Draft Guidance on Pimecrolimus

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form: Route: Cream; topical

Recommended Studies: Two options: (1) in vitro studies or (2) an in vivo study with clinical endpoint.

1. Option 1: In vitro studies

To qualify for the in vitro option to demonstrate bioequivalence for pimecrolimus topical cream, 1% the following criteria should be met:

A. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference product that may significantly affect the local or systemic availability of the active ingredient. For example, if the test and reference products are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the guidance for industry ANDA Submissions – Refuse-to-Receive Standards and the criteria below are also satisfied, the bioequivalence of the test product with respect to the reference product may be established using a characterization based (in vitro) bioequivalence approach.

B. The test and reference products should be physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three batches of the test and three batches (as available) of the reference product. The test and reference product batches should ideally represent the product at different ages throughout its shelf life. The comparison of the test and reference products should include characterizations of the following physical and structural attributes:

   i. Assessment of visual appearance
   
   ii. Microscopic examination with representative high resolution microscopic images at multiple magnifications
   
   iii. Analysis of particle size distribution, crystal habit and polymorphic form of pimecrolimus in the drug product, as applicable
   
   iv. Analysis of globule size distribution

Recommended Mar 2012; Revised Nov 2019
Analysis of the 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), and may include a complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified (when possible)

- 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

Analysis of pH, specific gravity, and any other potentially relevant physical and structural similarity characterizations

The test and reference products should have an equivalent rate of pimecrolimus release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one batch each of the test and reference products using an appropriately validated IVRT method. Refer to the Guidance on Acyclovir (for acyclovir topical cream, 5%) for additional information regarding the development, validation, conduct and analysis of IVRT methods/studies. The batches of test and reference products evaluated in the IVRT study should be included among those for which the physical and structural similarity is characterized and compared.

The test and reference products should have an equivalent rate and extent of pimecrolimus permeation through excised human skin based upon an acceptable in vitro permeation test (IVPT) comparing a minimum of one batch each of the test and reference products using an appropriately validated IVPT method. Refer to the Guidance on Acyclovir (for acyclovir topical cream, 5%) for additional information regarding the development, validation, conduct and analysis of acceptable IVPT methods/studies. The batches of test and reference products evaluated in the IVPT study should be the same as those evaluated in the IVRT study.

Analytes to measure (in appropriate biological fluid): Pimecrolimus in IVPT receptor solution

Bioequivalence based on (90% CI): Pimecrolimus

Waiver request of in vivo testing: Not applicable

1 Product specific guidance: Guidance on Acyclovir for acyclovir topical cream, 5%
2. Option 2: In Vivo study with clinical endpoint

Type of study: Bioequivalence study with clinical endpoint
Design: Randomized, double blind, parallel, placebo controlled, in vivo
Strength: 1%
Subjects: Non-immunocompromised males and females with clinical diagnosis of mild to moderate atopic dermatitis (AD)
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 bioequivalence study with clinical endpoint:

1. The Office of Generic Drugs (OGD) recommends conducting a bioequivalence study with a clinical endpoint in the treatment of mild to moderate AD comparing the test product versus the reference product and vehicle control, each applied as a thin layer twice daily to the affected area(s) for 14 days (2 weeks). The primary endpoint is the proportion of subjects with treatment success (a grade of clear or almost clear; a score of 0 or 1, 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. A placebo control arm (vehicle of test product) is recommended to demonstrate that the test product and reference product are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products.

3. Inclusion Criteria (sponsor may add additional criteria):
   a) Non-immunocompromised male or female aged 12 years and older with a clinical diagnosis of mild to moderate AD that has failed to respond adequately to other topical prescription treatments for AD, or for whom those treatments are not advisable. If the enrollment of subjects younger than aged 12 years is necessary due to the difficulty of recruiting sufficient subjects into the study, the OGD recommends limiting the subject’s age to 8 years and older. If pediatric subjects are included, ensure that the age distribution is similar in all treatment groups.
   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 at least 5% body surface area (BSA) at baseline as defined by the criteria of Hanifin and Rajka.²

Table 1. IGA of Disease Severity

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

4. Exclusion Criteria (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 Netherton’s Syndrome, immunological deficiencies or diseases, HIV, diabetes, malignancy, serious active or recurrent infection, clinically significant severe renal insufficiency or severe hepatic disorders
   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, or 10) pimecrolimus
   g) Use within 14 days of baseline of: 1) systemic antibiotics, 2) calcipotriene or other vitamin D preparations, or 3) retinoids
   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 pimecrolimus or any other component of the test product or reference product

k) Not willing to minimize or avoid natural and artificial sunlight exposure during treatment

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) 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, immunosuppressive drugs, immunomodulator (e.g., tacrolimus), 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., sun screen, 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)

6. When applying assigned study treatment after a bath or shower, the skin should be dry. Caregivers applying study treatment to a subject, or subject who is not treating their hands should wash their hands with soap and water after applying study treatment.

7. 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, and consideration should be given to performing a skin biopsy in such cases to rule out malignancy.

8. The primary endpoint is the proportion of subjects in the per protocol population in each treatment group with treatment success (i.e., a grade of clear or almost clear; a score of 0 or 1, within all treatment areas) based on the IGA of Disease Severity (see Table 1) at the end of treatment (week 2 visit; study Day 15). This is the earliest time at which a significant success proportion is expected. This shorter treatment duration would be most likely to detect differences between test and reference products and is intended to minimize systemic exposure to the drug and the potential cancer risk.

9. The secondary endpoints are change in severity from baseline to week 2 (study Day 15) of four individual signs and symptoms of AD (i.e., erythema, induration/papulation,
lichenification and pruritus; see Table 2) and are considered supportive information. It is recommended that pruritus be assessed by questioning the subject or the subject’s parent/legal guardian regarding the intensity of overall itching/scratching/discomfort in the 24 hours prior to the visit.

Table 2. Individual Signs and Symptoms of AD

<table>
<thead>
<tr>
<th>Erythema</th>
<th>0</th>
<th>None</th>
<th>No erythema present</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>Mild</td>
<td>Slight erythema: very light-pink</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Moderate</td>
<td>Dull red, clearly distinguishable</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Severe</td>
<td>Deep/dark red</td>
</tr>
<tr>
<td>Induration/Papulation</td>
<td>0</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Mild</td>
<td>Slightly perceptible elevation</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Moderate</td>
<td>Clearly perceptible elevation but not extensive</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Severe</td>
<td>Marked and extensive elevation</td>
</tr>
<tr>
<td>Lichenification</td>
<td>0</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Mild</td>
<td>Slight thickening of the skin discernible only by touch and with skin markings minimally exaggerated</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Moderate</td>
<td>Definite thickening of the skin with skin marking exaggerated so that they form a visible criss-cross pattern</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Severe</td>
<td>Thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Mild</td>
<td>Occasional, slight itching/scratching</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Moderate</td>
<td>Constant or intermittent itching/scratching/discomfort which is not disturbing sleep</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Severe</td>
<td>Bothersome itching/scratching/discomfort which is disturbing sleep</td>
</tr>
</tbody>
</table>

10. 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 (study Day 15) should receive continuing treatment with the reference product and appropriate follow-up according to the standard of care.

11. Please 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., cm²)  
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 (%) Body Surface Area (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)  

12. Please 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 product, placebo  
g) Location of Dose Administration: application site  
h) Safety population flag (yes/no)  
i) Modified ITT population flag (yes/no)  
j) Per-protocol (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)

13. Please refer to the product-specific guidance on adapalene; benzoyl peroxide topical gel 0.3%; 2.5% entitled Guidance on Adapalene; Benzoyl Peroxide for a recommended approach to statistical analysis and study design for bioequivalence studies with clinical endpoints.

14. Study data should be submitted in a standardized format. Please refer to the study data standards published at www.fda.gov.³

³ Study Data Standards for Submission to CDER and CBER available at: https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber