

Draft Guidance on Calcipotriene

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Cream/Topical

Recommended studies: 1 study

Type of study: Bioequivalence (BE) Study with Clinical Endpoint

Design: Randomized, double blind, parallel, placebo controlled, in vivo

Strength: 0.005%

Subjects: Healthy males and nonpregnant females with clinical diagnosis of plaque psoriasis

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 conducting a bioequivalence study with a clinical endpoint in the treatment of stable plaque psoriasis comparing the test product versus the reference listed drug (RLD) and placebo control, each administered twice daily to the affected area for 56 days (8 weeks). The two co-primary endpoints are the proportions of subjects with treatment success on the Physician's Global Assessment (PGA) and clinical success on the Psoriasis Area Severity Index (PASI) scale at the end of treatment (study Day 56).
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. A rescue clause should be included to allow for discontinuation due to lack of treatment response or worsening disease.
3. Inclusion Criteria (the sponsor may add additional criteria)
 - a. Male or nonpregnant females with a clinical diagnosis of stable (at least 3 months) plaque-type psoriasis involving 5 to 20% BSA, not including the face, scalp, groin, hands, and feet.
 - b. A PGA of disease severity of at least moderate disease severity (grade ≥ 3 , per Table 1).
 - c. A minimum plaque elevation of at least moderate severity (grade ≥ 3 , per Table 2) at the target lesion site. The most severe lesion at baseline should be identified as the target lesion.

Table 1. Physician’s Global Assessment (PGA) of Disease Severity

Score	Grade	Definition
0	None	No plaque elevation above normal skin level; may have residual non-erythematous discoloration; no psoriatic scale
1	Minimal	Essentially flat with possible trace elevation; faint erythema; no psoriatic scale
2	Mild	Slight but definite elevation of plaque above normal skin level; may have up to moderate erythema (red coloration); fine scales with some lesions partially covered
3	Moderate	Moderate elevation with rounded or sloped edges to plaque; moderate erythema (red coloration); somewhat coarse scales with most lesions partially covered
4	Severe	Marked elevation with hard, sharp edges to plaque; severe erythema (very red coloration); coarse, thick scales with virtually all lesions covered and a rough surface
5	Very Severe	Very marked elevation with very hard, sharp edges to plaque; very severe erythema (extreme red coloration); very coarse, thick scales with all lesions covered and a very rough surface

Table 2. Severity of Psoriasis Area Severity Index (PASI) at the Target Lesion Site

Score	Grade	Erythema	Scaling	Plaque Elevation
0	Clear	No evidence of erythema	No evidence of scaling	No evidence of plaques above normal skin level
1	Almost Clear	Pink discoloration, minimal erythema	Occasional fine scales hardly noticeable	Slight, just discernable elevation above normal skin level
2	Mild	Light red coloration	Slight but definite roughness, fine scale present, no cracking	Discernable elevation above normal skin level upon examination, but not pronounced
3	Moderate	Moderate redness, but not dark	Moderate roughness, somewhat coarse scaling	Definite plaque formation with rounded/sloped edges to plaque
4	Severe	Dark red coloration	Marked roughness, coarse/thick scaling, cracking may be evident	Marked elevation with hard, distinct edges to plaque
5	Very Severe	Very dark red coloration with induration present	Very thick scales covering extensive area severe cracking/fissures may be evident	Very marked elevation, very hard and sharp edges to plaque

4. Body Surface Area (BSA) percentage is no longer requested as an individual component sign in the PASI scale but the BSA percentage and distribution should be recorded at baseline.
5. Exclusion Criteria (the sponsor may add additional criteria)
 - a. Females who are pregnant, breast feeding, or planning a pregnancy.
 - b. Current diagnosis of unstable forms of psoriasis in the treatment area, including guttate, erythrodermic, exfoliative or pustular psoriasis.
 - c. Other inflammatory skin disease in the treatment area that may confound the evaluation of the plaque psoriasis (e.g., atopic dermatitis, contact dermatitis, tinea corporis).
 - d. Presence of pigmentation, extensive scarring, or pigmented lesions in the treatment areas, which could interfere with the rating of efficacy parameters.
 - e. History of psoriasis unresponsive to topical treatments.

- f. History of hypersensitivity to any component of the test product or RLD.
 - g. Current or past history of hypercalcemia, vitamin D toxicity, severe renal insufficiency, or severe hepatic disorders.
 - h. Current immunosuppression.
 - i. Use within one month prior to baseline of: 1) systemic steroids, 2) systemic antibiotics, 3) systemic antipsoriatic treatment, 4) PUVA therapy, 5) UVB therapy, or 6) systemic anti-inflammatory agents.
 - j. Use within 2 weeks prior to baseline of: 1) topical anti-psoriatic drugs (e.g., salicylic acid, anthralin, coal tar, calcipotriene, tazarotene), 2) topical corticosteroids, 3) immunosuppressive drugs (e.g., tacrolimus, pimecrolimus), or 4) topical retinoids.
6. 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. Topical product other than the assigned treatment (including moisturizers, new brands of make-up, creams, ointments, lotions, and powders) applied on or near the treatment area.
 - b. Topical or systemic antipsoriatic treatment (e.g., anthralin, coal tar, tazarotene, retinoids, tacalcitol, infliximab, adalimumab, alefacept, PUVA therapy, UVB therapy).
 - c. Topical or systemic corticosteroids.
 - d. Immunosuppressive drugs.
 - e. Calcium supplements.
 - f. More than 400 IU/day of Vitamin D or vitamin D analogs.
 - g. Initiation of or changes to non antipsoriatic concomitant medication that could affect psoriasis (e.g., beta blockers, lithium) during the study.
 - h. Tanning booths, sun lamps, or nonprescription UV light sources.
 - i. Phototherapy.
 - j. The treated areas should not be bandaged, covered or wrapped as to be occlusive.
 - k. Subjects should be instructed to minimize exposure to natural sunlight, to not allow the ointment to come in contact with the face or eyes and to always wash hands thoroughly after use.
7. The recommended co-primary endpoints are:
- a. the proportion of subjects in each treatment group with treatment success (defined as absent or very mild disease, a score of 0 or 1, within the treatment area) on the PGA of disease severity at the week 8 visit (Study Day 56), and
 - b. the proportion of subjects in each treatment group with clinical success (defined as absent or mild, a score of 0 or 1, at the target lesion site) on the PASI at the week 8 visit (Study Day 56). Each psoriatic sign of scaling, erythema, and plaque elevation should have a score of 0 or 1 at week 8 (Study Day 56) for the subject to be considered a success. The target lesion is to be identified at baseline as the most severe lesion.
8. 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 meet all inclusion/exclusion criteria, 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 all 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.
9. 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 their plaque psoriasis 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 Last Observation Carried Forward (LOCF).
 10. Due to the possibility of elevated serum calcium levels with calcipotriene absorption, serum calcium, serum albumin and albumin-corrected serum calcium levels should be included in serum chemistry analysis. Subjects with elevation in serum calcium outside the normal range should be discontinued from the study. The serum calcium level should be corrected for serum albumin level as follows:
“corrected” serum calcium=serum calcium mg/dL + (0.8 x[4.0-albumin g/dL])
 11. Calcium levels of subjects in study treatment groups should be evaluated to ensure similar effects are seen with both active treatments. The number of subjects with elevated serum calcium levels and the mean albumin corrected calcium levels at baseline and at week 8 should also be compared in all study treatment groups.
 12. 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.
 13. 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.
 14. Application site reactions such as erythema, 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 these expected application site reactions.
 15. If the inactive ingredients 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. Due to the possibility of hypercalcemia from systemic calcipotriene absorption, the data should demonstrate that those changes in inactive ingredients in the formulation will result in no greater systemic absorption of calcipotriene with the use of the test product than with use of the RLD.
 16. 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.

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, the 90% confidence interval of the test - reference difference between products for both co-primary endpoints (success proportion) must be contained within [-0.20, +0.20] for dichotomous variables (success versus failure), using the PP population.
21. As a parameter for determining adequate study sensitivity, the test product and RLD should be statistically superior to placebo ($p < 0.05$, two-sided) for both co-primary endpoints (success proportion) using the mITT study population and LOCF.
22. The site and size of the treatment area should be compared and tabulated for each treatment group.
23. The following Statistical Analysis Method is recommended for equivalence testing for a dichotomous variable (success/failure):

Equivalence Analysis

Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in success proportions between test and reference treatment must be contained within [-0.20, +0.20] in order to establish equivalence.

The compound hypothesis to be tested is:

$$H_0: p_T - p_R < -0.20 \text{ or } p_T - p_R > 0.20$$

versus

$$H_A: -0.20 \leq p_T - p_R \leq 0.20$$

where p_T = success rate of test treatment and p_R = success rate of reference treatment.

Let

n_T = sample size of test treatment group

$c n_T$ = number of successes in test treatment group

n_R = sample size of reference treatment group

$c n_R$ = number of successes in reference treatment group

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

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

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

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

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

We reject H_0 if $L \geq -0.20$ and $U \leq 0.20$

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

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

25. 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 (e.g., arm, trunk, or legs)
 - j. Duration of Treatment (total exposure in days)
 - k. Size of Treatment Area (e.g., cm²)

- l. Previous use of antipsoriatic treatment (yes/no)
- m. Completed the study (yes/no)
- n. Reason for premature discontinuation of subject
- o. Subject required additional treatment for plaque psoriasis due to unsatisfactory treatment response (yes/no)
- p. Per Protocol (PP) population inclusion (yes/no)
- q. Reason for exclusion from PP population
- r. Modified Intent to Treat (mITT) population inclusion (yes/no)
- s. Reason for exclusion from mITT population
- t. Safety population inclusion (yes/no)
- u. Reason for exclusion from Safety population
- v. Percent (%) Body Surface Area (BSA) involvement at baseline
- w. PGA score at baseline and at week 8
- x. Severity of PASI score at baseline and at week 8
- y. Individual component score of erythema, scaling, and plaque elevation at baseline and at week 8
- z. Albumin corrected calcium level at baseline and at week 8
- aa. Final designation of treatment outcome (success/failure) based on PGA
- bb. Final designation of clinical outcome (success/failure) based on severity of PASI
- cc. Treatment compliance: number of missed doses per subject
- dd. Concomitant medication (yes/no)
- ee. Adverse event(s) reported (yes/no)

Please refer to Table 3 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 3: Example of a summary dataset containing one line listing for each subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXLOC	EXDUR	size_tx	prev_ps	completd	disc_rs	add_trt	pp	pp_rs	mitt	mitt_rs
101	1	01	54	YEARS	F	1	A	RL	14			Y		N	Y		Y	
101	2	01	58	YEARS	F	1	B	RA	14			Y		N	Y		Y	

safety	safety_rs	bsa_b	pga_b	pga_8	pasi_b	pasi_8	eyth_b	eyth_8	scale_b	scale_8	plaque_b	plaque_8	alcalc_b	alcalc_8	tx_out	clin_out	complan	CM	AE
Y		8	3	0	3	4	3	2	2	2	3	3					0	Y	Y
Y		10	4	1	3	0	2	2	3	1	4	4					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 control
EXLOC:	Location of Treatment Area, e.g., A=arm, L=leg, etc.
EXDUR:	Duration of Treatment (total exposure in days)
size_tx:	Size of Treatment area (e.g., cm ²)
prev_ps:	Previous use of antipsoriatic treatment , e.g., Y=Yes, N=No
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 psoriasis 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.
bsa_b:	Percent (%) of Body Surface Area (BSA) involvement at baseline
pga_b:	PGA score at baseline
pga_8:	PGA score at week 8
pasi_b:	Severity of PASI score at baseline
pasi_8:	Severity of PASI score at week 8
eryth_b:	Erythema at baseline
eryth_8:	Erythema at week 8
scale_b:	Scaling at baseline
scale_8:	Scaling at week 8
plaque_b:	Plaque Elevation at baseline
plaque_8:	Plaque Elevation at week 8
alcalc_b:	Albumin adjusted serum calcium at baseline
alcalc_8:	Albumin adjusted serum calcium at week 8
tx_out:	Final designation of treatment outcome (A=success, B=failure) based on PGA
clin_out:	Final designation as clinical outcome (A=success, B=failure) based on Severity of PASI
complan:	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

26. Please provide a dataset containing a separate line listing for each visit per subject (if data exist) using the following headers, if applicable:
- Study identifier
 - Subject identifier
 - Name of Actual Treatment (exposure): test product, RLD, placebo control
 - Location of Dose Administration: application site

- e. Visit number
- f. Visit date
- g. Number of days since baseline visit
- h. Evaluator: identity of evaluator
- i. PGA score
- j. Total PASI score
- k. Individual erythema PASI score
- l. Individual scaling PASI score
- m. Individual plaque elevation PASI score
- n. Skin reaction scores for each sign and symptom evaluated (e.g., erythema, dryness, burning/stinging, erosion, edema, pain, itching, etc.)
- o. Concomitant medication reported during this visit (yes/no)
- p. Adverse event reported during this visit (yes/no)
- q. Laboratory testing during this visit (yes/no)
- r. Serum calcium level
- s. Serum albumin level
- t. Albumin-corrected serum calcium level

Please refer to Table 4 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 4: Example of dataset containing one line listing for each visit per subject

STUDYID	SUBJID	EXTRT	EXLOC	VISITNUM	SVSTDTC	ELTMBS	EVAL	pga	pasi_tot	pasi_ery	pasi_sca	pasi_pla	erythema	dryness	burning
101	1	A	F	1	2004-07-01	1							2	2	1

erosion	edema	pain	itching	CMrpt	AErpt	LBtest	calc	alb	alcalc
1	1	1	Y	Y	Y	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
- 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)
- ELTML: Elapsed Time since Baseline (days)
- EVAL: Evaluator: identity of the evaluator

pga:	PGA score
pasi_tot:	Total PASI score
pasi_ery:	Individual erythema PASI score
pasi_sca:	Individual scaling PASI score
pasi_pla:	Individual plaque elevation PASI score
erythema:	Skin reaction erythema score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
dryness:	Skin reaction dryness score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
burning:	Skin reaction burning score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
erosion:	Skin reaction erosion score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
edema:	Skin reaction edema score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
pain:	Skin reaction pain score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
itching:	Skin 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
LBtest:	Laboratory Testing performed during this visit, e.g., Y=Yes, N=No
calc:	Serum calcium level
alb:	Serum albumin level
alcalc:	Albumin-corrected serum calcium level

27. 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 calcipotriene.