Contains Nonbinding Recommendations

Draft Guidance on Tretinoin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Cream; topical

Recommended Study: One study

Type of study: Bioequivalence study with clinical endpoint
Design: Randomized, double blind, parallel, placebo controlled in vivo
Strength: 0.025%
Subjects: Males and nonpregnant, nonlactating females with acne vulgaris.
Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Not applicable

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Not applicable

Applicants intending to propose an alternative approach by which to demonstrate bioequivalence should refer to the guidance for industry *Controlled Correspondence Related to Generic Drug Development* and the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.

Additional comments regarding the bioequivalence study with clinical endpoint:

1. An abbreviated new drug application (ANDA) for an intermediate (0.05%) strength of tretinoin cream containing sufficient data may be approved without conducting an in vivo bioequivalence study with clinical endpoint. This would be based on:

    - A prior determination of two acceptable bioequivalence studies with clinical endpoint conducted on a lower strength (0.025%) and a higher strength (0.1%) of the same product.

- The formulations of the lower, intermediate, and higher strengths of the test product are exactly the same, except for the amount of tretinoin.

- The intermediate strength of the test product should be physically and structurally similar to the higher and lower strengths of the test product, based upon acceptable comparative physicochemical characterization of a minimum of three batches of the test products at each strength. The comparison of the lower, intermediate, and higher strength test products should include characterizations of the following physical and structural attributes:

  i. Assessment of visual appearance.

  ii. Microscopic examination with representative high resolution microscopic images at multiple magnifications.

  iii. Characterization of the globule size distribution of the drug product.

  iv. Analysis of the particle size distribution, crystal habit and polymorphic forms of tretinoin in the drug product, if applicable.

  v. Analysis of the 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), and may include a complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified (when possible).

     - 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.

  vi. Analysis of pH, specific gravity, and any other potentially relevant physical and structural similarity characterizations.

- An acceptable in vitro release test (IVRT) comparing a minimum of one batch the test product at each strength using an appropriately validated IVRT method. The release rate of tretinoin from the test products of the lower, intermediate, and higher strength should be proportional to their strength.

To pursue a strength of tretinoin not already listed in the Orange Book, submit a suitability petition to request a change in dosage form per 21 CFR § 314.93, 10.20 and 10.30.

2. The Office of Generic Drugs recommends conducting a bioequivalence study with clinical endpoints in the treatment of acne vulgaris. Subjects are to be randomized to

receive the generic tretinoin cream, 0.025%, the reference product 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).

3. Inclusion Criteria (the sponsor may add additional criteria)
    a. Male or nonpregnant, nonlactating 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[1]

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.

4. Exclusion Criteria (the sponsor 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, acneform eruptions caused by medications, steroid acne, steroid folliculitis, or bacterial folliculitis).

[1] Guidance for Industry: *Acne Vulgaris: Developing Drugs for Treatment.* Clinical/Medical. Accessed at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acne-vulgaris-establishing-effectiveness-drugs-intended-treatment

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 (e.g., Accutane®) 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.

5. 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.

6. 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.

7. 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.

8. 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.

9. 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.

10. Please refer to the product-specific guidance on adapalene; benzoyl peroxide topical gel, 0.3%; 2.5% entitled *Guidance on Adapalene; Benzoyl Peroxide* for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.

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

[2] Study Data Standards for Submission to CDER and CBER available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm