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Draft – Not for Implementation

Draft Guidance on Ruxolitinib Phosphate

November 2023

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Ruxolitinib phosphate

Dosage Form: Cream

Route: Topical

Strength: EQ 1.5% Base

Recommended Study: One comparative clinical endpoint bioequivalence study

1. Type of study: Comparative clinical endpoint bioequivalence study
   Design: Randomized, double-blind, parallel-group, placebo-controlled, in vivo
   Strength: EQ 1.5% Base
   Subjects: Non-immunocompromised male and female adults (age ≥18 years) with a clinical diagnosis of mild to moderate atopic dermatitis (AD)
   Additional comments: Specific recommendations are provided below.

Additional comments regarding the comparative clinical endpoint bioequivalence study:

1. FDA recommends conducting a comparative clinical endpoint bioequivalence study in the treatment of mild to moderate AD comparing the test product versus reference standard and placebo (vehicle) control, each applied as a thin layer twice daily to the affected area(s) up to 20% body surface area (BSA). The primary endpoint is the proportion of subjects with treatment success (a grade of clear or almost clear; a score of 0 or 1 with a ≥ 2-grade improvement from baseline, within the treatment area) based on the Investigator's Global Assessment (IGA) of Disease Severity (see Table 1) at the end of treatment (study Day 15).

2. Inclusion criteria (the sponsor may add additional criteria):
    a. Non-immunocompromised males or females aged 18 years and older with a clinical diagnosis of mild to moderate AD
    b. Had a diagnosis of AD for at least 3 months
    c. An IGA of disease severity of mild or moderate at baseline (per Table 1, a score of 2 or 3)
    d. Affected area of AD involvement of up to 20% BSA at baseline as defined by the criteria of Hanifin and Rajka[1]

Table 1. IGA of Disease Severity

Score	Category	Definition
0	Clear	Minor residual discoloration, no erythema or induration/papulation, no oozing/crusting
1	Almost clear	Trace faint pink erythema with almost no induration/papulation and no oozing/crusting
2	Mild disease	Faint pink erythema with mild induration/papulation and no oozing/crusting
3	Moderate disease	Pink-red erythema with moderate induration/papulation and there may be some oozing/crusting
4	Severe disease	Deep/bright red erythema with severe induration/papulation with oozing/crusting

3. Exclusion criteria (the sponsor may add additional criteria):
    a. Females who are pregnant, breast feeding, or who wish to become pregnant during the study period
    b. Active cutaneous bacterial or viral infection in any treatment area at baseline (e.g., clinically infected AD)
    c. Sunburn, extensive scarring, or pigmented lesion(s) in any treatment area at baseline, which would interfere with evaluations
    d. History of confounding skin conditions (e.g., psoriasis, rosacea, erythroderma, or ichthyosis)
    e. History or presence of immunological deficiencies or diseases, clinically significant or uncontrolled cardiovascular disease, HIV, diabetes, malignancy, serious active or recurrent infection, clinically significant severe renal insufficiency, severe hepatic disorders, or any other condition that in the Investigator's opinion may put the subject at increased risk
    f. Use within one month prior to baseline of 1) oral or intravenous corticosteroids, 2) ultraviolet A (UVA)/ultraviolet B (UVB) therapy, 3) psoralen plus ultraviolet A (PUVA) therapy, 4) tanning booths, 5) nonprescription ultraviolet (UV) light sources, 6) immunomodulators or immunosuppressive therapies, 7) interferon, 8) cytotoxic drugs, 9) tacrolimus, 10) pimecrolimus, or 11) ruxolitinib or other JAK inhibitor
    g. Use within 14 days of baseline of 1) systemic antibiotics, 2) calcipotriene or other vitamin D preparations, or 3) retinoids

[1] Hanifin JM and Rajka G. Diagnostic Features of Atopic Dermatitis. Acta Derm Venereol. 1980; Suppl. 92: 44-7.

h. Use within 7 days prior to baseline of 1) antihistamines, 2) topical antibiotics, 3) topical corticosteroids or 4) other topical drug products
i. Use within 24 hours prior to baseline of any topical product (e.g., sunscreens, lotions, creams bland emollient/moisturizer) in the areas to be treated
j. Known allergy or hypersensitivity to ruxolitinib or any other component of the test product or reference standard
k. Not willing to minimize or avoid natural and artificial sunlight exposure during treatment

4. 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. Other treatments for AD, including the use of bland emollient
    b. Topical or systemic corticosteroid, topical or systemic antibiotic, topical or systemic antifungal, oral or topical antihistamine, topical or systemic immunosuppressive drugs, topical or systemic immunomodulator (e.g., tacrolimus or JAK inhibitors), calcipotriene or other vitamin D preparations, retinoids, interferon, cyclosporine, methotrexate, azathioprine or antihistamines (e.g., diphenhydramine, hydroxyzine)
    c. CYP3A inhibitor (e.g., erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers cimetidine, grapefruit or grapefruit juice)
    d. Topical product, other than the assigned treatment (e.g., sunscreen, new brand of cosmetic or cleanser, cream, lotion, ointment, powder, or bland emollient) applied on or near the treatment area(s)
    e. Phototherapy, e.g., PUVA, UVA or UVB therapy
    f. Bathing, showering or swimming right after applying study treatment
    g. Prolonged baths (i.e., longer than 5 minutes), excessive exposure to sunlight, or use of tanning booths, sun lamps or nonprescription UV light sources
    h. Covering any treated area with bandage(s), dressing(s) or wrap(s)
    i. Allowing the study treatment to come in contact with the eyes, nose, mouth, vagina, or rectum (mucous membranes)

5. It is the sponsor's responsibility to include a provision in the protocol and subject consent form to ensure appropriate referral for continued therapy and follow-up of subjects according to the standard of care after the end of the study. If there is worsening during the treatment period, no improvement in the follow-up period, or signs and symptoms persist beyond the treatment period, subjects must be evaluated by a healthcare provider for careful re-evaluation.

6. If the signs and symptoms of AD resolve during treatment, subjects should continue the application of the study drug for at least 2 weeks and should not stop treatment. Subjects should not be discontinued early from the study due to lack of treatment effect. Subjects who do not show complete clearing of all lesions by the end of the study (Day 15) should receive continuing treatment with the reference standard and appropriate follow- up according to the standard of care.

7. Provide Subject-Level Analysis Dataset (ADSL), one record per subject, using the following headings, if applicable:
    a. Study identifier
    b. Unique subject identifier
    c. Subject identifier
    d. Study site identifier
    e. Age
    f. Age units (years)
    g. Sex
    h. Race
    i. Name of planned treatment
    j. Name of actual treatment
    k. Safety population flag (yes/no)
    l. Reason for exclusion from safety population
    m. Modified Intent-to-Treat (mITT) population flag (yes/no)
    n. Reason for exclusion from mITT
    o. Per-Protocol (PP) population flag (yes/no)
    p. Reason for exclusion from PP population
    q. Randomized population flag (yes/no)
    r. Date/time of first exposure to treatment
    s. Date/time of last exposure to treatment
    t. End of study date
    u. End of study status
    v. Subject required additional treatment due to unsatisfactory treatment response (yes/no)
    w. Specific reason for use of this product (e.g., A= failure to respond adequately to other topical prescription treatments for AD, B= when those treatments are not advisable)
    x. Location of Treatment Area (i.e., neck, elbow, knee, hand, wrist, ankle)
    y. Size of Treatment Area (e.g., cm^2)
    z. Previous use of AD treatment (yes/no)
    aa. Reason for premature discontinuation of subject
    bb. Percent (%) Body Surface Area (BSA) involvement at baseline
    cc. Percent (%) BSA involvement at study Day 15
    dd. IGA score at baseline
    ee. IGA score at study Day 15
    ff. Final designation of treatment outcome (success/failure) based on IGA
    gg. Compliance rate (%)
    hh. Subject missed pre-specified number of scheduled doses for more than pre-specified number of consecutive days (yes/no)
    ii. Adverse event reported (yes/no)
    jj. Concomitant medication (yes/no)

8. Provide the basic data structure (BDS) dataset with records per subject, per visit, per analysis timepoint, using the following headings, if applicable:
    a. Study identifier

b. Unique subject identifier
c. Subject identifier for the study
d. Study site identifier
e. Name of planned treatment
f. Name of Actual Treatment (exposure): test product, reference standard, placebo
g. Location of Dose Administration: application site
h. Safety population flag (yes/no)
i. Modified ITT population flag (yes/no)
j. PP population flag (yes/no)
k. Analysis visit
l. Analysis date
m. Study visit within designated window (yes/no)
n. IGA score
o. Individual signs and symptoms of AD score for erythema, induration/papulation, lichenification, and pruritus
p. Skin reaction score for each sign and symptom evaluated (e.g., dryness, burning/stinging, erosion, edema, pain)
q. Additional treatment required during the visit (yes/no)
r. Concomitant medication during the visit (yes/no)
s. Adverse event reported during the visit (yes/no)
t. Laboratory testing during the visit (yes/no)

9. Refer to the most recent version of the FDA product-specific guidance on *Adapalene; Benzoyl Peroxide Topical Gel* (NDA 207917)[a] for a recommended approach to statistical analysis and study design for comparative clinical endpoint bioequivalence study.

10. Refer to the Study Data Standards Resources website (https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources).

Applicants intending to propose an alternative approach by which to demonstrate bioequivalence should refer to the most recent version of the FDA guidance for industry on *Controlled Correspondence Related to Generic Drug Development*[b] and the most recent version of the FDA guidance for industry on *Formal Meetings between FDA and ANDA Applicants of Complex Products Under GDUFA*[b] for additional information describing the procedures on how to clarify regulatory expectations regarding your individual drug development program.

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[a] For the most recent version of a product-specific guidance, check the FDA product-specific guidance website at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.
[b] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.