Draft Guidance on Ketoconazole

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Recommended studies: 1 study

   Type of study: Bioequivalence (BE) Study with Clinical Endpoint
   Design: Randomized, double blind, parallel, placebo controlled, in vivo
   Strength: 1%
   Subjects: Healthy males and nonpregnant females with dandruff.
   Additional comments: Specific recommendations are provided below.

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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 dandruff comparing the ketoconazole shampoo, 1% test product versus the reference listed drug (RLD) and placebo (vehicle) control, each applied twice weekly for 4 weeks (i.e., on study days 1, 5, 8, 12, 15, 19, 22, 26). At each application, subjects are to wet hair thoroughly, apply enough shampoo to raise a lather [approximately 15 cc (0.5 ounce)], generously lather, rinse thoroughly and repeat process. The primary endpoint "success" is to be evaluated at the end of the treatment 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 nonpregnant female aged ≥ 18 with a clinical diagnosis of at least moderate dandruff at baseline, defined as a scaling score of at least 3 (per Scale 1) AND/OR an erythema score of at least 2 (per Scale 2).
   b. Willing to refrain from use of any other antidandruff shampoo or antidandruff treatment during the 4-week treatment period.

Scale 1: Scaling

Score	Severity	Description
0	None	
1	Slight	Barely perceptible scale - small flakes resembling a coarse grayish powder
2	Mild	Minimal to intermediate scale
3	Moderate	Definite scale - large flakes very loosely attached to the scalp and forming an irregular whitish surface
4	Pronounced	Prominent scale - flakes apparently congealed together into yellowish plates adhering to the scalp
5	Severe	Excessive thick yellowish and crusted adherent scale

Scale 2: Erythema

Score	Severity	Description
0	None	
1	Slight	Barely perceptible
2	Mild	Slightly pink
3	Moderate	Moderately pink
4	Pronounced	Deep pink to red
5	Severe	Deep red to severely red

4. Exclusion Criteria (the sponsor may add additional criteria)
   a. Presence of any scalp condition that would interfere with the diagnosis or assessment of dandruff (e.g., scalp psoriasis, active skin infection of the scalp, eczema, ichthyosis).
   b. Atopic dermatitis.
   c. Insulin-dependent diabetes mellitus.
   d. History of hypersensitivity or allergy to ketoconazole and/or any component of the test product or RLD.
   e. 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).
   f. Use within 2 weeks prior to baseline of 1) topical steroids, 2) topical antifungal treatments including over-the-counter preparations, 3) topical anti-inflammatory agents, 4) topical antibiotics, or 5) antidandruff or antiseborrheic topical treatment (e.g., antidandruff shampoos, antiseborrheic shampoos, coal tar preparations).

5. 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 shampoo other than study product.
   b. Topical product, other than study product, applied to scalp.
   c. Systemic steroids, systemic anti-inflammatory agents or immunosuppressive drugs.
   d. Ketoconazole tablets and any other systemic antifungal agents
   e. Antipruritics, including antihistamines, within 24 hours of study visits.
   f. Subjects should be instructed to not use the study product if the scalp is broken or inflamed and to not allow the shampoo to come in contact with the eyes.

6. The recommended primary endpoint of the study is the proportion of subjects with treatment success/cure, defined as score of 0 or 1 (per Scale 3) at the end of the treatment period (study day 28; week 4).

Scale 3: Investigator's Global Evaluation Scale

Score	Severity	Description
0	None	
1	Slight	Barely perceptible scale and erythema
2	Mild	Slight scale and minimal erythema
3	Moderate	Moderate scale and moderate erythema
4	Pronounced	Pronounced scale and pronounced erythema
5	Severe	Severe scale and/or severe erythema

7. 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 (+/- 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 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.

8. Subjects who are discontinued early from the study due to lack of treatment effect after completing 2 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 dandruff 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.

9. 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.

10. 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.

11. Application site reactions such as 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.

12. 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.

13. 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.

14. 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.

15. 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.

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

17. To establish bioequivalence, the 90% confidence interval of the difference between products for the primary endpoint (proportion of subjects with treatment success/cure) must be within [-0.20, +0.20] for a dichotomous variable (success/cure versus failure) using the PP population for analysis.

18. 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 proportion of subjects with treatment success/cure at Day 28 (week 4) using the mITT study population and Last Observation Carried Forward (LOCF).

19. The following Statistical Analysis Method is recommended for equivalence testing for a dichotomous variable:

Equivalence Analysis

Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in success rates between test and reference treatment should be contained within (-.20, +.20) in order to establish equivalence.

The compound hypothesis to be tested is:

H_0: $p_T - p_R \leq -.20$ or $p_T - p_R \geq .20$

versus

H_A : $-.20 < p_T - p_R < .20$

where:

p_T = success/cure rate of test treatment group

p_R = success/cure rate of reference treatment group

Let

n_T = sample size of test treatment group

$c\,n_T$ = number of success/cured patients in test treatment group

n_R = sample size of reference treatment group

$c\,n_R$ = number of success/cured patients in reference treatment group

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

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

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

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

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

We reject H_0 if $L \geq -.20$ and $U \leq .20$

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

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

21. 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 acne vulgaris 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. Scaling Score at baseline
   u. Erythema at baseline
   v. Scaling Score at Day 28 (Week 4)
   w. Erythema Score at Day 28 (Week 4)
   x. Investigator's Global Evaluation Score at Day 28 (Week 4)
   y. Treatment Success at Day 28 (Week 4) (yes/no)
   z. Concomitant medication (yes/no)
   aa. 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	EXDUR	completd	disc_rs	add_trt	pp	pp_rs	mitt	mitt_rs
101	1	01	21	YEARS	F	1	A	56	Y		N	Y		Y	
101	2	01	30	YEARS	F	1	B	56	Y		N	Y		Y	

safety	safe_rs	scale_b	eryth_b	scale_28	eryth_28	ige_28	cure_28	complian	CM	AE
Y		3	4	1	1	1	Y	0	Y	Y
Y		4	4	2	1	2	N	0	N	N

<u>Note</u>: 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
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 acne 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.

scale_b: Scaling Score at baseline, e.g., 0 to 5
eryth_b: Erythema Score at baseline, e.g., 0 to 5
scale_28:   Scaling Score at Day 28 (Week 4), e.g., 0 to 5
eryth_28:   Erythema Score at Day 28 (Week 4), e.g., 0 to 5
ige_28:   Investigator's Global Evaluation Score at Day 28 (Week 4), e.g., 0 to 5
cure_28:   Treatment Success at Day 28 (Week 4), e.g., Y=Yes, N=No
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

22. 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. Visit number
   e. Visit date
   f. Number of days since baseline visit
   g. Evaluator: identity of evaluator
   h. Scaling Score
   i. Erythema Score
   j. Investigator's Global Evaluation Score
   k. Scalp reaction scores for each sign and symptom evaluated (e.g., dryness, burning/stinging, erosion, edema, pain, itching, etc.)
   l. Concomitant medication reported during this visit (yes/no)
   m. Adverse event reported 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	VISITNUM	SVSTDTC	ELTMBS	EVAL	scale	erythema	ige	dryness	burning	erosion	edema	pain	itching	CMrpt	AErpt
101	1	A	1	2004-07-01	1		3	4	7	0	0	1	0	0	0	Y	Y

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

scale: Scaling Score, e.g. 0 to 5

erythema: Erythema Score, e.g. 0 to 5

ige: Investigator's Global Evaluation Score, e.g., 0 to 5

dryness: Scalp reaction dryness score, e.g., 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)

burning: Scalp reaction burning/stinging score, e.g., 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3-severe (marked, intense)

erosion: Scalp reaction erosion score, e.g., 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)

edema: Scalp reaction edema score, e.g., 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)

pain: Scalp reaction pain score, e.g., 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)

itching: Scalp reaction itching 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

23. 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.