spray products, the templates in the following links should be used, to ensure completeness and consistency of the data:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM209446.pdf>

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM271017.pdf>

- In addition to submission of all raw data, the following supporting documentation for Droplet Size Distribution by Laser Diffraction, Spray Pattern, and Plume Geometry should be provided:
 - Documentation includes instrument output reports and photographic or graphic material, as applicable. Documents should be clearly labeled to indicate the product (e.g., T or R), batch number, and testing conditions (e.g., distance, lifestage, delay time), as appropriate.
 - For Droplet Size Distribution by Laser Diffraction, profiles of droplet size and obscuration or percent transmission over the complete life of the single sprays should be submitted.
 - Supporting documentation for Droplet Size Distribution by Laser Diffraction, Spray Pattern, and Plume Geometry should include representative copies, preferably electronic, of > 20% of the total observations.
 - For Spray Pattern and Plume Geometry quantitated by automatic image analysis, representative electronic images rather than paper copies of > 20% of the total observations should be submitted, as electronic files are definitive. For automated image analysis of Spray Pattern and Plume Geometry, in addition to the electronic images, it is

recommended that paper copies of a few screen images be submitted as reference samples.

Pharmacokinetic (PK) BE Study

Type of study: Fasting

Design: Single-dose, two-way crossover

Strength: EQ 0.125 mg base/0.05 mg per spray

Dose: Azelastine hydrochloride EQ 0.5 mg base and fluticasone propionate 0.2 mg, administered as two sprays in each nostril

Subjects: Healthy males and nonpregnant females, general population

Additional comments: 1) Follow the reference listed drug (RLD) labeling for the method of drug administration; 2) The analytical method should have sufficient sensitivity to adequately quantify the concentration of fluticasone propionate and azelastine in blood [for fluticasone propionate, assay method with Limit of Quantification (LOQ) ≤ 1 pg/mL is suggested].

Analytes to measure: Fluticasone propionate and azelastine in plasma

Equivalence based on: AUC and C_{\max} for fluticasone propionate and azelastine. The 90% confidence intervals for the geometric mean T/R ratios of AUC and C_{\max} should fall within the limits of 80.00–125.00%

Clinical Endpoint BE Study

The following BE study with a clinical endpoint is recommended.

The recommendations provided here supersede information provided in the draft guidance for industry *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (April 2003). These recommendations are specific to this product and may not be appropriate for BE studies of any other product, including any other dosage form or strength of azelastine hydrochloride and fluticasone propionate.

Type of study: BE Study with Clinical Endpoint²

Design: Randomized, double-blind, three-arm, placebo-controlled, parallel group

Strength: EQ 0.125 mg/0.05 mg per spray

Dose: EQ 0.25 mg/0.1 mg twice-daily, administered as one spray in each nostril

Subjects: Subjects with seasonal allergic rhinitis

Additional comments: Specific recommendations are provided below

² A clinical endpoint BE study is recommended because of an inability at the present time to adequately characterize drug particle size distribution (PSD) in aerosols and sprays. Drug PSD in suspension formulations has the potential to influence the rate and extent of drug availability to nasal sites of action and to systemic circulation.

Additional comments regarding the BE study with clinical endpoint:

1. The FDA recommends conducting a single BE study with clinical endpoint in the treatment of seasonal allergic rhinitis (SAR) consisting of 2 periods: a 7-day, single-blinded, placebo run-in period (Study days -7 to -1) to establish a baseline and to identify placebo responders, followed by a 14-day treatment period (Study Days 1 to 14). Prime each product as per RLD labeling instructions prior to initial dosing. During the placebo run-in period, all subjects are to receive the placebo vehicle administered as one spray in each nostril twice daily for 7 days. All subjects who qualify after the placebo run-in period are to be randomized to receive the test product, reference, or placebo (vehicle) control during the treatment period, administered as one spray in each nostril twice daily for 14 days. The primary endpoint is the difference in the mean change in reflective total nasal symptom scores from baseline to the treatment period.
2. A multicenter study is recommended to avoid potential investigator bias.
3. A double dummy design is not recommended for study blinding due to a concern that the doubled fluid volume may result in washing the drug from its nasal deposition sites, potentially resulting in an altered safety and efficacy profile.
4. Inclusion criteria, at a minimum, should include the following:
 - a. Males and nonpregnant females, 18 years of age and older.
 - b. For female subjects of childbearing potential: agreement to practice an approved method of birth control.
 - c. History of seasonal allergic rhinitis (SAR).
 - d. Positive test for relevant specific allergens (e.g., allergen skin test).
 - e. Demonstration of significant symptoms during screening and randomization, as measured by a reflective total nasal symptom score of, for example, at least 6 at the time of enrollment (see items 7 and 8).
5. Exclusion criteria, at a minimum, should include the following:
 - a. For females: Pregnancy, lactating, or planning to become pregnant during the study period.
 - b. Active or quiescent tuberculous infections of the respiratory tract; untreated local or systemic fungal, bacterial, viral, or parasitic infections.
 - c. Presence of glaucoma, cataracts, ocular herpes simplex, conjunctivitis, or other eye infection.
 - d. Presence of any nasal mucosal erosion, nasal septal ulcers, or septum perforation on focused nasal examination at screening or randomization.
 - e. Recent nasal or sinus surgery or nasal trauma.
 - f. Other nasal disease(s) likely to affect deposition of intranasal medication, such as chronic sinusitis, rhinitis medicamentosa, clinically significant polyposis, or nasal structural abnormalities.
 - g. Presence or history of any clinically significant condition that, in the opinion of the

- investigator, would compromise the safety of the subject or the conduct of the study.
- h. Planned travel outside of the pollen area during the trial.
 - i. Use of any investigational drug within 30 days prior to screening.
 - j. Any hypersensitivity to azelastine hydrochloride, fluticasone propionate, similar drugs, or any of the inactive ingredients.
 - k. Respiratory tract infection requiring antibiotic within 14 days prior to screening
 - l. History of significant pulmonary disease, including asthma (with the exception of mild intermittent asthma) or COPD.
 - m. Use of any prohibited medications and treatments (including antihistamines, decongestants, leukotriene antagonists, corticosteroids, other nasal therapies, potent cytochrome P450 3A4 inhibitors such as ketoconazole, etc.) prior to screening [the sponsor should provide a list of treatments with justification/rationale provided for duration of the washout period prior to screening].
6. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as antihistamines decongestants, leukotriene antagonists, corticosteroids, anti-IgE antibodies (e.g., omalizumab), immunosuppressive therapy, and potent cytochrome P450 3A4 inhibitors such as ketoconazole.
 7. Subjects should self-score their symptoms twice daily (AM and PM, 12 hours apart at the same times daily) throughout the 7-day placebo run-in period and the 14-day randomized treatment period. Scoring should be made immediately prior to each dose (and 12 hours after the AM dose for once-daily dosing), to reflect the previous 12 hours (*reflective* scores) and how the subject is feeling at the time of evaluation, i.e., at the end of dosing interval (*instantaneous* scores). Each of the following symptom should be scored using the following scale:
 - a. Symptoms: runny nose, sneezing, nasal itching, and congestion.
 - b. Scoring Scale: The following is an example of an acceptable scale. Each score should be objectively defined.

Table 1: Sample Scoring Scale

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

8. Total nasal symptom score (TNSS) is the sum of each individual symptom rating for runny nose, sneezing, nasal itching, and congestion.

9. Baseline mean reflective TNSS (rTNSS) is the mean of the final seven scores from the placebo run-in period. The final seven scores from the placebo run-in period consist of the AM and PM scores on Days -3, -2, and -1 and the AM score (prior to drug dosing) on Day 1 of the 14-day randomized treatment period.
10. Placebo responders should be identified based on demonstration of significant symptoms during screening and randomization, as measured by reflective TNSS at the baseline, for example, mean rTNSS of at least 6. Placebo responders should be excluded from the study to increase the ability to show a significant difference between active and placebo treatments, and to increase sensitivity to detect potential differences between active products.
11. Treatment mean rTNSS is the average of 27 scores from the randomized treatment period. The 27 scores consist of the PM score on Day 1 and the AM and PM scores on Days 2 to 14.
12. The recommended primary endpoint is the change from the baseline mean rTNSS to the treatment mean rTNSS, expressed in absolute units rather than percent change from baseline.
13. The recommended secondary endpoint is the change from the baseline mean instantaneous (iTNSS) and the treatment mean iTNSS, expressed in absolute units rather than percent change from baseline.
14. The protocol should clearly, prospectively define the per-protocol (PP), modified intent-to-treat (mITT), and safety populations.
 - a. The accepted PP population used for BE evaluation includes all randomized subjects who meet all inclusion/exclusion criteria, take a pre-specified proportion of the scheduled doses (e.g., at least 75% to no more than 125% overall compliance) of the assigned product for the specified duration of the study, do not miss the scheduled study drug administrations for more than 3 consecutive days, record a prespecified number of qualifying rTNSS scores (e.g., 75% to 125%), and complete the evaluations as prespecified in the protocol at approximately the same time of the day, with no protocol violations that would affect the treatment evaluation. The protocol should specify how compliance will be verified, e.g., by the use of subject diaries.
 - b. The mITT population includes all subjects randomized into the treatment period who have taken at least one dose of assigned product during the treatment period (see comment #26 for applied use of mITT population).
 - c. The safety population includes all randomized subjects who received at least one dose of study product treatment.
15. Subjects who discontinue early from the study due to a lack of treatment effect should be included in the mITT and PP populations. Only subjects discontinued from the study for other reasons clearly not related to a lack of efficacy or emergence of safety concerns should be excluded from the PP population, but should remain in the mITT population.

16. The start and stop dates of concomitant medication use during the study should be provided in the dataset in addition to the reason for the medication use. The sponsor should clearly explain whether the medication was used prior to baseline visit, during the study, or both.
17. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome, and date of resolution. This information is needed to determine whether the incidence and severity of adverse reactions is different between the test product and reference product.
18. The quantitative information of inactive ingredients of the placebo control should be provided. OGD recommends that the inactive ingredients in the placebo product be qualitatively and quantitatively the same as the inactive ingredients in the RLD formulation.
19. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test, reference, and placebo products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. Neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject in the presence of the evaluator at the study center.
20. OGD recommends that each of the test and reference batches used in the clinical endpoint BE study be at least one of the three batches used for the in vitro BE studies.
21. Refer to 21 CFR 320.38, 320.63, and the guidance for industry *Handling and Retention of BA and BE Testing Samples* regarding retention of study drug samples. Refer to 21 CFR 320.36 for requirements for maintenance of records of BE testing. In addition, the investigators should follow the procedures of ICH E6, *Good Clinical Practice: Consolidated Guideline*, for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). At least 50 units each of the test, reference, and placebo products, with not less than 5 units per each shipment per site, should be retained as reserve samples. Retention samples should be randomly selected from each drug shipment by each study site and retained by the investigator or an independent third party not involved with packaging and labeling of the study products. Retention samples should not be returned to the sponsor at any time.
22. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
23. Subjects who discontinued from the study early should be identified, and the protocol should clearly, prospectively state how missing data will be handled in the statistical analyses and provide appropriate justification for the method chosen. The protocol

should also include subject retention strategies and other plans to minimize missing data.

24. We recommend using a statistical model for the endpoint data that takes into account baseline values. If the study was conducted at multiple clinical centers, center should also be considered in the data analysis.
25. To establish BE for a continuous endpoint, the Agency recommends the following compound hypotheses be tested using the PP population:

$$H_0: \mu_T/\mu_R < -\theta_1 \text{ or } \mu_T/\mu_R > \theta_2 \text{ versus } H_A: \theta_1 \leq \mu_T/\mu_R \leq \theta_2$$

where μ_T = mean of the primary endpoint for the test group, and
 μ_R = mean of the primary endpoint of the reference group

The null hypothesis, H_0 , is rejected with a type I error (α) of 0.05 (two one-sided tests) if the estimated 90% CI for the ratio of the means between T and R (μ_T/μ_R) is contained within the interval $[\theta_1, \theta_2]$, where $\theta_1 = 0.80$ and $\theta_2 = 1.25$. Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

26. To establish sensitivity within the study for a continuous primary endpoint, both the test and reference products should be statistically superior to the placebo. Conduct an appropriate inferential test with a type I error (α) of 0.05, using the mITT population and the primary endpoint.
27. The method of randomization should be described in the protocol and the randomization schedule provided as a SAS data set in .xpt format (created using SAS XPORT). The Agency recommends that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.
28. Study data should be submitted to the Office of Generic Drugs (OGD) in electronic format. All data should be submitted as an SAS .xpt file, created using SAS XPORT (not CPORT).
 - a. Include a list of file names, a description of the content of each file, an explanation of the variables within each file, and a description of all variable codes (for example, for the treatment variable, A = TEST and B = Reference).
 - b. Provide two primary data sets: one with raw data (as collected) and one dataset modified for missing data as specified prospectively.
 - c. Provide a separate data set for demographic, vital sign, adverse event, disposition (including reason for discontinuation of treatment), trial arms, subject visits, concomitant medication, medical history, compliance, protocol deviation, pollen count, and comment variables.

29. Provide a summary data set containing a separate line listing for each subject (if data exist) using the following headings, if applicable:
- a. Study identifier
 - b. Subject identifier
 - c. Site identifier: study center
 - d. Age
 - e. Age units (years)
 - f. Sex
 - g. Race
 - h. Name of Actual Treatment (exposure): test product, reference, placebo control
 - i. Total number of doses taken during the placebo run-in period
 - j. Total number of doses taken during the treatment period
 - k. Completed the study (yes/no)
 - l. Reason for premature discontinuation of subject
 - m. Subject required additional treatment for seasonal allergic rhinitis due to unsatisfactory treatment response
 - n. Per Protocol (PP) population inclusion (yes/no)
 - o. Reason for exclusion from PP population
 - p. Modified Intent to Treat (mITT) population inclusion (yes/no)
 - q. Reason for exclusion from mITT population
 - r. Safety population inclusion (yes/no)
 - s. Reason for exclusion from Safety population
 - t. Baseline rTNSS total score
 - u. Total number of baseline rTNSS ratings
 - v. Treatment period rTNSS total score
 - w. Total number of treatment period rTNSS ratings
 - x. Baseline iTNSS total score
 - y. Total number of baseline iTNSS ratings
 - z. Treatment period iTNSS total score
 - aa. Total number of treatment period iTNSS ratings
 - bb. Baseline mean rTNSS
 - cc. Treatment period mean rTNSS
 - dd. Mean change from baseline in rTNSS
 - ee. Baseline mean iTNSS
 - ff. Treatment period mean iTNSS
 - gg. Mean change from baseline in iTNSS
 - hh. Treatment compliance: number of missed doses per subject
 - ii. Concomitant medication (yes/no)
 - jj. Adverse event(s) reported (yes/no)

Table 2 provides an example. Note: This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 2: Example of a Summary Data Set Containing One Line Listing for Each Subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	dose_pla	dose_trt	completd	disc_rs	add_trt	pp	pp_rs	mitt	mitt_rs
101	1	01	21	YEARS	F	1	A			Y	C		Y		Y	
101	2	01	30	YEARS	F	1	B			Y	D		Y		Y	

safety	safe_rs	rs_base	rn_base	rs_trt	rn_trt	is_base	in_base	is_trt	in_trt	rtss_b	rtss_tt	rtss_ch	itss_b	itss_tt	itss_ch	complan	CM	AE
Y																		
Y																		

NOTE: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final, dated 11/12/08.

STUDYID: Study Identifier
SUBJID: Subject Identifier for the Study
SITEID: Study Site Identifier
AGE: Age
AGEU: Age units (years)
SEX: Sex, e.g., M=Male, F=Female, U=Unknown
RACE: Race, e.g., 1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders
EXTRT: Name of Actual Treatment (exposure), e.g., A=test product, B= reference, C=placebo control
dose_pla: Total number of doses taken during the placebo-run-in period
dose_trt : Total number of doses taken during the treatment period
completd: Subject completed the study, e.g., Y=Yes, N=No
disc_rs: Reason for premature discontinuation from the study, e.g., A=adverse event, B=death, C=lost to follow-up, D=non-compliance with treatment, E=treatment unblinded, F=subject moved out of area, G=unsatisfactory treatment response, H=withdrew consent, I=protocol violation, K=other event
add_trt: Subject required additional treatment for seasonal allergic rhinitis due to unsatisfactory treatment response, e.g., Y=Yes, N=No
pp: Per Protocol (PP) population inclusion, e.g., Y=Yes, N=No

pp_rs:	Reason for exclusion from PP population, e.g., A=prematurely discontinued, B=lost to follow-up, C=subject moved out of the area, D=noncompliant, etc.
mitt:	Modified Intent to Treat (mITT) population inclusion, e.g., Y=Yes, N=No
mitt_rs:	Reason for exclusion from mITT population, e.g., A=never treated, etc.
safety:	Safety population inclusion, e.g., Y=Yes, N=No
safe_rs	Reason for exclusion from Safety population, e.g., A=never treated, etc.
rs_base:	Baseline rTNSS total score
rn_base:	Total number of baseline rTNSS ratings
rs_trt	Treatment period rTNSS total score
rn_trt:	Total number of treatment period rTNSS ratings
is_base:	Baseline iTNSS total score
in_base:	Total number of baseline iTNSS ratings
is_trt:	Treatment period iTNSS total score
in_trt:	Total number of treatment period iTNSS ratings
rtcss_b:	Baseline mean rTNSS, e.g., 0 to 12
rtcss_tt:	Treatment period mean rTNSS, e.g., 0 to 12
rtcss_ch:	Mean change from baseline in rTNSS
itnss_b:	Baseline mean iTNSS, e.g., 0 to 12
itnss_tt:	Treatment period mean iTNSS, e.g., 0 to 12
itnss_ch:	Mean change from baseline in iTNSS
complan:	Treatment compliance, e.g., number of missed doses per subject
CM:	Concomitant medication, e.g., Y=Yes, N=No
AE:	Adverse event(s) reported, e.g., Y=Yes, N=No

30. Provide a data set containing a separate line listing for each study day per subject (if data exist). The following headers are recommended, if applicable:
- a. Study identifier
 - b. Subject identifier
 - c. Name of Actual Treatment (exposure): test product, reference, placebo control
 - d. Study day sequence number
 - e. Actual date of study day
 - f. Number of days since baseline visit
 - g. Reflective Runny nose score
 - h. Reflective Sneezing score
 - i. Reflective Nasal itching score
 - j. Reflective Congestion score
 - k. Reflective total nasal symptom score
 - l. Instantaneous Runny nose score
 - m. Instantaneous Sneezing score
 - n. Instantaneous Nasal itching score
 - o. Instantaneous Congestion score
 - p. Instantaneous total nasal symptom score
 - q. Date of symptom scoring
 - r. Time of symptom scoring (e.g., AM, PM)
 - s. Date of dosing

t. Time of dosing (e.g., AM, PM)

Table 3 provides an example. Note: This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 3: Example of Data Set Containing One Line Listing for Each Study Day Per Subject

STUDYID	SUBJID	EXTRT	studydy	studydt	ELTMBS	rrunny_s	rsneeze_s	ritch_s	rconge_s	rtnss	irunny_s	isneeze_s	iitch_s	iconge_s	itnss
101	1	A	1												

scrdtc	scrttc	dosedtc	dosettc
	am		am

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final, dated 11/12/08.

STUDYID: Study Identifier
 SUBJID: Subject Identifier for the Study
 EXTRT: Name of Actual Treatment (exposure), e.g., A=test product, B= reference, C= placebo control
 studydy: Study day sequence number, e.g., -7 to 14
 studydt: Actual date of study day
 ELTMBS: Elapsed Time since Baseline Visit (days)
 rrunny_s: Reflective runny nose score, e.g., 0 to 3
 rsneeze_s: Reflective sneezing score, e.g., 0 to 3
 ritch_s: Reflective nasal itching score, e.g., 0 to 3
 rconge_s: Reflective congestion score, e.g., 0 to 3
 rtnss: Total reflective nasal symptom score e.g., 0 to 12
 irunny_s: Instantaneous runny nose score, e.g., 0 to 3
 isneeze_s: Instantaneous sneezing score, e.g., 0 to 3
 iitch_s: Instantaneous nasal itching score, e.g., 0 to 3
 iconge_s: Instantaneous congestion score, e.g., 0 to 3
 itnss: Total instantaneous nasal symptom score , e.g., 0 to 12

scrdtc:	Date of symptom scoring
scrttc:	Time of symptom scoring, e.g., AM, PM
dosedtc:	Date of dosing
dosettec:	Time of dosing

Additional Information

Number of Reserve Samples:

At least 50 units of each of three batches should be retained for each of T and R products used in in vitro or in vivo PK BE studies. If these studies include placebo product, at least 50 units of each placebo batch should also be retained. If these studies are conducted at multiple sites, the number of BE retention samples is recommended to be not less than 10 units per batch per site.

Formulation and Device:

The generic product formulation is recommended to be qualitatively (Q1)³ and quantitatively (Q2)⁴ the same as the R product. The generic product is recommended to deliver the same number of doses as the R product, and the device should be similar in shape, size, and external operating principles to ensure substitutability with the R product without additional need to retrain patients upon use of the generic product.

³ Q1 (qualitative sameness) means that the T product uses the same inactive ingredient(s) as the R product.

⁴ Q2 (quantitative sameness) means that concentration of the inactive ingredient(s) used in the T product are within $\pm 5\%$ of those used in the R product.