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Draft Guidance on Ruxolitinib Phosphate

November 2024

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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 Studies:	Two options: (1) two in vitro bioequivalence studies and other characterization tests or (2) one comparative clinical endpoint bioequivalence study

I. Option 1: Two in vitro bioequivalence studies and other characterization tests

To demonstrate bioequivalence for ruxolitinib phosphate topical cream, EQ 1.5% Base using in vitro studies, the following criteria should be met:

1. The test (T) product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard (RS) that may significantly affect the local or systemic availability of the active ingredient. For example, if the T product and RS are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the most recent version of the FDA guidance for industry on *ANDA Submissions – Refuse-to-Receive Standards*[a], and the criteria below are also satisfied, the bioequivalence of the T product may be established using a characterization-based bioequivalence approach.

2. The T product and RS should have the same physicochemical and structural (Q3) attributes, based upon acceptable comparative Q3 characterization tests with a minimum of three batches of the T product and three batches (as available) of the RS. The T

product and RS batches should ideally represent the product at different ages throughout its shelf life. Refer to the most recent version of the FDA guidance for industry on *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs*[a] for additional information regarding comparative Q3 characterization tests. The comparison of the T product and RS should include characterizations of the following Q3 attributes:

a. Characterization of visual appearance and texture
b. Characterization of phase states and structural organization of matter
    - Microscopic examination with representative high-resolution microscopic images at multiple magnifications
    - Analysis of globule size distribution
c. Characterization of rheological behavior which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms. The following evaluations are recommended:
    - A characterization of shear stress vs. shear rate and viscosity vs. shear rate. At minimum, this should consist of numerical viscosity data at three shear rates (low, medium, and high).
    - A complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified.
    - Yield stress values should be reported if the material tested exhibits plastic flow behavior.
    - The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported. Any non-linear viscosity behavior over a range of shear rates should also be investigated, measured, and reported.
d. Characterization of water activity
e. Characterization of specific gravity
f. Characterization of pH

3. The T product and RS should have an equivalent rate of ruxolitinib release based upon an acceptable in vitro release test (IVRT) bioequivalence study comparing a minimum of one batch each of the T product and RS using an appropriately validated IVRT method.

    Type of study: Bioequivalence study with IVRT endpoint
    Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an occluded pseudo-infinite dose, in vitro
    Strength: EQ 1.5% Base
    Test system: A synthetic membrane in a diffusion cell system
    Analyte to measure: Ruxolitinib in receptor solution
    Bioequivalence based on: Ruxolitinib (IVRT endpoint: drug release rate)
    Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVRT methods/studies. The batches of T product and RS evaluated in the IVRT bioequivalence study should be included among those for which the Q3 attributes are characterized.

4. The T product and RS should have an equivalent rate and extent of ruxolitinib permeation through excised human skin based upon an acceptable in vitro permeation test (IVPT) bioequivalence study comparing a minimum of one batch each of the T product and RS using an appropriately validated IVPT method.

   Type of study: Bioequivalence study with IVPT endpoints
   Design: Single-dose, two-treatment, parallel, multiple-replicate per treatment group study design using an unoccluded finite dose, in vitro
   Strength: EQ 1.5% Base
   Test system: Barrier-competent human skin from male and/or female donors of at least 18 years of age in a diffusion cell system
   Analyte to measure: Ruxolitinib in receptor solution
   Bioequivalence based on: Ruxolitinib (IVPT endpoints: total cumulative amount (AMT) and maximum flux (J_{max}))
   Additional comments: Refer to the most recent version of the FDA guidance for industry on *In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs*[a] for additional information regarding the development, validation, conduct and analysis of acceptable IVPT methods/studies. The batches of T product and RS evaluated in the IVPT bioequivalence study should be the same as those evaluated in the IVRT bioequivalence study.

II. Option 2: One in vivo bioequivalence study with clinical endpoint

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 T product versus RS 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).

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

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]

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 Janus Kinase (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 T product or RS
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 a 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 RS 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 (%) 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): T product, RS, 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)[b] 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.

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatoryinformation/search-fda-guidance-documents.
[b] 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.