

Draft Guidance on Tazarotene

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Cream; topical

Recommended Studies: One study

Type of study: Bioequivalence Study with Clinical Endpoint

Design: Randomized, double blind, parallel, placebo controlled, in vivo

Strength: 0.1%

Subjects: Males and nonpregnant 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. The Office of Generic Drugs (OGD) recommends conducting a single bioequivalence study with clinical endpoint in the treatment of acne vulgaris comparing the tazarotene topical cream, 0.1% test product versus the reference product and placebo control, each applied once daily in the evening for 12 weeks. The two co-primary endpoints, percent change from baseline in the inflammatory (papules and pustules) and non-inflammatory (comedones) lesion counts, are to be evaluated at the end of treatment (Study Day 84; Week 12).
2. Inclusion Criteria (the sponsor may add additional criteria)

- a. Male or nonpregnant 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).
 - 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, the subject must have a negative result for a pregnancy test having sensitivity down to at least 50 mIU/mL for hCG within 2 weeks prior to starting treatment, begin treatment during a normal menstrual period, and be willing to use an acceptable form of birth control throughout the study.
3. Exclusion Criteria (the sponsor may add additional criteria)
 - a. Females who are pregnant, breast feeding, planning a pregnancy or do not agree to use an acceptable form of birth control throughout the study.
 - b. 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).
 - c. Facial sunburn.
 - d. Excessive facial hair (e.g. beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of acne vulgaris.
 - e. History of hypersensitivity or allergy to tazarotene, retinoids and/or any component of the test or reference product.
 - f. 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).
 - g. Use for less than 3 months prior to baseline of estrogens or oral contraceptives; use of such therapy must remain constant throughout the study.
 - h. Use on the face within 1 month prior to baseline or during the study of 1) cryodestruction or chemodestruction, 2) dermabrasion, 3) photodynamic therapy, 4) acne surgery, 5) intralesional steroids, or 6) x-ray therapy.
 - i. 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.
 - j. 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. Scale to be used for evaluation of baseline disease severity and treatment effect:

Table 1. Sample IGA Scale for Acne Vulgaris¹

¹ U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Draft Guidance for Industry: Acne Vulgaris: Developing Drugs for Treatment. Clinical/Medical.

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 to be described in the safety evaluation.

5. Tazarotene cream is designated as pregnancy category X. Therefore, in a bioequivalence study with clinical endpoint, all females of childbearing potential should be maintained on an appropriate method of contraception throughout the study. The informed consent form must clearly discuss the potential risk of teratogenicity.
6. It is recommended to repeat the urine pregnancy test (with sensitivity down to at least 50 mIU/mL hCG) for all females of childbearing potential during the study visits at Study Day 28 (Week 4), Study Day 56 (Week 8) and end of treatment (Study Day 84; Week 12). If a female of childbearing potential discontinues prematurely, the pregnancy test should be performed at the exit visit.
7. Subjects should gently clean and dry the face and then apply the product onto the affected areas of the face once daily, in the evening, avoiding contact with the eyes, eyelids and mouth.
8. 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. Medicated soaps used on face.
 - b. Topical product other than the assigned treatment (including moisturizers, new brands of make-up, creams, ointments, lotions, and powders) applied on or near the treatment area.
 - c. Photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides).
 - d. Application of study treatment to unaffected skin.
 - e. More than 10,000 IU/day of Vitamin A supplements.
 - f. Spironolactone.

September 2005. Accessed at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071292.pdf>

- g. Oral retinoids, therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed) or other systemic treatment for acne vulgaris.
 - h. Systemic (e.g., oral or injectable) antibiotics.
 - i. Systemic steroids, systemic anti-inflammatory agents or immunosuppressive drugs.
 - j. Antipruritics, including antihistamines, within 24 hours of study visits.
 - k. 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.
 - l. The treated areas should not be bandaged, covered or wrapped as to be occlusive.
 - m. Tanning booths, sun lamps, or nonprescription UV light sources.
 - n. Phototherapy.
 - o. Subjects should be instructed to minimize exposure to natural sunlight. to use sunscreens of at least SPF 15 and wear protective clothing during the day, to not allow the cream to come in contact with the eyes, eyelids, or mouth, to not use study treatment on skin that has eczema, and to always wash hands thoroughly after application of study medication.
9. The recommended two co-primary endpoints of the study are percent change from baseline to Week 12 in the inflammatory (papules and pustules) lesion counts and in the noninflammatory (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.
10. 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.
11. If the Tazarotene Cream/Topical, 0.1% test product demonstrates bioequivalence for the acne vulgaris indication, it is not necessary to conduct an additional bioequivalence study with clinical endpoint for the psoriasis indication. If a sponsor requests approval of their Tazarotene Cream/Topical, 0.1% test product for both reference products, submits the appropriate labeling for both reference products, and their test product demonstrates bioequivalence in the acne vulgaris indication, it is not necessary to conduct an additional bioequivalence study with clinical endpoint for the indication “as an adjunctive agent for use in the mitigation (palliation) of facial fine wrinkling, facial mottled hyper- and hypopigmentation, and benign facial lentiginosities in patients who use comprehensive skin care and sunlight avoidance programs.”
12. 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.²

² Product-Specific Guidances for Generic Drug Development available at:
<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>

13. Study data should be submitted in a standardized format. Please refer to the study data standards published at www.fda.gov³

³ Study Data Standards for Submission to CDER and CBER available at:
<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>