Contains Nonbinding Recommendations

Draft Guidance on Triamcinolone Acetonide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Triamcinolone acetonide

Dosage Form; Route: Metered, spray; Nasal

Strength: 0.055 mg/spray

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) and reference (R) nasal sprays containing triamcinolone acetonide.

In Vitro Studies

FDA recommends that applicants conduct the following in vitro BE studies 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. FDA recommends that three primary stability batches be also used to demonstrate in vitro BE. The batches should be prepared from three different batches of the drug substance, different batches of critical excipients, and different batches of the same device components (e.g., pump and actuator). The following in vitro BE tests are recommended:

1. Single actuation content
2. Droplet size distribution by laser diffraction
3. Drug in small particles/droplets
4. Spray pattern
5. Plume geometry
6. Priming and repriming

Additional Comments: Refer to the product-specific guidance for *Fluticasone Propionate Nasal Spray Metered* for recommendations on design and equivalence criteria for the aforementioned in vitro BE studies, and general recommendations on the conduct of the in vitro BE studies and data submission.

Pharmacokinetic (PK) BE Study

Type of study: Fasting

Design: Single-dose, two-way crossover
Strength: 0.055 mg/spray
Dose: 0.22 mg, administered as two sprays in each nostril
Subjects: Healthy males and non-pregnant, non-lactating 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 triamcinolone acetonide in plasma

Analyte to measure (in appropriate biological fluid): Triamcinolone acetonide in plasma

Equivalence based on: AUC and C_{max} for triamcinolone acetonide. The 90% confidence intervals for the geometric mean T/R ratios of baseline-corrected AUC and C_{max} should fall within the limits of 80.00-125.00%.

Comparative 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 comparative clinical endpoint BE studies of any other product, including any other dosage form or strength of triamcinolone acetonide.

Type of study: BE Study with Clinical Endpoint
Design: Randomized, double-blind, three-arm, placebo-controlled, parallel group
Strength: 0.055 mg/spray
Dose: 0.22 mg once-daily, administered as two 0.055 mg sprays in each nostril
Subjects: Males and non-pregnant, non-lactating females with seasonal allergic rhinitis
Additional comments: Specific recommendations are provided below

Additional comments regarding the comparative clinical endpoint BE study

1. The Office of Generic Drugs (OGD) recommends conducting a BE study with clinical endpoint in the treatment of seasonal allergic rhinitis 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 the RLD labeling prior to initial dosing. During the placebo run-in period, all subjects are to receive the placebo vehicle administered as two sprays in each nostril once daily for 7 days. All subjects who qualify after the placebo run-in period are to be randomized to receive the test product, RLD, or placebo (vehicle) control during the treatment period, administered as two sprays in each nostril once daily for 14 days. The primary endpoint is the difference in the mean change in reflective total nasal symptom scores from baseline through the treatment period.

2. A multi-center 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 (the sponsor may add additional criteria):

    a. Males and non-pregnant, non-lactating females, 18 years of age and older. For female subjects of childbearing potential, agreement to practice an approved method of birth control
    b. History of seasonal allergic rhinitis (SAR) for at least 2 years
    c. A positive test for relevant specific allergens (e.g., allergen skin test)
    d. Demonstration of significant symptoms during screening and randomization visits, measured by reflective total nasal symptom score (rTNSS) (see items 7 and 8)

5. Exclusion criteria (the sponsor may add additional criteria):

    a. Pregnant or lactating or planning to become pregnant during the period of the study
    b. Asthma, with the exception of mild intermittent asthma
    c. Presence of glaucoma, cataracts, ocular herpes simplex, conjunctivitis or other eye infection
    d. Presence of any condition or abnormality in the upper airway, e.g., nasal polyps, obstruction, recent nasal surgery, structural abnormality, rhinitis medicamentosa etc.)
    e. History of tuberculosis
    f. 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
    g. Respiratory tract infection requiring antibiotic within 4 weeks prior to screening
    h. Subjects who have a history of recurrent sinus infections, or have experienced a sinus infection within the 30 days preceding visit 1
    i. Use of any investigational drug within 30 days prior to screening
    j. Use of any prohibited medications and treatments (e.g., systemic corticosteroids, immunotherapy, topical (>1%) or ophthalmic steroids, systemic or intranasal decongestants, tricyclic antidepressants, anti-allergy therapy as antihistamines, leukotriene antagonists,) prior to screening [the sponsor should provide a list of medications and treatments with justification/rationale provided for duration of the washout period prior to screening]
    k. Planned travel outside of the pollen area during the enrollment to completion of the study
    l. Known hypersensitivity to triamcinolone acetonide, or to any of the components of the study medications

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 systemic or intranasal decongestants, anti-allergy therapy as antihistamines, leukotriene antagonists,

corticosteroid therapy (parenteral, intranasal, oral, inhaled, or potent topical), anti-IgE antibodies (e.g., omalizumab), immunosuppressive therapy, and potent cytochrome P450 3A4 inhibitors 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 symptoms 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 (no symptom evident)
1	mild (symptom clearly present, but minimal awareness; easily tolerated)
2	moderate (definite awareness of symptom that is bothersome but tolerable)
3	severe (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 rTNSS is the mean of the final 7 scores from the placebo run-in period. The final 7 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 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 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 and in vivo PK BE studies.

14. 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, the center should also be considered in the data analysis.

15. Refer to the product-specific guidance on Adapalene; Benzoyl Peroxide Topical Gel 0.3%; 2.5% for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.[1]

16. Study data should be submitted in a standardized format. Please refer to the study data standards published at www.fda.gov.[2]

Alternative approach to the comparative clinical endpoint BE study

A comparative clinical endpoint BE study is recommended for T triamcinolone acetonide nasal spray product because of an inability to adequately characterize drug particle size distribution (PSD) in aerosols and sprays using commonly used analytical methods. 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. If drug PSD in the T and R products can be accurately measured using a validated analytical method such as morphology-directed Raman spectroscopy or any other advanced methodology, sponsors may submit comparative particle size distribution data as part of their drug characterization within their ANDA application. In such case, comprehensive method validation data should be submitted to demonstrate the adequacy of the selected method in identifying and measuring the size of the drug particles without any interference from the excipient particles that are also suspended in the formulation. An orthogonal method may be required if the selected methodology is not sensitive to measure particles beyond a certain size range. Equivalence between T and R drug PSD should be based on PBE analysis on D_{50} and span.

Bioequivalence for other configurations

If multiple configurations of the T products are developed with different fill weight (i.e., 120, 60, and/or 30 actuations), the weight-of-evidence approach outlined above should be adopted for configuration with the highest number of labeled actuations. Bioequivalence for the lower number of labeled actuations will be based on (i) acceptable bioequivalence studies on configuration with highest number of labeled actuations, (ii) same formulation composition across all configurations, and (iii) same container and closure components critical to the product performance across all configurations.

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[1] Product-Specific Guidances for Generic Drug Development available at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

[2] Study Data Standards for Submission to CDER and CBER available at: https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm587508.htm

Additional Information

Number of Reserve Samples:

Please 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 and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of 21 CFR 58 and 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). Retention samples should be randomly selected from the drug supplies received for each shipment prior to dispensing to subjects. Retention samples should not be returned to the Applicant at any time.

Formulation:

FDA recommends that the T formulation be qualitatively (Q1)[3] and quantitatively (Q2)[4] the same as the R formulation.

Device:

Sponsors should refer to the FDA guidance for industry entitled, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*, which, when finalized, will provide the Agency's current thinking on the identification and assessment of any differences in the design of the user interface for a proposed generic drug-device combination product when compared to its RLD.

FDA recommends that applicants consider the following characteristics of the R product in designing the T product:

- External operating principles and external critical design attributes of the R product
- Size and shape of the R product
- Number of doses in the R product

In addition, in vitro studies should be conducted to support the functionality, accuracy, and robustness of the proposed T product.[5]

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

[4] Q2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the T formulation are within ± 5% of those used in the R formulation.

[5] Refer to the FDA *Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation* for relevant principles regarding studies to support nasal spray devices.