

Draft Guidance on Tretinoin

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Tretinoin (NDA 019963)

Form/Route: Cream/Topical

Recommended studies: 1 study

Type of study: Bioequivalence (BE) with Clinical Endpoint Study

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

Strength: 0.05%

Subjects: Healthy Caucasian males and nonpregnant 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

Additional comments regarding the BE 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, 0.02%, 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. A placebo control arm is recommended to demonstrate that the test product and RLD are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products.
3. Inclusion Criteria (the sponsor may add additional criteria)
 - a. Healthy 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) or moderate (grade 3) fine wrinkling of facial skin [**NOTE:** fine wrinkles of the face disappear upon stretching, whereas coarse wrinkles do not], AND
 - iii. Mild (grade 2) or moderate (grade 3) 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.
4. 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, 1 or 4 fine wrinkling of facial skin.
 - d. Subject with grade 0, 1 or 4 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 five 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 the 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 or hyperpigmentation 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.
5. 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.
6. 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 one hour after applying study product, and to not wash their face for at least one 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.

7. 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.
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. 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 or hyperpigmentation, other than assigned treatment.
 - d. Drugs known to be photosensitizers (e.g., thiazides, tetracyclines, quinolones, 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.
9. The two co-primary endpoints of the study are 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

10. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations in the protocol.
 - a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who apply a prespecified proportion of the scheduled applications (e.g., 75% to 125%) of the assigned product for the specified duration of the study, do not miss the scheduled applications for more than 5 consecutive days, and complete the Week 24 evaluation within the designated visit window (+/- 7 days) with no protocol violations that would affect the treatment evaluation. The protocol should specify how compliance will be verified, e.g., by the use of subject diaries.

- b. The mITT population includes all randomized subjects who met the inclusion/exclusion criteria, apply at least one dose of assigned product, and return for at least one post-baseline evaluation visit.
 - c. The safety population includes all randomized subjects who received study product.
11. Subjects who are discontinued early from the study due to lack of treatment effect after completing 20 weeks of treatment should be included in the PP population as treatment failures. Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of facial fine wrinkling during the study should be discontinued, included in the PP population analysis, and provided with effective treatment. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using LOCF.
 12. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use.
 13. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD.
 14. 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.
 15. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the sponsor is to clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy and/or systemic or local availability of the drug.
 16. The method of randomization should be described in the protocol. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.
 17. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test, reference and placebo products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.
 18. 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 prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.

19. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
20. To establish bioequivalence, the 90% confidence interval for the difference in success proportions between test and reference treatment from baseline to week 24 in facial fine wrinkling should be contained within [-0.20, 0.20], using the PP study population. To establish bioequivalence, the 90% confidence interval for the difference in success proportions between test and reference treatment from baseline to week 24 in facial mottled hyperpigmentation should be contained within [-0.20, 0.20], using the PP study population.
1. As a parameter for determining adequate study sensitivity, the test product and RLD should be statistically superior to placebo ($p < 0.05$) with regard to the difference in success proportions between test and reference treatment from baseline to week 24 in facial fine wrinkling using the mITT study population and Last Observation Carried Forward (LOCF). As a parameter for determining adequate study sensitivity, the test product and RLD should be statistically superior to placebo ($p < 0.05$) with regard to the difference in success proportions between test and reference treatment from baseline to week 24 in facial mottled hyperpigmentation using the mITT study population and Last Observation Carried Forward (LOCF).
21. The following Statistical Analysis Method is recommended for equivalence testing for a dichotomous variable (success/failure):

Equivalence Analysis

Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in success proportions between test and reference treatment must be contained within [-0.20, +0.20] in order to establish equivalence.

The compound hypothesis to be tested is:

$$H_0: p_T - p_R < -0.20 \text{ or } p_T - p_R > 0.20$$

versus

$$H_A: -0.20 \leq p_T - p_R \leq 0.20$$

where p_T = success rate of test treatment and p_R = success rate of reference treatment.

Let

n_T = sample size of test treatment group

$c n_T$ = number of successful patients in test treatment group

n_R = sample size of reference treatment group

$c n_R$ = number of successful patients in reference treatment group

$$\hat{p}_T = c n_T / n_T, \quad \hat{p}_R = c n_R / n_R,$$

$$\text{and se} = \left(\hat{p}_T (1 - \hat{p}_T) / n_T + \hat{p}_R (1 - \hat{p}_R) / n_R \right)^{1/2}.$$

The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

$$L = (\hat{p}_T - \hat{p}_R) - 1.645 \text{ se} - (1/n_T + 1/n_R)/2$$

$$U = (\hat{p}_T - \hat{p}_R) + 1.645 \text{ se} + (1/n_T + 1/n_R)/2$$

We reject H_0 if $L \geq -0.20$ and $U \leq 0.20$

Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

22. Study data should be submitted to the OGD in electronic format.
 - a. A list of file names, with a simple description of the content of each file, should be included. Such a list should include an explanation of the variables included in each of the data sets.
 - b. Please provide a "pdf" document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population).
 - c. All SAS transport files, covering all variables collected in the Case Report Forms (CRFs) per subject, should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
 - d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
 - e. Please provide a separate dataset for variables such as demographics, facial skin fine wrinkling grade/category, facial pigmentation grade/category, vital signs, adverse events, disposition (including reason for discontinuation of treatment), concomitant medications, medical history, compliance and comments, etc.

23. Please provide a summary dataset containing a separate line listing for each subject (if data exist) using the following headings, if applicable:
 - a. Study identifier
 - b. Subject identifier
 - c. Site identifier: study center
 - d. Age
 - e. Age units (years)
 - f. Sex
 - g. Race
 - h. Name of Actual Treatment (exposure): test product, RLD, placebo control
 - i. Location of Treatment Area
 - j. Duration of Treatment (total exposure in days)
 - k. Completed the study (yes/no)
 - l. Reason for premature discontinuation of subject

- m. Subject required additional treatment for facial wrinkling or hyperpigmentation due to unsatisfactory treatment response (yes/no)
- n. Per Protocol (PP) population inclusion (yes/no)
- o. Reason for exclusion from PP population
- p. Modified Intent to Treat (mITT) population inclusion (yes/no)
- q. Reason for exclusion from mITT population
- r. Safety population inclusion (yes/no)
- s. Reason for exclusion from Safety population
- t. Grade of fine wrinkling of face at baseline
- u. Grade of fine wrinkling of face at Week 24
- v. Grade of mottled hyperpigmentation of face at baseline
- w. Grade of mottled hyperpigmentation of face at Week 24
- x. Final designation for fine wrinkling of the face (success/failure)
- y. Final designation for mottled hyperpigmentation of the face (success/failure)
- z. Treatment compliance: number of missed doses per subject
- aa. Concomitant medication (yes/no)
- bb. Adverse event(s) reported (yes/no)

Please refer to Table 1 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 1: Example of a summary dataset containing one line listing for each subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXLOC	EXDUR	completd	disc_rs	add_trt	pp	pp_rs	mitt	mitt_rs
101	1	01	21	YEARS	F	1	A	Face	14	Y		N	Y		Y	
101	2	01	30	YEARS	F	1	B	Face	14	Y		N	Y		Y	

safety	safe_rs	gr_wr_b	gr_wr_24	gr_mh_b	gr_mh_24	suc_wr	suc_mh	complan	CM	AE
Y		3	3	2	2	F	F	0	Y	Y
Y		3	2	2	1	S	S	0	N	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

STUDYID: Study Identifier
 SUBJID: Subject Identifier for the Study
 SITEID: Study Site Identifier
 AGE: Age
 AGEU: Age units (years)
 SEX: Sex, e.g., M=Male, F=Female, U=Unknown

RACE:	Race, e.g., 1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders
EXTRT:	Name of Actual Treatment (exposure), e.g., A=test product, B= RLD, C=placebo control
EXLOC:	Location of Treatment Area, e.g. F=face, etc.
EXDUR:	Duration of Treatment (total exposure in days)
completd:	Subject completed the study, e.g., Y=Yes, N=No
disc_rs:	Reason for premature discontinuation from the study, e.g., A=adverse event, B=death, C=lost to follow-up, D=non-compliance with treatment, E=treatment unblinded, F=subject moved out of area, G=unsatisfactory treatment response, H=withdrew consent, I=protocol violation, K=other event
add_trt:	Subject required additional treatment for fine wrinkling or hyperpigmentation due to unsatisfactory treatment response, e.g., Y=Yes, N=No
pp:	Per Protocol (PP) population inclusion, e.g., Y=Yes, N=No
pp_rs:	Reason for exclusion from PP population, e.g., A=prematurely discontinued, B=lost to follow-up, C=subject moved out of the area, D=noncompliant, etc.
mitt:	Modified Intent to Treat (mITT) population inclusion, e.g., Y=Yes, N=No
mitt_rs:	Reason for exclusion from mITT population, e.g., A=never treated, etc.
safety:	Safety population inclusion, e.g., Y=Yes, N=No
safe_rs:	Reason for exclusion from Safety population, e.g., A=never treated, etc.
gr_wr_b:	Grade of fine wrinkling of face at baseline, e.g., 2 or 3
gr_wr_24:	Grade of fine wrinkling of face at Week 24, e.g., 0, 1, 2, 3 or 4
gr_mh_b:	Grade of mottled hyperpigmentation of face at baseline, e.g., 2 or 3
gr_mh_24:	Grade of mottled hyperpigmentation of face at Week 24, e.g., 0, 1, 2, 3 or 4
suc_wr:	Final designation for fine wrinkling of face, e.g., S=Success; F=Failure
suc_mh:	Final designation for mottled hyperpigmentation of face, e.g., S=Success; F=Failure
complan:	Treatment compliance, e.g., number of missed doses per subject
CM:	Concomitant medication, e.g., Y=Yes, N=No
AE:	Adverse event(s) reported, e.g., Y=Yes, N=No

24. Please provide a dataset containing a separate line listing for visit per subject (if data exist) using the following headers, if applicable:
- Study identifier
 - Subject identifier
 - Name of Actual Treatment (exposure): test product, RLD, placebo control
 - Location of Dose Administration: application site
 - Visit number
 - Visit date
 - Number of days since baseline visit
 - Evaluator: identity of evaluator
 - Grade of fine wrinkling of face
 - Grade of mottled hyperpigmentation of face
 - Skin reaction scores for each sign and symptom evaluated (e.g., erythema and irritation)
 - Concomitant medication reported during this visit (yes/no)
 - Adverse event reported during this visit (yes/no)
 - Laboratory testing during this visit (yes/no)

Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 2: Example of dataset containing one line listing for each visit per subject

STUDYID	SUBJID	EXTRT	EXLOC	VISITNUM	SVSTDTC	ELTMBS	EVAL	gr_wr	gr_mh	erythema	irritat	CMrpt	AErpt	LBtest
101	1	A	F	1	2004-07-01	1		3	3	1	0	Y	Y	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

STUDYID: Study Identifier
SUBJID: Subject Identifier for the Study
EXTRT: Name of Actual Treatment (exposure), e.g., A=test product, B=RLD, C= placebo control
EXLOC: Location of Treatment Area: specific anatomical site of application, e.g., F=face etc.
VISITNUM: Visit Sequence Number
SVSTDTC: Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
ELTMBS: Elapsed Time since Baseline (days)
EVAL: Evaluator: identity of the evaluator
gr_wr: Grade of fine wrinkling of face, e.g., 0, 1, 2, 3 or 4
gr_mh: Grade of mottled hyperpigmentation of face, e.g., 0, 1, 2, 3 or 4
erythema: Skin reaction erythema score, e.g., 0=absent, 1=minimal, 2=mild (slight, barely perceptible), 3=moderate (distinct presence), 4=severe (marked, intense)
irritat: Skin reaction irritation score, e.g., 0=absent, 1=minimal, 2=mild (slight, barely perceptible), 3=moderate (distinct presence), 4=severe (marked, intense)
CMrpt: Concomitant Medication reported during this visit, e.g., Y=Yes, N=No
AErpt: Adverse Event reported during this visit, e.g., Y=Yes, N=No
LBtest: Laboratory Testing performed during this visit, e.g., Y=Yes, N=No

25. These recommendations are specific to this product and may not be appropriate for bioequivalence studies of any other product, including any other dosage form or strength of tretinoin.