

Draft Guidance on Fluocinolone Acetonide, Hydroquinone, and Tretinoin

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Active Ingredients: Fluocinolone acetonide, hydroquinone, and tretinoin

Dosage Form; Route: Cream; topical

Recommended Studies: One study

Type of study: Bioequivalence (BE) study with clinical endpoint

Design: Randomized, double blind, parallel, three-arm, placebo-controlled in vivo

Strength: 0.01%, 4%, 0.05%

Subjects: Healthy males and nonpregnant females with moderate to severe melasma of the face

Additional comments: Specific recommendations are provided below

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

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: N/A

Dissolution test method and sampling times: N/A

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 the treatment of moderate to severe melasma of the face comparing the fluocinolone acetonide 0.01%, hydroquinone 4% and tretinoin 0.05% topical cream test product versus the reference listed drug (RLD) and placebo (vehicle) control, each administered after gently washing the face with a mild cleanser, rinsing and patting the skin dry and then applying a thin film of the assigned study treatment to the affected area including about ½ inch of normal appearing skin surrounding each lesion once daily, at least 30 minutes before bedtime, for 56 days (8 weeks).
2. A placebo (vehicle) 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 males and nonpregnant females aged ≥ 18 years having skin type I-IV (using the Fitzpatrick Skin Type rating scale) and a diagnosis of moderate to severe melasma of the face, which has been stable for at least 3 months prior to study entry, with macular lesions which are neither depressed nor atrophic
 - b. Melasma severity of ≥ 2 on a 0 to 3 scale, with 2 indicating moderate severity at baseline (screening) visit
 - c. Subjects using hormonal forms of birth control, such as oral contraceptives, and subjects using estrogen replacement therapy should be on a stable dose for at least 6 months prior to the study, and have no plans to change or adjust therapy during the study period
 - d. Willingness to refrain from the use of any products on the face during the 8-week treatment period, other than the provided study treatment, the provided sunscreen, the provided mild facial cleanser, the provided mild moisturizer, and the subject's usual daytime cosmetics.
4. Exclusion criteria (the sponsor may add additional criteria):
 - a. Females who are pregnant, breast feeding, or planning a pregnancy.
 - b. Females of childbearing potential who do not agree to utilize an adequate form of contraception during the study duration.
 - c. Fitzpatrick Skin Types V and VI.
 - d. Any facial skin condition that would interfere with the diagnosis of melasma and/or with determination of melasma severity
 - e. Immunocompromised or under immunosuppressive treatment.
 - f. Allergic to sulfites.
 - g. Known hypersensitivity reactions to systemic or topical corticosteroids, topical hydroquinone, topical or oral tretinoin, or any of the test product or RLD excipients
 - h. Use within four weeks prior to the baseline visit of any topical or oral corticosteroids, bleaching products, ultraviolet (UV) light therapy, sunbathing or topical retinoids
 - i. Use within 3 months prior to the baseline visit of any acitretin, azathioprine, cyclosporine, interferon, isotretinoin, methotrexate, mycophenolate mofetil, sirolimus, tacrolimus, or any photoallergic, phototoxic, or photosensitizing drugs
 - j. Sunbathing
 5. Recommend performing urine pregnancy test at baseline (screening) visit, at Week 4 visit, and at Week 8 or early discontinuation visit for all women of childbearing potential or who are less than one year postmenopausal.
 6. All subjects should be provided with the same mild facial cleanser, sunscreen (with both UVB and UVA protection), and mild moisturizer to use as needed throughout the study. Subjects may use the provided moisturizer during the day.
 7. The importance of avoiding exposure to sunlight, sunlamp, tanning beds and ultraviolet light to the face and using sunscreen should be thoroughly explained to the subject. Protective clothing should also be recommended to subjects. Subjects should be instructed to: 1) use a sunscreen (SPF of at least 30) each morning, regardless if it is sunny or cloudy, 2) keep study treatment away from the eyes, nose, angles of the mouth,

or open wounds, 3) not bandage or cover the treated skin after applying the study treatment, and 4) not sunbathe.

8. Subjects may use cosmetics during the day.
9. 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. Use of acitretin, azathioprine, cyclosporine, interferon, isotretinoin, methotrexate, mycophenolate mofetil, sirolimus, tacrolimus, or any photoallergic, phototoxic, or photosensitizing drugs
 - b. Use of bleaching agents, retinoids, tetracyclines, thiazides, or phenytoin
 - c. Use of systemic (e.g., oral, inhaled, injectable, intravenous) or topical corticosteroids
 - d. Use of any lotions, creams, gels, ointments, emollients, or similar topical products on the face, other than the provided study treatment; the provided sunscreen, the provided mild facial cleanser, the provided mild moisturizer, and the subject’s usual daytime cosmetics
 - e. UV light therapy or sunbathing
10. Determination of the facial melasma severity score should be performed at baseline and Weeks 1, 4 and 8 visits and at any early discontinuation visit using a 4-point scale of 0 to 3, with 0 = cleared, 1 = mild, 2 = moderate and 3 = severe (see Table 1). Each score on the scale should have an objective description in order to maintain consistency between centers. Whenever possible, the same investigator should perform all clinical assessments for a given subject and anticipate evaluating the subject at each subsequent visit.

Table 1: Investigator’s Assessment of Melasma Severity

0	Cleared	Melasma lesions approximately equivalent to surrounding normal skin or with a minimal residual hyperpigmentation
1	Mild	Melasma lesions slightly darker than the surrounding normal skin
2	Moderate	Melasma lesions moderately darker than the surrounding normal skin
3	Severe	Melasma lesions markedly darker than the surrounding normal skin

11. The recommended primary endpoint is treatment success, defined as the proportion of subjects with improvement in the facial melasma severity score by at least two points from the baseline visit to the Week 8 visit, i.e., improvement from “2” (moderate) facial melasma at the baseline visit to “0” (cleared), or improvement from “3” (severe) facial melasma at the baseline visit to “1” (mild) or “0” (cleared).
12. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT), and safety populations.
 - a. The accepted PP population used for BE evaluation includes all randomized subjects who meet all inclusion/exclusion criteria, take a pre-specified proportion of the scheduled doses (e.g., 75% to 125%) of the assigned product for the specified duration of the study, do not miss the scheduled study drug administrations for more than 4 consecutive days, and undergo determination of the facial melasma severity score at the Week 8 visit within the designated visit window (+/- 4 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 meet all inclusion/exclusion criteria, take at least one dose of the assigned product, and return for at least one post-baseline evaluation visit.
 - c. The safety population includes all randomized subjects who received the study product.
13. Subjects who are discontinued early from the study due to lack of treatment effect should be included in the PP population as treatment failures. Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of their facial melasma 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 Last Observation Carried Forward (LOCF).
 14. The start and stop dates of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use. The sponsor should clearly explain whether the medication was used prior to the baseline visit, during the study, or both.
 15. 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.
 16. If the inactive ingredients of the test product are different from those contained in the RLD or are present in significantly different amounts, the sponsor must 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.
 17. The method of randomization should be described in the protocol and the randomization schedule provided as a SAS data set in .xpt format (created using SAS XPORT). 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 the site inspection to allow for verification of the treatment identity of each subject.
 18. 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.

19. 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.

20. It is the sponsor’s responsibility to enroll sufficient subjects for the study to demonstrate BE between the products.

21. To establish BE for a dichotomous endpoint, it is recommended the following compound hypotheses be tested using the per protocol population:

$$H_0: \pi_T - \pi_R \leq \Delta_1 \text{ or } \pi_T - \pi_R \geq \Delta_2 \quad \text{versus} \quad H_A: \Delta_1 < \pi_T - \pi_R < \Delta_2$$

where π_T = the success rate of the primary endpoint for the treatment group, and
 π_R = the success rate of the primary endpoint for the reference group.

The null hypothesis, H_0 , is rejected with a type I error (α) of 0.05 (two one-sided tests) if the estimated 90% confidence interval for the difference of the success rates between test and reference products ($\pi_T - \pi_R$) is contained within the interval $[\Delta_1, \Delta_2]$, where $\Delta_1 = -0.20$ and $\Delta_2 = 0.20$. Rejection of the null hypothesis supports the conclusion of equivalence of the two products.

22. To establish sensitivity within the study for either a dichotomous or continuous primary endpoint, the test and reference product should both be statistically superior to the placebo. Conduct an appropriate inferential test with a type I error (α) of 0.05, using the mITT population and the primary endpoint.

23. Study data should be submitted to the OGD in electronic format. All data should be submitted as a SAS .xpt file, created using SAS XPORT (not CPORT).

- a. Include a list of file names, a description of the content of each file, an explanation of the variables within each file, and a description of all variable codes (for example, for the treatment variable, A = RLD and B = TEST).
- b. Provide a SAS program to open the SAS .xpt files.
- c. Provide two primary data sets, one with No Last Observation Carried Forward (NO-LOCF - pure data set) and one with the Last Observation Carried Forward (LOCF - modified data set).
- d. Provide a separate dataset for demographic, vital sign, adverse event, disposition (including reason for discontinuation of treatment), concomitant medication, medical history, compliance, and comment variables.

24. Applicants should provide a summary dataset that contains 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. Duration of treatment (total exposure in days)
 - j. Completed the study (yes/no)
 - k. Reason for premature discontinuation of subject
 - l. Subject required additional treatment for duodenal ulcer due to unsatisfactory treatment response (yes/no)
 - m. Per Protocol (PP) population inclusion (yes/no)
 - n. Reason for exclusion from PP population
 - o. Modified Intent to Treat (mITT) population inclusion (yes/no)
 - p. Reason for exclusion from mITT population
 - q. Safety population inclusion (yes/no)
 - r. Reason for exclusion from safety population
 - s. Facial melasma score at baseline visit
 - t. Facial melasma score at Week 1 visit
 - u. Facial melasma score at Week 4 visit
 - v. Facial melasma score at Week 8 visit
 - w. Final designation of treatment success/cure (yes/no)
 - x. Treatment compliance: number of missed doses per subject
 - y. Concomitant medication (yes/no)
 - z. Adverse event(s) reported (yes/no)

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	EXDUR	completd	disc_rs	add_trt	pp	pp_rs	mitt	mitt_rs	safety	safe_rs
101	1	01	30	YEARS	F	1	A	56	Y		N	Y		Y		Y	
101	2	01	28	YEARS	F	1	B	56	Y		N	Y		Y		Y	

melsco_b	melsco_1	melsco_4	melsco_8	succes_8	complan	CM	AE
3	3	2	1	N	0	Y	Y
3	3	1	0	Y	0	N	N

Note: Capitalized headings are from the 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
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 unmasked, 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 duodenal ulcer 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.
melsco_b:	Facial melasma severity score at Baseline visit, e.g., 2 or 3
melsco_1:	Facial melasma severity score at Week 1 visit, e.g., 0, 1, 2 or 3
melsco_4:	Facial melasma severity score at Week 4 visit, e.g., 0, 1, 2 or 3
melsco_8:	Facial melasma severity score at Week 8 visit, e.g., 0, 1, 2 or 3
succes_8:	Treatment success (cure) at Week 8 visit, e.g., Y=Yes, N=No
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

25. These recommendations are specific to this drug product and may not be appropriate for BE studies of any other drug product, including any other dosage form or strength of fluocinolone acetonide, hydroquinone, and/or tretinoin as either the only active ingredient in a drug product or as a combination drug product containing two or more of these active ingredients.