Contains Nonbinding Recommendations

Draft Guidance on Naftifine Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Cream; topical

Recommended Studies: One study

1. Type of study: Bioequivalence (BE) Study with Clinical Endpoints
   Design: Randomized, double blind, parallel, placebo-controlled in vivo
   Strength: 2%
   Subjects: Healthy males and females with interdigital tinea pedis due to *Trichophyton rubrum.*
   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 a clinical endpoint bioequivalence study in the treatment of interdigital tinea pedis. Subjects are to be randomized to receive the generic Naftifine Hydrochloride topical cream, 2%, the reference listed drug (RLD), or placebo. Sufficient study drug is to be applied to cover affected and immediate surrounding areas once daily for 14 consecutive days (i.e., 2 weeks). The primary endpoint is to be evaluated at the test-of-cure visit (study Week 6, four weeks after the end of treatment).

2. Although all tinea pedis lesions on both feet are to be treated in this study, a target lesion on one foot is to be identified as the most severe lesion and evaluated at the baseline visit and at each study visit. The following signs and symptoms should be evaluated:
   a. **Signs**: fissuring/cracking, erythema, maceration, and scaling
   b. **Symptoms**: pruritus and burning/stinging

   Each sign and symptom should be objectively defined. The following is an example of an acceptable scale.

   0 = none (complete absence of any signs or symptoms)
   1 = mild (slight)
   2 = moderate (definitely present)

3 = severe (marked, intense)

3. Inclusion Criteria (the sponsor may add additional criteria):
   a. Healthy males and females 18 years of age or older.
   b. Clinical diagnosis of tinea pedis with lesions localized to the interdigital spaces or predominantly interdigital, but may extend to other areas of the foot (the non-interdigital lesions should not be hyperkeratotic, i.e., characteristic of tinea pedis moccasin), and provisionally confirmed at baseline by a positive potassium hydroxide (KOH) wet mount preparation (i.e., skin scrapings from the target site are placed on a microscope slide with a drop of 10% KOH, and microscopic examination reveals segmented fungal hyphae).
   c. The sum of the clinical signs and symptoms scores of the target lesion is at least 4, including a minimum score of at least 2 for erythema AND a minimum score of 2 for either scaling or pruritus (on a scale of 0-3, where 2 indicates moderate severity).

4. Exclusion Criteria (the sponsor may add additional criteria):
   a. Pregnant or lactating or planning to become pregnant during the study period.
   b. Use of antipruritics, including antihistamines, within 72 hours prior to entry into the study.
   c. Use of topical corticosteroid, antibiotics or antifungal therapy within 2 weeks prior to entry into the study.
   d. Use of systemic (e.g., oral or injectable) corticosteroid, antibiotics or antifungal therapy within 1 month prior to entry into the study.
   e. Use of oral terbinafine or itraconazole within 2 months prior to entry into the study.
   f. Use of immunosuppressive medication or radiation therapy within 3 months prior to entry into the study.
   g. Confluent, diffuse moccasin-type tinea pedis of the entire plantar surface.
   h. Presence of any other infection of the foot or other disease process that might confound the treatment evaluation, such as onychomycosis.
   i. History of dermatophyte infections unresponsive to systemic or topical antifungal drugs.
   j. Known hypersensitivity to Naftifine Hydrochloride or to any component of the formulation.

5. A positive skin fungal culture at baseline should not be an inclusion criterion due to the time lag between obtaining the culture specimen and receiving the culture results. However, a skin fungal culture must be obtained at baseline at the target site. Testing should be performed to identify the isolates at the species level (e.g., *Trichophyton rubrum, Trichophyton mentagrophytes,* or *Epidermophyton floccosum*). Only subjects with a pretreatment baseline skin fungal culture from the target site that is positive for *Trichophyton rubrum* should be included in the per protocol (PP) and modified intent to treat (mITT) populations for the primary endpoint analysis. Subjects with a negative baseline fungal culture should be excluded from the PP and mITT populations, but included in the safety population for the safety analyses.

6. The RLD is indicated for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organism *Trichophyton rubrum*. Therefore, this study is limited to subjects with fungal cultures positive for *T. rubrum* upon entry into the study.

7. The protocol should include a list of the prescription and over-the-counter drug products that are prohibited during the study, such as:
   a. Any other topical products applied to the target site
   b. Systemic (e.g., oral or injectable) antibiotics or antifungals.
   c. Systemic corticosteroid or immunosuppressive drugs.

d. Antipruritics, including antihistamines, within 24 hours of study visits.

8. Subjects should avoid the use of occlusive dressings or wrappings over the treatment application site.

9. 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 at the lower end of the dose/response curve.

10. The recommended primary endpoint is the proportion of subjects with therapeutic cure at Week 6 (+/- 4 days) following 2 weeks of treatment (study day 38-46). Therapeutic cure defined as both mycological cure and clinical cure. Mycological cure is defined as a negative KOH test AND a negative fungal culture. Clinical cure defined as total signs and symptoms severity score ≤ 2 and each sign and symptom score ≤ 1. Sign and symptoms to be assessed are: erythema, maceration, scaling, fissuring/cracking, pruritus, burning/stinging on a 4 point ordinal scale; 0 = absent, 1 = mild, 2 = moderate, 3 = marked.

    The recommended secondary endpoint of the study is the proportion of subjects with complete cure (mycological cure and clinical cure) at Week 6, where clinical cure is defined as absence of Erythema, Scaling, and Pruritus (grade 0 for each).

11. The protocol should clearly define the PP, mITT and safety populations:

    a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who met all inclusion/exclusion criteria, were compliant with the assigned study treatment, and completed the evaluation at the test-of-cure visit within the designated visit window (+/- 4 days; i.e., study Day 38-46) with no protocol violations that would affect the treatment evaluation. The protocol should provide a definition of compliant subjects (e.g., used at least 75% and no more than 125% of study drug doses) and specify how compliance will be verified (e.g., by the use of subject diaries).

    b. The mITT population includes all randomized subjects who had a positive baseline skin fungal culture for *Trichophyton rubrum,* and applied at least one dose of study product.

    c. The safety population includes all randomized subjects who applied the study product at least once.

12. Subjects who are discontinued early from the study due to insufficient or lack of treatment should be included in PP population as treatment failures and assigned the longest time to healing observed in the study. 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).

13. 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. The sponsor should clearly explain whether the medication was used prior to baseline visit, during the study, or both.

14. 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.

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 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 the randomization code 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 from the onset of the study 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 for cure versus failure, it is recommended the following compound hypotheses be tested using the per protocol population:

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

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_O, 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.

21. To establish sensitivity within the study for cure versus failure, 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

22. Study data should be submitted to the OGD in electronic format. All data should be submitted as 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 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).
    c. 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.

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
    i. Duration of Treatment (total exposure in days)
    j. Per Protocol (PP) population inclusion (yes/no)
    k. Reason for exclusion from PP population
    l. Modified Intent to Treat (mITT) population inclusion (yes/no)
    m. Reason for exclusion from mITT population
    n. Safety population inclusion (yes/no)
    o. Reason for exclusion from safety population
    p. Final designation as therapeutic cure (yes/no)
    q. Treatment compliance: number of missed doses per subject
    r. Concomitant medication (yes/no)
    s. 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	pp	pp_rs	mitt	mitt_rs	safety	safe_rs	cure	complian	CM	AE
101	1	01	22	YEARS	F	1	A	28	Y		Y		Y		N	0	Y	Y
101	2	01	30	YEARS	F	1	B	28	Y		Y		Y		Y	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
EXDUR:	Duration of Treatment (total exposure in days)
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, B=negative baseline culture, 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. cure:	Final designation e.g., Y=Yes (therapeutic cure), N=No (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

24. Please provide a dataset containing a separate line listing for each 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. Fissuring/Cracking score
    i. Erythema score
    j. Maceration score
    k. Scaling score
    l. Pruritus score
    m. Burning/Stinging score
    n. Composite (total) signs and symptoms score
    o. KOH result
    p. Culture result
    q. Mycological cure (yes/no)
    r. Clinical cure (yes/no)
    s. Therapeutic cure (yes/no)
    t. Concomitant medication reported during this visit (yes/no)
    u. Adverse event reported during this visit (yes/no)
    v. 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	VISITNUM	SVSTDTC	ELTMBS	EVAL	fisscrac	erythema	macerati	scaling	pruritus	burnstin	compss	koh	culture	mycocure	clincure	thercure	CMrpt	AErpt	LBtest
101	1	A	1	2004-07-01	0	JB	0	2	1	2	0	0	5	Pos	Pos				Y	N	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
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, e.g., initials
fisscrac:	Fissuring/Cracking score, e.g., 0=none (complete absence), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
erythema:	Erythema score, e.g., 0=none (complete absence), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
macerati:	Maceration score, e.g., 0=none (complete absence), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
scaling:	Scaling score, e.g., 0=none (complete absence), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
pruritus:	Pruritus score, e.g., 0=none (complete absence), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
burnstin:	Burning/Stinging score, e.g., 0=none (complete absence, 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
compss:	Composite (total) signs and symptoms score
koh:	KOH result, e.g., Pos=Positive, Neg=Negative
culture:	Culture result, e.g., A=Positive for *T. rubrum*, B =Positive for other organism, C=No growth
mycocure:	Mycological cure, e.g., Y=Yes, N=No
clincure:	Clinical cure, e.g., Y=Yes, N=No
thercure:	Therapeutic cure, e.g., Y=Yes, N=No
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. The study data should be submitted in standardized format. Please refer to more details at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

26. 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 Naftifine Hydrochloride.