

Draft Guidance on Tretinoin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: 0.05%

Subjects: Caucasian males and nonpregnant, nonlactating females with fine wrinkling and mottled hyperpigmentation of the skin.

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 BE study with clinical endpoint in Caucasians with fine wrinkling and mottled hyperpigmentation of the skin. Subjects are to be randomized to receive the generic tretinoin topical cream, 0.05%, the reference listed drug (RLD) or placebo. The study drug is to be administered once daily before retiring to the face for 24 weeks. The two co-primary endpoints are to be evaluated at baseline (Day 0) and at the end of treatment (Study Week 24).

2. Inclusion Criteria (the sponsor may add additional criteria)

- a. Caucasian male or nonpregnant female aged ≥ 40 years with:
 - i. Fitzpatrick skin types I, II, III or IV (where Type I = always burn and never tan, Type II = always burn then slightly tan, Type III = sometimes burn and always tan, Type IV = never burn and always tan, Type V = heavily pigmented, Type VI = Black skin), AND
 - ii. Mild (Grade 2) moderate (Grade 3) or severe (Grade 4) fine wrinkling of facial skin [**NOTE**: fine wrinkles of the face disappear upon stretching, whereas coarse wrinkles do not],
 - iii. Mild (Grade 2), moderate (Grade 3) or severe (Grade 4) mottled hyperpigmentation of facial skin.

Grade	Category
0	No evidence
1	Minimal
2	Mild
3	Moderate
4	Severe

- b. If female of childbearing potential, willing to use an acceptable form of birth control during the study.
- c. Subjects should not have applied any emollients to the face for at least 24 hours prior to the baseline visit, or cosmetics on the day of the baseline visit.

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. Subject with Fitzpatrick skin type V or VI.
- c. Subject with Grade 0 or 1 fine wrinkling of facial skin.
- d. Subject with Grade 0 or 1 mottled pigmentation of facial skin.
- e. History of allergy or hypersensitivity to tretinoin and/or any of the study medication ingredients.
- f. History of subject's skin being highly sensitive to sunlight.
- g. History of blepharoplasty, facelift, facial silicone injection, or facial silicone implant.
- h. History of malignant melanoma.
- i. History within the past 5 years of facial basal cell or facial squamous cell carcinoma.
- j. Current facial eczema or other chronic skin conditions (e.g., psoriasis or multiple actinic keratoses of the face) that may require concomitant therapy or may interfere with diagnosis or assessment of facial fine wrinkling.
- k. Excessive facial hair (e.g. beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of fine wrinkling.
- l. Current use of any drug known to be photosensitizers (e.g., thiazides, tetracyclines, quinolones, phenothiazines, sulfonamides).

- m. Use on the face within 6 months prior to baseline of Botulinum Toxin.
 - n. Use on the face within 3 months prior to baseline of: 1) topical retinoids, 2) topical anti-wrinkling treatments including over-the-counter preparations, 3) skin peel, 4) cryodestruction or chemodestruction, 5) dermabrasion, 6) photodynamic therapy, 7) acne surgery, 8) intralesional steroids, or 9) x-ray therapy.
 - o. Use within 3 months prior to baseline of prescription systemic retinoids.
 - p. Use within 1 month prior to baseline of systemic steroids.
 - q. Use within 2 weeks prior to baseline of: 1) topical steroids, or 2) topical anti-inflammatory agents.
4. At the time of randomization, consider stratifying subjects by severity (e.g., grade) of facial skin wrinkling and severity of facial mottled hyperpigmentation, in order to balance the treatment group allocation with respect to these two variables.
 5. Instruct subjects to gently wash their face with a mild or soapless, non-medicated cleanser, pat the skin dry, wait 20 to 30 minutes before applying the study product, and then apply a pea-sized amount of cream to cover the entire face once daily before retiring. Instruct subjects to avoid contact of the study product with the eyes, ears, nostrils, angles of the nose, and mouth, to wash their hands after application, to not apply another skin care product or cosmetic for at least 1 hour after applying study product, and to not wash their face for at least 1 hour after applying study product. In the morning, subjects should apply a moisturizing sunscreen, SPF 15 or greater. Study product is not to be applied if facial skin is sunburned or irritated.
 6. Subjects should not apply new brands of make-up, creams, lotions, powders or any topical product other than the study product, recommended moisturizer or recommended sunscreen to the treatment area. Subjects should minimize exposure to sunlight, including sunlamps, while using the product. Use of sunscreen products with a minimum SPF of 15 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. Topical products applied to face, other than the assigned treatment, recommended moisturizer or recommended sunscreen.
 - b. Medicated or abrasive soaps used on face.
 - c. Any treatment for skin wrinkling, other than assigned treatment.
 - d. Drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides).
 - e. Oral retinoids, therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins containing the recommended daily allowance of vitamin A are allowed), systemic steroids, systemic anti-inflammatory agents or immunosuppressive drugs.
 - f. Use on the face of: 1) cryodestruction or chemodestruction, 2) dermabrasion, 3) photodynamic therapy, 4) acne surgery, 5) intralesional steroids, 6) x-ray therapy, or 7) skin peel.

- g. Use of tanning booths, sunbathing, or excessive exposure to the sun.
8. The two co-primary endpoints of the study is subject self-assessment of: 1) “success, fine wrinkling”, defined as change from one category of severity to at least the next lower category (e.g., a change from moderate to mild OR a change from mild to minimal, per following table) for fine wrinkling from baseline to Week 24, and 2) “success, mottled hyperpigmentation,” defined as change from one category of severity to at least the next lower category for mottled hyperpigmentation from baseline to Week 24.

Grade	Category
0	No evidence
1	Minimal
2	Mild
3	Moderate
4	Severe

9. Application site reactions such as erythema and irritation 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 the Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
- a. Study identifier
 - b. Unique subject identifier
 - c. Subject identifier for the study
 - d. Study site identifier (if applicable)
 - e. Age
 - f. Age units (years)
 - g. Sex
 - h. Race
 - i. Name of planned treatment
 - j. Name of actual treatment (exposure): test product, RLD, placebo control
 - k. Location of treatment area
 - l. Duration of treatment (total exposure in days)
 - m. Completed the study (yes/no)
 - n. Reason for premature discontinuation of subject
 - o. Subject required additional treatment for facial wrinkling or hyperpigmentation due to unsatisfactory treatment response (yes/no)
 - p. Per Protocol (PP) population inclusion (yes/no)
 - q. Reason for exclusion from PP population
 - r. Modified Intent to Treat (mITT) population inclusion (yes/no)
 - s. Reason for exclusion from mITT population
 - t. Safety population inclusion (yes/no)
 - u. Reason for exclusion from Safety population

- v. Randomized population flag (yes/no)
 - w. Date/time of first exposure to treatment
 - x. Date/time of last exposure to treatment
 - y. Grade of fine wrinkling of face at baseline
 - z. Grade of fine wrinkling of face at Week 24
 - aa. Grade of mottled hyperpigmentation of face at baseline
 - bb. Grade of mottled hyperpigmentation of face at Week 24
 - cc. Final designation for fine wrinkling of face (success/failure)
 - dd. Final designation for mottled hyperpigmentation of the face (success/failure)
 - ee. Compliance rate (%)
 - ff. Subject missed the pre-specified number of scheduled doses for more than the pre-specified number of consecutive days (yes/no)
 - gg. Concomitant medication (yes/no)
 - hh. Adverse event(s) reported (yes/no)
11. Please provide the basic data structure (BDS) dataset with records per subject, per visit, per analysis timepoint, using the following headings, if applicable:
- a. Study identifier
 - b. Unique subject identifier
 - c. Subject identifier for the study
 - d. Study site identifier (if applicable)
 - e. Name of planned treatment
 - f. Name of actual treatment (exposure): test product, RLD, placebo control
 - g. Location of dose administration: application site
 - h. Safety population flag (yes/no)
 - i. Modified ITT population flag (yes/no)
 - j. Per protocol population flag (yes/no)
 - k. Analysis date
 - l. Analysis visit
 - m. Study visit within the analysis window
 - n. Number of days since baseline visit
 - o. Evaluator: identity of evaluator
 - p. Grade of fine wrinkling of face
 - q. Grade of mottled hyperpigmentation of face
 - r. Skin reaction scores for each sign and symptom evaluated (e.g., erythema and irritation)
 - s. Additional treatment required during the visit (yes/no)
 - t. Concomitant medication reported during this visit (yes/no)
 - u. Adverse event reported during this visit (yes/no)
12. 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.

13. Study data should be submitted in a standardized format. Please refer to the study data standards published at www.fda.gov¹

¹ Study Data Standards for Submission to CDER and CBER available at:
<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>