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Draft Guidance on Tretinoin

May 2024

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Active Ingredient: Tretinoin

Dosage Form: Gel

Route: Topical

Strengths: 0.04%, 0.06%, 0.08%, 0.1%

Recommended Studies: Four comparative clinical endpoint bioequivalence studies (one study for each strength). See below for possible waiver request if evaluating bioequivalence concurrently for all four strengths

1. Type of study: Comparative clinical endpoint bioequivalence study
   Design: Randomized, double-blind, parallel, placebo-controlled, in vivo
   Strength: 0.04%, 0.06%, 0.08%, or 0.1%
   Subjects: Males and non-pregnant, non-lactating females with acne vulgaris
   Additional comments: Specific recommendations are provided below.

Waiver request for 0.06% and 0.08% strengths:

1. An abbreviated new drug application (ANDA) for the intermediate (0.06% and 0.08%) strengths of tretinoin (microsphere-based) topical gel containing sufficient data may be approved without conducting in vivo comparative clinical endpoint bioequivalence studies. This would be based on:
   a. A prior determination of two acceptable comparative clinical endpoint bioequivalence studies for the lowest strength (0.04%) and the highest strength (0.1%) of the drug product, conducted using the bioequivalence approach outlined above.

b. The formulations of the four strengths of the test product are exactly the same, except for the amount of tretinoin loaded microspheres and the corresponding change in the amount of the diluent, and have the same manufacturing process.

c. Acceptable comparative physicochemical and structural (Q3) characterization tests using a minimum of three batches of each strength of the test product; the relationship of the Q3 attributes of the four strengths of the test product should be compared to the relationship of the Q3 attributes of the four strengths of the reference standard. Refer to the most recent version of the FDA guidance for industry on *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs*[a] for additional information regarding Q3 characterization tests. The comparison of the lowest, intermediate, and highest strength products should include characterizations of the following Q3 attributes:
   i. Characterization of visual appearance and texture
   ii. Characterization of phase states and structural organization of matter
      - Microscopic examination with representative high-resolution microscopic images at multiple magnifications
      - Analysis of particle size distribution of microspheres in the drug product
   iii. Characterization of rheological behavior which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms. The following evaluations are recommended:
      - A characterization of shear stress vs. shear rate and viscosity vs. shear rate. At minimum, this should consist of numerical viscosity data at three shear rates (low, medium, and high).
      - A complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.
      - Yield stress values should be reported if the material tested exhibits plastic flow behavior.
      - The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported. Any non-linear viscosity behavior over a range of shear rates should also be investigated, measured and reported.
   iv. Characterization of pH
   v. Characterization of specific gravity
   vi. Characterization of any other potentially relevant Q3 attributes

d. An acceptable in vitro release test (IVRT) with a minimum of one batch of each strength of the test product and one batch of each strength of the reference standard using an appropriately validated IVRT method. The release rates of tretinoin should be proportional across all strengths. Refer to the most recent version of the FDA guidance for industry on *In Vitro Release Test (IVRT) Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVRT methods/studies. The batches of test product and reference standard evaluated in

the IVRT study should be included among those for which the Q3 attributes are characterized.

The approach outlined above would be appropriate for establishing bioequivalence of the intermediate strengths (0.06% and 0.08%) of tretinoin (microsphere-based) topical gel in a given packaging configuration (e.g., pump) when the recommended comparative clinical endpoint bioequivalence studies are conducted using the lowest strength (0.04%) and the highest strength (0.1%) of the drug product dispensed using the in the same packaging configuration.

Additional comments regarding the comparative clinical endpoint bioequivalence study:

1. FDA recommends conducting a comparative clinical endpoint bioequivalence study in the treatment of acne vulgaris. Applicants should conduct independent comparative clinical endpoint bioequivalence studies for each strength of this product unless the above-mentioned waiver strategy is utilized. Subjects are to be randomized to receive the generic tretinoin (microsphere-based) topical gel, the corresponding strength of the reference standard or placebo. The study drug is to be administered once daily in the evening for 12 weeks. The primary endpoints are to be evaluated at the end of treatment (Study Week 12).

2. Inclusion criteria (the prospective applicant may add additional criteria):
    a. Male or non-pregnant, non-lactating female aged ≥ 12 and ≤ 40 years with a clinical diagnosis of acne vulgaris.
    b. On the face, ≥ 25 non-inflammatory lesions (i.e., open and closed comedones) AND ≥ 20 inflammatory lesions (i.e., papules and pustules) AND ≤ 2 nodulocystic lesions (i.e., nodules and cysts).
    c. Investigator's Global Assessment (IGA) of acne severity Grade 2, 3, or 4 (per Table 1).

Table 1. Sample IGA Scale for Acne Vulgaris[a]

Grade	Description
0	Clear skin with no inflammatory or noninflammatory lesions
1	Almost clear; rare noninflammatory lesions with no more than one small inflammatory lesion
2	Mild severity; greater than Grade 1; some noninflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Moderate severity; greater than Grade 2; up to many noninflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4*	Severe; greater than Grade 3; up to many noninflammatory lesions and may have some inflammatory lesions, but no more than a few nodular lesions

* The Case Report Forms for acne studies can allow for reporting by investigators of lesion worsening beyond Grade 4 with treatment. It is recommended that enrollment of acne vulgaris subjects not include subjects with nodulocystic acne. Subjects who worsen beyond Grade 4 are escribed in the safety evaluation.

   d. Willing to refrain from use of all other topical acne medications or antibiotics during the 12-week treatment period.
   e. If female of childbearing potential, willing to use an acceptable form of birth control during the study

3. Exclusion criteria (the prospective applicant may add additional criteria):
   a. Presence of any skin condition that would interfere with the diagnosis or assessment of acne vulgaris (e.g., on the face: rosacea, dermatitis, psoriasis, squamous cell carcinoma, eczema, acne form eruptions caused by medications, steroid acne, steroid folliculitis, or bacterial folliculitis).
   b. Excessive facial hair (e.g., beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of acne vulgaris.
   c. History of hypersensitivity or allergy to tretinoin, retinoids, or any of the study medication ingredients.
   d. Use within 6 months prior to baseline of oral retinoids or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).
   e. Use for less than 3 months prior to baseline of estrogens or oral contraceptives; use of such therapy must remain constant throughout the study.
   f. Use on the face within 1 month prior to baseline of (1) cryodestruction or chemodestruction, (2) dermabrasion, (3) photodynamic therapy, (4) acne surgery, (5) intralesional steroids, or (6) x-ray therapy.
   g. Use within 1 month prior to baseline of (1) spironolactone, (2) systemic steroids, (3) systemic antibiotics, (4) systemic treatment for acne vulgaris (other than oral retinoids, which require a 6-month washout), or (5) systemic anti-inflammatory agents.
   h. Use within 2 weeks prior to baseline of (1) topical steroids, (2) topical retinoids, (3) topical acne treatments including over-the-counter preparations, (4) topical anti-inflammatory agents, or (5) topical antibiotics

4. Subjects should cleanse the face with a mild or soapless, non-medicated cleanser, dry skin gently, wait 20 to 30 minutes before applying the study product, and then apply enough product to lightly cover the entire affected areas of the face once daily at bedtime. The subject should be instructed to avoid contact of the study product with the corners of the nose, mouth, eyes and open wounds, and to wash their hands after application.

5. Subjects should not apply moisturizers, new brands of make-up, creams, lotions, powders or any topical product other than the assigned treatment to the treatment area. Subjects should minimize exposure to sunlight, including sunlamps, while using the product. Use of sunscreen products and protective clothing over treated areas is recommended when sun exposure cannot be avoided.

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:
    a. Any other topical products applied to face.
    b. Medicated soaps used on face.
    c. Spironolactone.
    d. Oral retinoids, therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed) or other systemic treatment for acne vulgaris.
    e. Systemic (e.g., oral or injectable) antibiotics.
    f. Systemic steroids, systemic anti-inflammatory agents or immunosuppressive drugs.
    g. Antipruritics, including antihistamines, within 24 hours of study visits.
    h. Use on the face of (1) cryodestruction or chemodestruction, (2) dermabrasion, (3) photodynamic therapy, (4) acne surgery, (5) intralesional steroids, or (6) x-ray therapy.
    i. Use of tanning booths, sunbathing, or excessive exposure to the sun.

7. The recommended two primary endpoints of the study are (1) mean percent change from baseline to Week 12 in the inflammatory (papules and pustules) lesion counts and (2) mean percent change from baseline to Week 12 in the non-inflammatory (open and closed comedones) lesion counts. The protocol should clearly define papules, pustules, open comedones, closed comedones, nodules and cysts. When counting facial acne lesions, it is important that all lesions be counted, including those present on the nose. Counts of nodules and cysts should be reported separately and not included in the inflammatory or non-inflammatory lesion counts.

8. Application site reactions such as erythema, dryness, burning/stinging, erosion, edema, pain and itching are to be recorded at each visit to allow a comparison between treatment groups. A descriptive analysis comparing the application site reactions for each treatment group is recommended. It is important to ensure that the test product is not worse than the reference product with regard to the expected and unexpected application site reactions.

9. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[b] for a recommended approach to statistical analysis and study design for the comparative clinical endpoint bioequivalence study.

10. Refer to the Study Data Standards Resources website https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[b] For the most recent version of a product-specific guidance, check the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.