Contains Nonbinding Recommendations

Draft Guidance on Ketoconazole

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Ketoconazole

Form/Route: Gel; Topical

Recommended studies: 1 study

Type of study: Bioequivalence (BE) study with clinical endpoint
Design: Randomized, double-blind, parallel, placebo-controlled, in vivo
Strength: 2%
Subjects: Healthy males and females with seborrheic dermatitis
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 single bioequivalence study with clinical endpoint in the treatment of seborrheic dermatitis comparing the topical gel, 2% test product versus the reference listed drug (RLD) and placebo (vehicle) control, each applied once daily to the affected area(s) for 14 days (2 weeks). The primary endpoint, overall cure, is to be evaluated at the end of the follow-up period (study day 28; week 4).

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 male or female aged ≥ 12 years with a clinical diagnosis of seborrheic dermatitis. Affected area(s) in at least one of the following locations: scalp, face [e.g., hairline, eyebrow(s), bridge of nose, naso-labial fold(s)], behind the ears, chest and upper back.
   b. Baseline erythema score of at least 2, baseline scaling score of at least 2 and baseline pruritus score of at least 1 (per Scale 1)
   c. Baseline Investigator's Global Assessment (IGA) seborrheic dermatitis score of at least 3 (per Scale 2).
   d. Willing to refrain from use of all other topical medications or antibiotics during the treatment and observation periods (i.e., from Day 0 through Day 28).

e. If female of childbearing potential, the subject had 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 and is willing to use an acceptable form of birth control throughout the study.

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. Clinically significant systemic disease (e.g., immunological deficiencies, AIDS, current malignancies, uncontrolled diabetes mellitus).
   c. Presence of any skin condition that would interfere with the diagnosis or assessment of seborrheic dermatitis (e.g., atopic dermatitis, psoriasis, acne).
   d. Excessive facial hair (e.g. beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of seborrheic dermatitis.
   e. History of hypersensitivity or allergy to ketoconazole and/or any component of the test product or RLD.
   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 within 1 month prior to baseline of 1) systemic antifungals, 2) systemic steroids, 3) systemic antibiotics, 4) systemic anti-inflammatory agents or 5) cytostatic or immunomodulating drugs (e.g., cyclosporine, tacrolimus, pimecrolimus).
   h. Use within 2 weeks prior to baseline of 1) topical steroids, 2) topical retinoids, 3) topical antifungal treatments including over-the-counter preparations, 4) topical anti-inflammatory agents, 5) topical antibiotics or 6) topical treatment for seborrheic dermatitis (e.g., coal tar preparations, antiseborrheic and antidandruff shampoos).

5. Scales to be used for evaluation of baseline disease severity and treatment effect:

Scale 1. Sample Sign and Symptom Scales for Erythema, Scaling and Pruritus

Symptom	Score	Description
Erythema	0	**None**: No evidence of erythema
	1	**Mild**: Barely perceptible erythema which is faint or patchy, blanches easily to the touch
	2	**Moderate**: Distinct erythema, more difficult to blanch
	3	**Severe**: Intense (fiery red) erythema, does not blanch
Scaling	0	**None**: No scaling evident on lesions
	1	**Mild**: Barely detectable, scattered, small flaking scales
	2	**Moderate**: Scales clearly visible and prominent
	3	**Severe**: Coarse, thick scales, with flaking into clothes or skin
Pruritus	0	**None**: No evidence of pruritus
	1	**Mild**: Present with minimal discomfort
	2	**Moderate**: Appreciable discomfort which interferes with daily activities
	3	**Severe**: Extreme discomfort which prevents the completion of daily activities and may disrupt sleep

Scale. 2. Sample IGA Scale for Seborrheic Dermatitis Overall Status of Disease Severity

Score	Description
0	**Complete clear**
1	**Almost Clear**: Only slight pink color or trace amounts of scaling
2	**Mild**: Pink to red color, or slight scaling
3	**Moderate**: Distinct redness or clearly visible scaling
4	**Severe**: Severe score in erythema or scaling

6. 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 over-the-counter (OTC) or prescription topical or systemic treatment for seborrheic dermatitis, including medicated shampoos to treat seborrheic dermatitis of the scalp.
   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. More than 10,000 IU/day of Vitamin A supplements.
   d. Spironolactone.
   e. Oral retinoids, therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed) or other systemic treatment for acne vulgaris.
   f. Systemic (e.g., oral or injectable) antifungals.
   g. Systemic steroids, systemic anti-inflammatory agents or immunosuppressive drugs.
   h. Radiation therapy.
   i. Antipruritics, including antihistamines, within 24 hours of study visits.
   j. Subjects should be instructed to avoid using study product near fire, flame or smoking during and immediately following application, to not allow the gel to come in contact with the eyes, nostrils, or mouth, and to always wash hands thoroughly after application of study medication.

7. The recommended primary endpoint is overall cure at Day 28 (week 4) of the study. Overall cure is defined as erythema and scaling scores of either 0 (None) if the baseline score was 2 OR ≤ 1 (Mild) if the baseline score was 3 AND Investigator Global Assessment score of ≤ 1 (Almost Clear).

8. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.
   a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who apply a pre-specified 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 3 consecutive days, and complete the evaluation within the designated visit window (+/- 3 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 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 receive study product.

9. Subjects who are discontinued early from the study due to lack of treatment effect after completing 1 week 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 seborrheic dermatitis 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.

10. 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.

11. 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.

12. Application site reactions such as dryness, burning/stinging, erosion, edema and pain 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.

13. If the inactive ingredients of the test product are different than those contained in the RLD or in significantly different amounts, then 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.

14. 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.

15. 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.

16. 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.

17. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.

18. To establish bioequivalence, the 90% confidence interval of the proportional difference between test and RLD for the primary endpoint at Day 28 (week 4) must be contained within [-0.20, +0.20] for dichotomous variables (cure versus failure) using the PP study population for analysis.

19. As a parameter for determining adequate study sensitivity, the test product and RLD should be statistically superior to placebo ($p<0.05$) for the primary endpoint at Day 28 (week 4) using the mITT study population and Last Observation Carried Forward (LOCF).

20. 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: $p_T - p_R < -0.20$ or $p_T - p_R > 0.20$

    versus

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

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

    Let
    n_T = sample size of test treatment group
    $c n_T$ = number of successes in test treatment group
    n_R = sample size of reference treatment group
    $c n_R$ = number of successes in reference treatment group

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

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

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

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

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

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.

21. 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, vital signs, adverse events, disposition (including reason for discontinuation of treatment), concomitant medications, medical history, compliance and comments, etc.

22. 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(s)
    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 seborrheic dermatitis 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. Erythema score at baseline
    u. Scaling score at baseline
    v. Pruritus score at baseline
    w. IGA score at baseline
    x. Erythema score at Day 28 (week 4)
    y. Scaling score at Day 28 (week 4)

z. Pruritus score at Day 28 (week 4)
aa. IGA score at Day 28 (week 4
bb. Final designation: (success/failure)
cc. Treatment compliance : number of missed doses per subject
dd. Concomitant medication (yes/no)
ee. 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	eryth_b	scal_b	prur_b	iga_b	eryth_28	scal_28	prur_28	iga_28	final_ds	complian	CM	AE
Y		3	2	2	3	2	1	1	2	F	0	Y	Y
Y		2	2	1	3	0	0	0	0	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 seborrheic dermatitis 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.
eryth_b:	Erythema score at baseline, e.g., 0=None, 1=Mild, 2=Moderate, 3=Severe
scal_b:	Scaling score at baseline, e.g., 0=None, 1=Mild, 2=Moderate, 3=Severe
prur_b:	Pruritus score at baseline, e.g., 0=None, 1=Mild, 2=Moderate, 3=Severe
iga_b:	IGA score at baseline, e.g., 0=Clear, 1=Almost Clear, 2=Mild, 3=Moderate, 4=Severe
eryth_28:	Erythema score at Day 28 (week 4), e.g., 0=None, 1=Mild, 2=Moderate, 3=Severe
scal_28:	Scaling score at Day 28 (week 4), e.g., 0=None, 1=Mild, 2=Moderate, 3=Severe
prur_28:	Pruritus score at Day 28 (week 4), e.g., 0=None, 1=Mild, 2=Moderate, 3=Severe
iga_28:	IGA score at Day 28 (week 4), e.g., 0=Clear, 1=Almost Clear, 2=Mild, 3=Moderate, 4=Severe
final_ds:	Final designation at Day 28 (week 4), e.g., S=Success; F=Failure
complian:	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

23. Please provide a dataset containing a separate line listing for visit per subject (if data exist) using the following headers, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Name of Actual Treatment (exposure): test product, RLD, placebo control
    d. Location(s) of Dose Administration: application site(s)
    e. Visit number
    f. Visit date
    g. Number of days since baseline visit
    h. Evaluator: identity of evaluator
    i. Erythema score
    j. Scaling score
    k. Pruritus score
    l. IGA score
    m. Skin reaction scores for each sign and symptom evaluated (e.g., dryness, burning/stinging, erosion, edema, pain, etc.)
    n. Concomitant medication reported during this visit (yes/no)
    o. Adverse event reported during this visit (yes/no)
    p. 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	erythema	scaling	pruritus	iga	dryness	burning	erosion	edema	pain	CMrpt	AErpt	LBtest
101	1	A	F	1	2004-07-01	1		3	2	2	3	0	0	1	0	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)
ELTMBL:	Elapsed Time since Baseline (days)
EVAL:	Evaluator: identity of the evaluator
erythema:	Erythema score, e.g., 0=None, 1=Mild, 2=Moderate, 3=Severe
scaling:	Scaling score, e.g., 0=None, 1=Mild, 2=Moderate, 3=Severe
pruritus:	Pruritus score, e.g., 0=None, 1=Mild, 2=Moderate, 3=Severe
iga:	IGA score, e.g., 0=Clear; 1=Almost clear, 2=Mild, 3=Moderate, 4=Severe
dryness:	Skin reaction dryness score, e.g., 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
burning:	Skin reaction burning/stinging score, e.g., 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3-severe (marked, intense)
erosion:	Skin reaction erosion score, e.g., 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
edema:	Skin reaction edema score, e.g., 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
pain:	Skin reaction pain score, e.g., 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=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

24. 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 ketoconazole.