

**Draft Guidance on Tacrolimus**

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

**Form/Route:** Ointment/Topical

**Recommended studies:** 1 study

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

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

Strength: 0.1%

Subjects: Non-immunocompromised male and female adults with clinical diagnosis of moderate to severe atopic dermatitis

Additional comments: Specific recommendations are provided below.

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**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 moderate to severe atopic dermatitis (AD) comparing the 0.1% test product versus the 0.1% reference listed drug (RLD) 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 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 RLD are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products.
3. Inclusion Criteria (the sponsor may add additional criteria)

- a. Non-immunocompromised male or female aged 18 years and older with a clinical diagnosis of moderate to severe atopic dermatitis that has failed to respond adequately to other topical prescription treatments for atopic dermatitis, or for whom those treatments are not advisable.
- b. Had a diagnosis of AD for at least 3 months.
- c. An Investigator's Global Assessment (IGA) of disease severity of at least moderate (per Table 1, a score of 3 or 4).
- d. Affected area of AD involvement at least 20% body surface area (BSA) at baseline, as defined by the criteria of Hanifin and Rajka.<sup>1</sup>
- e. Treated with a bland emollient for at least 7 days

**Table 1: Investigator's Global Assessment (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

4. 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 atopic dermatitis).
  - 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) UVA/UVB therapy, 3) PUVA (psoralen plus ultraviolet A) therapy, 4) tanning booths, 5) nonprescription 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.

<sup>1</sup> 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) in the areas to be treated, except for bland emollient (moisturizer).
  - j. Known allergy or hypersensitivity to tacrolimus or any other component of the test product or RLD.
  - 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. Treatment for atopic dermatitis, other than assigned treatment or bland emollient.
  - b. Topical or systemic corticosteroid, topical or systemic antibiotic, topical or systemic antifungal, oral or topical antihistamine, immunosuppressive drugs, immunomodulator (e.g., pimecrolimus), 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 assigned treatment or bland emollient, (e.g., sun screen, new brand of cosmetic or cleanser, cream, lotion, ointment, or powder) 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 or mouth.
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. The bland emollient (moisturizer) should be applied after the 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 (PP) 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 Investigator's Global Assessment 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**

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

10. The protocol should clearly define the PP, modified intent-to-treat (mITT) and safety populations.
  - a. The PP population includes all randomized subjects who met all inclusion/exclusion criteria, applied a prespecified proportion of the scheduled applications (e.g., 75% to 125%) of the assigned product for the specified duration of the study, did not miss the scheduled applications for more than 3 consecutive days, and completed the primary endpoint 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, and the protocol violations that would affect the treatment evaluation.
- b. The mITT population includes all randomized subjects who met all inclusion/exclusion criteria, applied at least one dose of assigned product, and returned for at least one post-baseline visit. The mITT population should be used to compare both test and reference products to placebo.
  - c. The safety population includes all randomized subjects who received study treatment.
11. If the signs and symptoms of atopic dermatitis 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 RLD and appropriate follow-up according to the standard of care. According to the RLD labeling, if signs and symptoms of atopic dermatitis do not improve within 6 weeks, subjects should be re-examined.
  12. Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of their AD during the study should be discontinued, included in the PP population analysis as treatment failures, 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). For example, subjects who develop a skin infection on the treated area should be discontinued, excluded from the PP population, but included in the mITT population, using LOCF.
  13. The OGD recommends blood sampling for tacrolimus trough serum concentrations on study Day 4 (prior to application of 8<sup>th</sup> dose of study treatment) as a safety measure to assure that the frequency and magnitude of measurable serum concentrations is not apparently greater with the generic than with the reference product. Based on previous PK data for tacrolimus, steady state concentrations are expected to be reached by study Day 4, and sampling at this time would likely reflect any systemic accumulation of tacrolimus with repeated applications to the same treatment area before significant healing takes place. Available data suggest that systemic exposure decreases as the lesions heal.

For measuring trough levels, the OGD recommends the following procedures on study Day 4

- 1) The blood should be sampled at the same time point for all patients.
- 2) The blood samples should not be taken from areas treated with tacrolimus ointment.
- 3) The study tube should be weighed (dose) before and after the morning dose on study Day 4.
- 4) The blood should be sampled just before the evening dose (i.e., 12 hours after the 7<sup>th</sup> dose was administered in the morning) on study Day 4.

5) To maintain blinding, tacrolimus trough concentrations should be taken from all study patients in the test, reference and placebo groups. Blood samples from the placebo group need not be analyzed to determine tacrolimus concentrations.

For serum concentrations obtained as a safety measure, the OGD does not require the sponsor to meet the usual pharmacokinetic bioequivalence limits used to determine equivalence.

14. 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.
15. 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.
16. Application site reactions such as dryness, burning/stinging, erosion, edema, and pain 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.
17. 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. If there is any significant difference in the inactive ingredients between the test and reference products or if any available data suggests that tacrolimus systemic exposure appears to be greater with the test product than with the RLD, a large comparative pharmacokinetic bioequivalence study may be requested. If designing a pharmacokinetic bioequivalence study for this product, the sponsor is advised to discuss the details of the protocol with the Division of Bioequivalence.
18. The quantitative information of inactive ingredients of the vehicle/placebo control should be provided.
19. 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.

20. 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.
21. 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.
22. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
23. To establish bioequivalence, the 90% confidence interval of the test - reference difference between products for the primary endpoint (success proportion) must be contained within [-0.20, +0.20] for dichotomous variables (success versus failure), using the PP population.
24. As a parameter for determining adequate study sensitivity, the test product and RLD should both be statistically superior to placebo control ( $p < 0.05$ , two-sided) for the primary endpoint using the mITT population and LOCF.
25. The size of the treatment area and the site of the treatment area should be compared and tabulated for each treatment group.
26. 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 proportions between test and reference was 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.

27. The Case Report Form (CRF) should clearly document the specific reason for use of this product, e.g., failure to respond adequately to other topical prescription treatments for atopic dermatitis or when those treatments are not advisable.
28. 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. Please 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. 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, disease severity (IGA), vital signs, adverse events, disposition (including reason for discontinuation of treatment), concomitant medications, medical history, compliance and comments, etc.
29. 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. Specific reason for use of this product (e.g., A= failure to respond adequately to other topical prescription treatments for atopic dermatitis, B=when those treatments are not advisable)
  - i. Name of Actual Treatment (exposure): test product, RLD, placebo control
  - j. Location of Treatment Area (i.e., neck, elbow, knee, hand, wrist, ankle)
  - k. Duration of Treatment (total exposure in days)
  - l. Size of Treatment Area (e.g., cm<sup>2</sup>)
  - m. Previous use of AD treatment (yes/no)
  - n. Completed the study (yes/no)
  - o. Reason for premature discontinuation of subject
  - p. Subject required additional treatment for AD due to unsatisfactory treatment response (yes/no)
  - q. Per Protocol (PP) population inclusion (yes/no)
  - r. Reason for exclusion from PP population
  - s. Modified Intent to Treat (mITT) population inclusion (yes/no)
  - t. Reason for exclusion from mITT population
  - u. Safety population inclusion (yes/no)
  - v. Reason for exclusion from Safety population
  - w. Percent (%) Body Surface Area (BSA) involvement at baseline
  - x. Percent (%) Body Surface Area (BSA) involvement at study Day 15
  - y. IGA score at baseline
  - z. IGA score at study Day 15
  - aa. Time and date of tacrolimus trough blood sample

- bb. Tacrolimus trough blood concentration (on study Day 4)
- cc. Weight of study drug before and after the morning dose on study Day 4
- dd. Final designation of treatment outcome (success/failure) based on IGA
- ee. Treatment compliance: number of missed doses per subject
- ff. Concomitant medication (yes/no)
- gg. 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	use_rs	EXTRT	EXLOC	EXDUR	size_tx	prev_ad	completd	disc_rs	add_tx	pp	pp_rs
101	1	01	21	YEARS	F	1		A	N	14			Y		N	Y	
101	2	01	19	YEARS	F	1		B	BE	14			Y		N	Y	

mitt	mitt_rs	safety	safety_rs	bsa_b	bsa_15	iga_b	iga_15	bl_time	bl_date	ser_tac	wgt_bef	wgt_aft	tx_out	complan	CM	AE
Y		Y		22	8	3	0						A	0	Y	Y
Y		Y		25	10	4	1						A	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
- use\_rs: Specific reason for use of this product, e.g., A= failure to respond adequately to other topical prescription treatments for atopic dermatitis, B=when those treatments are not advisable

EXTRT:	Name of Actual Treatment (exposure), e.g., A=test product, B= RLD, C=placebo
EXLOC:	Location of Treatment Area, e.g. N=neck, BE=both elbows, LE=left elbow, etc..
EXDUR:	Duration of Treatment (total exposure in days)
size_tx:	Size of Treatment area (e.g., cm <sup>2</sup> )
prev_ad:	Previous use of AD 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_tx:	Subject required additional treatment for AD 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
bsa_15:	Percent (%) of BSA involvement at study Day 15
iga_b:	IGA score at baseline, e.g., 0=Clear, 1=Almost Clear, 2=Mild, 3=Moderate, 4=Severe
iga_15:	IGA score at study Day 15, e.g., 0=Clear, 1=Almost Clear, 2=Mild, 3=Moderate, 4=Severe
bl_time:	Time of tacrolimus trough blood sample
bl_date:	Date of tacrolimus trough blood sample
ser_tac:	Serum tacrolimus concentration (on study Day 4)
wgt_bef:	Weight of study drug before morning dose on study day 4
wgt_aft:	Weight of study drug after morning dose on study day 4
tx_out	Final designation of treatment outcome based on IGA, e.g., A=success, B=failure
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

30. 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
- d. 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. IGA score
- j. Individual signs and symptoms of AD score for erythema, induration/papulation, lichenification, and pruritus
- k. Skin reaction score for each sign and symptom evaluated (e.g., dryness, burning/stinging, erosion, edema, pain)
- l. Concomitant medication reported during this visit (yes/no)
- m. Adverse event reported during this visit (yes/no)
- n. Laboratory testing during this visit (yes/no)

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	iga	ad_eryth_	ad_indur	ad_lich	ad_prur	sr_dryn	sr_burn	sr_eros	sr_edema	sr_pain	CMrpt	AErpt	LBtest
101	1	A	N	1	2004-07-01	1							2	1	1	1	1	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
- EXLOC: Location of Treatment Area: specific anatomical site of application, e.g., N=neck etc.
- VISITNUM: Visit Sequence Number
- SVSTDTC: Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
- ELTMBS: Elapsed Time since Baseline (days)
- EVAL: Evaluator: identity of the evaluator
- iga: IGA score, e.g., 0=Clear; 1=Almost clear, 2=Mild, 3=Moderate, 4=Severe
- ad\_eryth: Individual signs and symptoms of AD score for erythema
- ad\_indur: Individual signs and symptoms of AD score for induration/papulation
- ad\_lich: Individual signs and symptoms of AD score for lichenification

ad\_prur: Individual signs and symptoms of AD score for pruritus  
sr\_dryn: Skin reaction dryness score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)  
sr\_burn: Skin reaction burning score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)  
sr\_eros: Skin reaction erosion score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)  
sr\_edema: Skin reaction edema score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)  
sr\_pain: Skin reaction pain 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

31. 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 tacrolimus.